Yamada’s Textbook of Gastroenterology

Sixth Edition

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Preface

It has been nearly 25 years since the first edition of the Textbook of Gastroenterology was published. The textbook, conceived by its first editor-in-chief Dr. Tadataka Yamada, set out to make available a reference which was comprehensive in its coverage of the clinical discipline of gastroenterology in the context of the scientific foundations of current practices. The approach was reflective of the premise that a thorough grounding in the scientific basis of disease is the most dependable foundation for an understanding that would enable the astute clinician to care for patients.

The first edition, edited by a team including Tadataka Yamada, David H. Alpers, Chung Owyang, Don W. Powell, and Fred E. Silverstein, established the textbook as authoritative. That benchmark has since been sustained through four subsequent editions even as the outstanding group of editors evolved.

With this sixth edition, the baton has been passed, and a new group of editors has taken on the responsibility of stewardship of that legacy. In assuming our responsibilities, my colleagues and I aimed to make the new edition even more useful to our intended readers: students, specialty and subspecialty trainees, practicing clinicians and academicians. We took as basic premise that the textbook would continue to be comprehensive, incorporating all of the significant advances made since the last edition. This new edition also continues to take a global view of gastroenterology – encompassing disorders of the gastrointestinal tract which may be common and similar through most if not all regions of the world as well as those that are either specific to a given geography or population or in whom the manifestations and management differ by geography or population. In addition, the textbook provides an in depth consideration of ancillary fields and modalities that are a critical to the modern practice of gastroenterology including endoscopy, radiologic imaging, histology and pathology.

The editors judged that this edition would benefit from a number of changes beyond the overall refreshment of the content to reflect most current understanding and management approaches in clinical care. Readers will find a new section, “Approach to the patient with . . . ,” in which experts provide a framework for approaching the evaluation and management of patients presenting with the most common symptoms and signs that are the purview of the gastroenterologist, incorporating into the textbook material that had previously been found only in a separate volume. The editors judged it would be most useful to have these easily available to readers as it reflects a point of reference that is a common if not daily aspect of clinical practice.

Another change that readers familiar with past editions will note is the organization of chapters that collectively cover the common inflammatory bowel disorders into a separate section of their own. While the primary organization of this book beyond consideration of the basic biology and approach to the patient with symptoms of a gastrointestinal disorder is by anatomic organ, the editors considered that this was not well suited to coverage of the inflammatory bowel diseases. The rapid progress in understanding of the underlying pathogenesis and pathophysiology of inflammatory bowel diseases from a fundamental basis as well as significant new developments in the therapy and management of these patients warranted this new approach to make it both comprehensive and in a format most useful to those looking for an understanding of inflammatory bowel diseases.

This new edition reflects some formatting changes that are intended to facilitate ease of use. Management recommendations whether diagnostic or therapeutic are now highlighted within tables and offset by the common color green. Perhaps more importantly, the textbook is now more than a book. With this edition, the textbook is also supplemented by web based links which give the reader access to podcasts prepared by authors of select chapters. In selecting those chapters to be accompanied by a podcast, the editors focused especially on those in which knowledge and practice are changing most rapidly so that readers can have the benefit of most current knowledge and to hear it, literally, directly from experts most authoritative on the topic.

Finally, readers will find each chapter is followed by a short list of especially key references suggested as further readings by chapter authors. At the same time, definitive and comprehensive reference lists are accessible through the web. By using this media for the very extensive references provided by the authors, the editors endeavored to maintain the high standards of scholarship that readers should expect of this authoritative text while helping reduce the overall cost to make that available.

In this day and age of ready access to knowledge on the Internet, one might well ask the value or importance of a reference like the Textbook of Gastroenterology. Even as the Internet is a powerful source of information for experts and lay persons alike, there is paradoxically increased importance, particularly for the clinician or aspiring gastroenterologist to have a reliable
source that has vetted and distilled information to define state-
of-the-art understanding. Textbooks, to achieve that standard, are by nature less agile than other media and without doubt the committed student or teacher should supplement the foundational knowledge in textbooks with other sources that may give access to interval advances. Nonetheless, it is the hope of the editors that readers of this sixth edition of the Textbook of Gastroenterology will find it as a dependable source of knowledge that is essential to the student and practitioner of the field.

We thank the legions of mentors, colleagues, and patients who have taught us over the years. We are grateful for the work done by our predecessors as stewards of this textbook and especially appreciative of the enormous efforts made by contributing authors to provide content that fulfilled the high standards expected. We thank several individuals who worked most closely with this project including Oliver Walter, Jon Peacock, Andrew Hallam and Cathryn Gates at Wiley, Aileen Castell of PM Bookpublishing, and Elizabeth Paul. Plus a special thanks to Ms. Julia Kanellos whose outstanding editorial support was truly invaluable.

It is our hope that readers whether approaching this book from a standpoint of a student fresh in their interest in gastroenterology to the highly experience and seasoned clinicians will find this a resource to truly enable their work.

Daniel K. Podolsky, MD
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Anthony N. Kalloo, MD
Fergus Shanahan, MD
Timothy C. Wang, MD
In the near quarter century since the publication of the First Edition of this Textbook much has happened in the science and practice of gastroenterology. Scientists in our field have been at the forefront of some of the most exciting advances in modern biomedical science including developmental biology, mucosal immunology, cancer genetics, predictive toxicology, and microbiomics. Moreover we have seen the advent of important new medicines for the treatment of vexing problems such as inflammatory bowel disease and even cures for chronic debilitating problems such as peptic ulcer disease and hepatitis C as well as prevention of cancers which are the sequela of these disorders. There are now vaccines for rotavirus, one of the largest killers of children in the developing world and vaccines for the other lethal diarrheal disorder, Norovirus infection, are on the horizon. Widespread screening colonoscopy has had a remarkable effect on lowering the mortality of colorectal cancer and endoscopic surgery has become the mainstay of abdominal procedures, transforming the training and practice of general surgery. The Editors predicted as much as indicated in the Preface to the First Edition where they noted that: “We have witnessed a logarithmic growth in volume of information concerning the basic biology and biochemistry of the gut. This wealth of new knowledge not only has provided insight into the pathogenesis of gastrointestinal diseases but also has indentified the critical role of the gut in the physiology and pathology of other organ systems. There is every reason to expect that the pace of our scientific growth will continue in the years ahead.” Despite the emergence of on-line approaches to obtaining knowledge in medicine we hope that the Textbook has managed to keep up with the rapid developments in gastroenterology and live up to its expressed intent “to serve both as a guide for clinicians who need to understand the pathophysiology of their patients’ disorders and as a resource for serious students of gastroenterology.”

After five editions of the Textbook it seemed a good time for the editors to turnover much as we continually refreshed each edition with new authors. The new Editor, Dr. Daniel Podolsky, is amply qualified to take over the Textbook. He is a leading scientist and practitioner in the field of gastroenterology and was the chief of one of the finest gastroenterology divisions in the United States at the Massachusetts General Hospital for nearly 20 years. To take on the task he has assembled an expert group of associate editors who promise to uphold the quality that we strived to achieve with each new edition and to continue to “integrate the various demands of science, technology, expanding information, good judgment and common sense in the diagnosis and management of gastrointestinal patients” as we had hoped to do at the outset. To my former Associate Editors David Alpers, Don Powell and Chung Owyang who stayed with the Textbook for all of its first five editions and to Fred Silverstein, Loren Laine, Neil Kaplowitz and Tony Kalloo who served as Associated Editors for some of the editions, my deepest thanks for a job well done. It was my greatest honor to work with you all in the task of bringing the science and practice of gastroenterology to life for the reader of the Textbook. To Dan Podolsky and his new team of editors, my best wishes and fondest hopes that the tradition of the Textbook thrives under your stewardship. I will read each new edition with the eyes of a student trying to keep abreast of the developments in my chosen field of practice.

Tadataka Yamada, MD
About the companion website and companion digital edition

Companion website

This book is accompanied by a companion website:

www.yamadagastro.com/textbook

The website includes:

• Podcasts from the following chapters:
  Chapter 37, Approach to the patient with unintentional weight loss
  Chapter 40, Approach to the patient with gas and bloating
  Chapter 47, Genetic counselling for gastrointestinal patients
  Chapter 68, Tumors of the small intestine
  Chapter 72, Crohn's disease: clinical manifestations and management
  Chapter 96, Hepatitis C virus infection
  Chapter 103, Alcoholic liver disease
  Chapter 137, Endoscopic approaches to enteral nutrition
• Full lists of references
• Full digital edition access instructions

Companion digital edition

This book is also accompanied by a companion digital edition:

Simply find your unique companion digital edition redemption code on the inside front cover of this book by carefully scratching away the top coating on the label. Then visit http://www.vitalsource.com/software/bookshelf/downloads to get started.

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PART 5

Diagnostic and therapeutic modalities in gastroenterology
A Endoscopic

CHAPTER 131

General approach to endoscopy: sedation, monitoring, and preparation

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Introduction

Sedation reduces anxiety and fear associated with endoscopic procedures and improves patient safety, satisfaction, and acceptability of future procedures [1]. The incidence of colonoscopy complications increases with age and American Society of Anesthesiologists (ASA) class, and decreases with the use of sedation [2]. Sedation and analgesia improves the quality of colonoscopy [3], quality of upper endoscopy [4], rate of colonoscopy completion [5–8], as well as polyp detection, though detection is not affected by the level of sedation [3,9]. The goal of sedation is to provide amnesia, analgesia, and anxiety reduction without loss of airway patency or ventilator effort. Moderate sedation provides a high level of physician and patient satisfaction and a low risk of serious adverse events [6,10]. The level of sedation as well as the choice of sedative is based on the type of procedure (length and painfulness), patient characteristics, patient preferences, and the need for cooperation [11,12].

Continuum of depth of sedation

Table 131.1 shows the levels of sedation as defined by the ASA [13] and Joint Commission on Accreditation of Healthcare Organizations (JCAHO) in the US [14]. Continuous monitoring of depth of sedation is critical because patients may slip quickly from one stage to another [15]. The safety margin is wide around moderate sedation, and unintended excursion into a deeper level of sedation does not generally result in loss of ventilatory effort, though “at-risk” patients may develop airway obstruction [15]. Recent evidence indicates that the use of anesthesia specialists for endoscopy, a surrogate for deep sedation, is associated with an increased risk of aspiration pneumonia [16].

Pre-sedation preparation

Endoscopists should obtain informed consent personally [17]. Appropriate preprocedure counseling must be done regarding the risks and benefits of and alternatives to the procedure and sedation and the option of unsedated endoscopy may be offered [11,12,18,19]. Another option is “on-demand” sedation which enables the patient undergoing unsedated endoscopy to later receive medication in the event that they are unable to tolerate the procedure [20,21]. In patients receiving deep sedation, preprocedural anxiety does not affect sedative requirement [22].
A critical aspect of the preprocedure evaluation is to identify any characteristics that pose an increased risk for aspiration (e.g., ascites, full stomach, active bleeding), difficult airway (e.g., obesity, sleep apnea, prior difficult intubation, or high Mallampati score; Figure 131.1), or increased risk for cardiopulmonary complications (e.g., comorbidities, advanced age) [11,23]. In addition, prior experience with sedation, drug allergies, current medications, smoking, and alcohol or substance use should be solicited. A complete assessment of airway, baseline vital signs, respiratory rate and effort, and general neurological status should be done. Patients should fast for a minimum of 6 h before the procedure, though clear liquids can be consumed up to 2 h prior [24,25]. In emergency situations, when fasting is not practical, either the target level of sedation should be modified or endotracheal intubation should be considered given the incumbent risk for aspiration. Laboratory testing may be required when sedation is provided by an anesthesiologist [12,26]. Intravascular access should be obtained and maintained through recovery.

**Medication regimens**

The choice of sedatives depends on the endoscopist’s preference for and familiarity with different agents and regimens, as well as the type of procedure. Brief procedures can sometimes be completed with minimal amounts of sedation, whereas some therapeutic procedures may require deep sedation. There is no difference in polyp detection by colonoscopy using deep or moderate sedation [27]. Sedatives are given intravenously for endoscopy and must be administered slowly and titrated in small increments. Another approach is patient-controlled analgesia which allows patients to administer their own sedation [28,29]. The pharmacology of the commonly used agents is summarized in Table 131.2.
<table>
<thead>
<tr>
<th>Sedative</th>
<th>Mechanism of action</th>
<th>Properties</th>
<th>Onset/peak effect</th>
<th>Duration of action</th>
<th>Side effects</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Midazolam Binds to benzodiazepine receptors on postsynaptic GABA neuron in CNS, including the limbic system, reticular formation and enhances the inhibitory effect of GABA on neuronal excitability</td>
<td>Induces sedation and amnesia. No analgesic properties.</td>
<td>Onset 1–5 min</td>
<td>1–3 h</td>
<td>Respiratory depression (decreased tidal volume and/or respiratory rate); potentiated by concomitant use of opiates; respiratory arrest; apnea Hypotension CNS depression; drowsiness; oversedation Paradoxical agitation</td>
<td>i.v.: initial 0.5–2 mg over 2 min; repeat doses every 2–3 min; usual total dose: 2.5–5 mg Decrease doses in elderly and by 30% if opiates are administered concomitantly Maintenance: 25% of dose used to reach sedative effect</td>
</tr>
<tr>
<td></td>
<td>Diazepam Same as midazolam</td>
<td></td>
<td>Onset 3–10 min</td>
<td>2–8 h</td>
<td>Same as midazolam</td>
<td>i.v.: 2.5–5 mg; incremental doses of 2.5 mg at 3–4 min intervals</td>
</tr>
<tr>
<td>Opiates</td>
<td>Meperidine Binds to opiate receptors in CNS, causing inhibition of ascending pain pathways; produces generalized CNS depression</td>
<td>Analgesic with mild sedative properties. Slow onset and longer duration than other opioids. Used for longer procedures</td>
<td>Onset 1–3 min</td>
<td>2–3 h</td>
<td>Respiratory depression Hypotension Nausea; vomiting CNS depression</td>
<td>i.v.: initial 15–50 mg; redose 25 mg at 5 min intervals as needed</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Binds with receptors within CNS, increases pain threshold, alters pain reception, inhibits ascending pain pathways</td>
<td>Analgesic with mild sedative properties. Rapid onset and recovery; well suited for outpatient endoscopy</td>
<td>Onset 30 s; peak effect 5–8 min</td>
<td>0.5–1 h</td>
<td>Respiratory depression Hypotension; bradycardia CNS depression Nausea; vomiting</td>
<td>i.v.: initial 25–100 μg; redose 25–50 μg/dose every 1–2 min as needed</td>
</tr>
<tr>
<td>Propofol</td>
<td>Hindered phenolic compound with intravenous general anesthetic properties.</td>
<td>Rapid onset; Fast recovery; Smaller doses are required when used with narcotics or benzodiazepines No analgesia Weak amnesic effect</td>
<td>Onset 30–60 s</td>
<td>3–10 min</td>
<td>Hypotension Apnea Injection site stinging or pain</td>
<td>i.v.: initial 20–40 mg slow injection. Incremental boluses of 10–20 mg every 20 seconds</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Blocks postsynaptic dopaminergic receptors in the brain; α-adrenergic blocker; competes with histamine for the H1-receptor; reduces stimuli to the brainstem reticular system</td>
<td>Synergizes sedation; combats nausea</td>
<td>Onset 3–5 min</td>
<td>2–6 h</td>
<td>Hypertension Bradycardia Confusion Disorientation Rapid administration may cause transient hypotension</td>
<td>i.v.: 12.5–50 mg/dose Infused at a maximum rate of 25 mg/min</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Butyrophenone neuroleptic tranquilizer. Mild α-adrenergic inhibitory action</td>
<td>Exerts antiemetic and antianxiety effect Mild sedative EKG monitoring for 2–3 h after administration is suggested</td>
<td>Onset 3–10 min</td>
<td>2–4 h</td>
<td>QTc prolongation and torsades de pointes (dose dependent) Hypotension Tachycardia Restlessness; anxiety Extrapyramidal symptoms</td>
<td>i.v.: initial 2.5 mg; redose 1.25 mg to achieve desired effect Administered as a rapid IVP, over 30–60 s; Administer additional doses with caution; maximum dose 5 mg</td>
</tr>
</tbody>
</table>

CNS, central nervous system; EKG, electrocardiogram; GABA, γ-aminobutyric acid; IVP, intravenous push.
**Benzodiazepines**

Benzodiazepines enhance the effect of the neurotransmitter \( \gamma \)-aminobutyric acid (GABA) and induce relaxation, anxiolysis, and amnesia [30]. The most commonly used benzodiazepines for endoscopy are midazolam [31–33] and diazepam [34]. Midazolam is preferred because of better efficacy and tolerability [35], shorter duration, better amnesic properties, and 2–3 times greater potency than diazepam [36]. It also has a decreased incidence of phlebitis and results in superior patient satisfaction compared to diazepam [37]. Midazolam crosses the placenta and also enters breast milk. Both midazolam and diazepam are pregnancy category D. Although birth defects with benzodiazepines have occurred with chronic oral use by the mother, their use for endoscopic procedures in pregnancy is generally considered safe [38,39].

Benzodiazepines do not have analgesic properties and usually require coadministration of opiates. Dosages must be reduced in elderly or debilitated patients and in those receiving narcotics or other central nervous system (CNS) depressants concomitantly. Underlying liver disease must also be considered as benzodiazepines are metabolized by the liver [40].

Adverse effects include paradoxical agitation [33] and severe respiratory depression which is greatly potentiated by coadministration of opioids. Inadvertent overdose can cause severe respiratory depression, hypotension, general anesthesia, and apnea.

**Opiates**

Meperidine and fentanyl are among the most commonly used opiates for gastrointestinal endoscopy. They have sedative as well as analgesic properties. Meperidine has neurotoxic metabolites and should be avoided in the elderly. Renal impairment can lead to metabolite accumulation causing seizures. The dose should be reduced to 75% of normal for creatinine clearances of 10–50 mL/min and to 50% for creatinine clearances <10 mL/min. Meperidine can cause serotonin syndrome in patients taking monoamine-oxidase inhibitors. Fentanyl is a morphine-like compound, but 80–100 times more potent in analgesic activity with little effect on the cardiovascular system [41]. It produces profound analgesia and suppresses respiratory and cough centers. It has rapid onset and clearance and therefore patients recover more rapidly than with meperidine [42,43]. It also has reduced incidence of nausea compared to meperidine and does not have any dangerous metabolites. It has greater synergy with midazolam than meperidine. For these reasons, fentanyl is rapidly replacing meperidine for endoscopy. In high doses, fentanyl can cause chest wall rigidity and respiratory difficulty and therefore total doses are often limited to 200 \( \mu \)g/case [44]. Both meperidine and fentanyl are pregnancy category C and the agents are widely used for endoscopy during pregnancy.

All opiates should be used cautiously in patients taking other CNS depressants and avoided with monoamine oxidase inhibitors. Caution must be taken with liver disease. For the newer, ultra-short acting opiates (e.g., remifentanil and alfentanil), no significant benefit has been demonstrated in comparison to standard regimens [45–48]; however, shorter sedation times [49] makes these agents attractive for postprocedural workload [50,51].

**Propofol**

Propofol is a phenol derivative which promotes GABA activity in the brain by acting on a different subset of GABA receptors from those that mediate the effects of benzodiazepines [30]. In comparison to benzodiazepines/opioids, the mean time to onset of sedation is shorter, depth of sedation is greater, recovery is faster [52,53], and patient satisfaction is improved [54]. Postadministration nausea is very rare. Propofol induces amnesia when titrated to deep sedation or general anesthesia [55,56]. Rapid onset of sedation and rapid recovery may improve efficiency of endoscopy units [57] as well as cost-effectiveness [58]. Safety and efficacy of propofol has been demonstrated for colonoscopy, esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatoscopy (ERCP) [53,59–63].

Propofol has been administered by intermittent bolus [64,65], continuous infusion [64,66,67], and patient-controlled analgesia [68–73]. Target-controlled infusions deliver drugs according to computer-generated pharmacokinetic models [74–77]. The computer-assisted personalized sedation (CAPS) system is designed to facilitate safe administration of propofol [78]. It targets minimal to moderate sedation [79] and is not indicated for sedation of high-risk patients [80]. Physiological patient data are monitored and processed continuously by the device, which when using a computerized drug delivery algorithm, titrates sedation by varying propofol infusion and administering boluses [81]. It is also able to increase oxygen delivery in response to hypoxemia and apnea. Intermittent bolus allows faster onset of sedation and has been preferred for endoscopy [82]. Initial boluses when the drug is used as a single agent are typically 30–50 mg and are adjusted for age, weight, and comorbidities. Subsequent boluses are 10–20 mg. Local pain during injection occurs in 30% of patients, primarily when infused in a small vein and may be decreased by lidocaine [83]. Avoidance of respiratory depression is critically dependent on gradual titration [84,85]. Airway compromise may occur when used for advanced endoscopy especially in males, ASA >III and high BMI [86]. Propofol does not precipitate or aggravate encephalopathy in patients with cirrhosis [87–90] and therefore should be used as an alternative to midazolam in these patients [91,92]. Combination of propofol and fentanyl is more efficacious with a shorter recovery time compared with midazolam and fentanyl [93]. It is, overall, safe for gastrointestinal procedures [94] and is not associated with an increase in cardiopulmonary complications [63].

Propofol has been safely administered by nonanesthesiologists for endoscopy [95–98]. There are two methods of propofol administration under the direction of the endoscopist: (1) nurse-administered propofol sedation (NAPS) where propofol is used as a single agent and is titrated to deep sedation; and (2)
balanced propofol sedation (BPS) which is a combination of propofol with a small induction dose of benzodiazepine with or without opioid and is targeted to moderate sedation. The term endoscopist-directed propofol (EDP) encompasses both NAPS and BPS. Evidence from clinical studies supports the safety of nonanesthesiologist administered propofol [99–104]. Evidence also indicates that propofol sedation is the best practice for the pediatric patient undergoing endoscopy and can be administered by specifically trained nonanesthesiologists [105,106]. Nonanesthesiologist administration of propofol should be performed with caution in patients at increased risk of aspiration (e.g., achalasia, acute upper gastrointestinal bleeding, delayed gastric emptying), increased risk of airway obstruction (e.g., sleep apnea, high-risk airway assessment), and multiple comorbidities. Propofol is contraindicated with allergy to eggs or soybeans [107,108].

**Droperidol**

Droperidol is a neuroleptic and is used as an adjunct for complex endoscopic procedures and in patients who have paradoxical reactions to standard sedation or in whom narcotics and benzodiazepines are likely to be inadequate [109,110] (e.g., history of alcoholism, chronic benzodiazepine or opiate use, or prior difficulty with conscious sedation). Droperidol exerts a calming and antiemetic effect, has a mild sedative and α-adrenergic inhibitory action, and can cause prolonged postprocedural drowsiness. It does not exacerbate opioid-induced respiratory depression. Additional boluses should not be administered for agitation once the procedure has started because, by the time dosages take maximal effect, the procedure may be complete and recovery may be prolonged. Safety and efficacy have been demonstrated in several studies [111–113]. It prolongs the QTc interval on the electrocardiogram [114] and can induce torsades de pointes which prompted the American Food and Drug Administration (FDA) to issue a black box warning. Cardiac events, some fatal, have been reported by specifically trained nonanesthesiologists [105,106]. It is contraindicated if the QTc is prolonged >440 ms in males and >450 ms in females. Caution must be exercised in patients with risk factors for QT prolongation such as congestive heart failure, hypokalemia, hypomagnesemia, or concomitant use of drugs that prolong QT interval. The heart rhythm should be monitored for 3 h after administration. It is contraindicated in thyrotoxicosis, pheochromocytoma, and Parkinson disease, and it may cause extrapyramidal effects [116] and neuroleptic malignant syndrome. Guidelines for its use have been suggested by the American Society for Gastrointestinal Endoscopy (ASGE) [110]. Droperidol is pregnancy category C (Table 131.3). The use of droperidol has declined because of the need for prolonged monitoring.

**Ketamine**

Ketamine antagonizes the excitatory neurotransmitter glutamate and also binds to opioid receptors. The initial i.v. dose is 0.5 mg/kg, titrated to desired effect. Duration of effect is 10–15 min [117], and include analgesia, amnesia, and sedation while preserving airway protective reflexes and spontaneous breathing. Patients may experience emergence reactions which manifest as visual and auditory hallucinations, disorientation, and vivid dreams [118]. It is also known to increase systolic blood pressure, cause tachycardia, and cause muscle hyperactivity which can be attenuated with coadministration of benzodiazepines [119]. It is often used in the emergency setting because of its rapid onset and short duration of action [120]. It is used in combination with midazolam [121–123] or with dexmedetomidine [124] for pediatric endoscopic procedures [121–123]. Combination with propofol, midazolam, and pentazocine works well for ERCP [125]. Postsedation, patient should be kept in a quiet dark room without any stimulation.

**Nitrous oxide**

Nitrous oxide is a short-acting inhaled agent with anesthetic, analgesic, and anxiolytic properties. When administered continuously, it provides comparable analgesia to intravenous sedation [126]. The rapid psychomotor recovery enables quicker patient discharge and removes the need for patient to be chaperoned [127]. It is also given in combination with sedatives and analgesics [128]. Onset of action is 2–5 min, and oxygen should be coadministered. It should not be used during the first two trimesters of pregnancy (see Table 131.3).

**Dexmedetomidine**

Dexmedetomidine (DEX) is a reversible α₂ adrenergic agonist, associated with less respiratory depression than other sedative  

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<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy category</th>
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</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>D</td>
</tr>
<tr>
<td>Diazepam</td>
<td>D</td>
</tr>
<tr>
<td>Meperidine</td>
<td>C</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>C</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>C</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>C</td>
</tr>
<tr>
<td>Propofol</td>
<td>B</td>
</tr>
<tr>
<td>Promethazine</td>
<td>C</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>B</td>
</tr>
<tr>
<td>Droperidol</td>
<td>C</td>
</tr>
<tr>
<td>Ketamine</td>
<td>B</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>C</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>C</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>C</td>
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<tr>
<td>Naloxone</td>
<td>C</td>
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</table>
agents. It is used for procedural sedation as a loading dose followed by maintenance infusion. Rate of effective sedation is significantly higher than midazolam [129] and it ranks highly for patient and endoscopist satisfaction [130,131]. It is pregnancy category C (see Table 131.3).

**Combination regimens**

Combinations of benzodiazepines and opiates are often used [132,133] and are efficacious and well tolerated [59,65,68,99,134,135]. Addition of benzodiazepines to opioids enhances sedation and amnesia, and addition of opioids to benzodiazepines adds analgesia and sedative effect. Combination therapy results in better patient comfort and endoscopist satisfaction [136]. A combination of fentanyl and midazolam results in significantly shorter recovery times than meperidine plus midazolam [137].

In situations where high doses of narcotic and benzodiazepines provide inadequate sedation, phenergan or diphenhydramine [138] may be used in addition to synergize sedative effects. Phenergan is pregnancy category C, and diphenhydramine is B.

The combination of propofol with a benzodiazepine [139] and/or an opioid [140] enhances the sedative effects of propofol and allows propofol to be targeted to minimal or moderate sedation [141] without substantial loss of satisfaction and with shorter recovery times compared with propofol titrated to deep sedation [142]. Even small doses of opioid and/or benzodiazepine substantially ease total propofol doses and make titration of propofol easier [143–145]. These combinations result in less cognitive impairment compared to benzodiazepine and/or opioid [146]. Propofol’s amnestic effect is dependent on the depth of sedation. When titrated to moderate sedation amnesia is enhanced by coadministration of a benzodiazepine [140]. Premedication with oral midazolam followed by intravenous propofol also provides significant synergistic benefit [147–149]. Propofol itself has no analgesic properties, so addition of a narcotic is recommended for painful procedures when propofol is titrated to moderate sedation. The combination of propofol with midazolam or fentanyl works better than propofol alone in the pediatric population as well [150].

Balanced propofol sedation provides superior patient satisfaction and shorter recovery times than standard sedation [151]. BPS is also safe and effective for complex endoscopic procedures [152,153]. Music can also be used as an adjunct and is associated with reduced anxiety, lower doses of analgesia and sedation and shorter procedure times [154–156].

**Topical anesthetics**

Topical anesthetics essentially eliminate the gag reflex and are especially beneficial in unsedated upper endoscopy [157,158] and may improve tolerance in lightly sedated upper endoscopy [159]. They are not beneficial in moderate and deep sedation [160]. Benzocaine has a rapid onset and short duration. Posterior lingual lidocaine swab may work better than the spray [161]. Lidocaine lollipop is also well tolerated and safe [162]. Methemoglobinemia and anaphylactic reaction are rare but serious complications [159,163–166]. Methemoglobinemia occurs primarily with benzocaine but also with cetacaine and presents with clinical cyanosis despite a normal arterial PO₂ [167,168]. Treatment is intravenous methylene blue (2 mg/kg). Systemic effects such as arrhythmia and seizures due to absorption have been observed rarely [169,170]. Topical anesthetics have been implicated in the development of aspiration and pneumonia after EGD [171,172] and patients should be warned to take nothing by mouth until the anesthetic has worn off.

**Reversal agents**

Reversal agents should be used when patients develop severe respiratory depression. Patient age and medication dose are independent risk factors for reversal agent utilization [173].

Flumazenil binds to the GABA receptor complex, resulting in reversal of CNS depression due to benzodiazepines without reversing the amnesia. The dosage of 0.2 mg intravenously may be repeated at 1 min intervals to a maximum dose of 3 mg. It has limited efficacy in reversing respiratory depression due to opiates [174]. For this reason, naloxone should be tried before flumazenil in patients who develop severe respiratory depression after being given a combination of opiates and benzodiazepines. Flumazenil has a rapid onset of action (1–3 min). A patient may lapse back into a sedated state owing to the shorter half-life of flumazenil (40–80 min) compared to benzodiazepines. Flumazenil may also be used to treat paradoxical reactions to benzodiazepines. Flumazenil administration can precipitate acute withdrawal in patients on prolonged benzodiazepine therapy [175] and caution must be taken when administering it to patients using chloral hydrate, carbamazepine, and tricyclic antidepressants because it can induce seizures [176]. The drug is pregnancy category C [177] (see Table 131.3).

Naloxone is a nonselective competitive opioid antagonist that competes and displaces narcotics at opioid receptor sites. It reverses CNS effects of opioids including ventilatory depression, sedation, and analgesia [178]. The degree and extent of reversal is dose dependent. The usual dose is 0.4–2 mg i.v. over 30 s. The onset of action is 1–2 min and half-life is 30–45 min. It may be cleared faster than meperidine, thus sedation may recur. Repeat doses may be given at 2–3 min intervals to a maximum of 10 mg. Acute withdrawal and severe pain may occur in chronic opiate users. Acute reversal may cause tachycardia, arrhythmias, cardiac arrest, hypertension, or pulmonary edema due to the release of catecholamines as well as seizures. Therefore, caution must be exercised in elderly patients and those with cardiovascular disease. Very rapid reversal may cause nausea, vomiting, diaphoresis, and circulatory distress. Patients receiving naloxone should be monitored for up to 2 h [178]. It is pregnancy category B (see Table 131.3). Elective use of reversal agents for quicker recovery is not recommended at this time [13] and is only marginally supported by literature [179,180].
Use of anesthesiologists in endoscopic sedation

Routine sedation does not require the presence of an anesthesiologist and ASA class I–III patients are candidates for sedation by nonanesthesiologists with appropriate training and experience [181]. However, in the case of severely compromised patients (ASA class IV or V) or those with a difficult airway, advanced obstructive sleep apnea (OSA), restricted mobility of the cervical spine, or with previous adverse reaction to or difficulty with moderate sedation [182–184], such consultation is often warranted. Laryngeal mask airway (LMA) may be used for airway protection [185]. Anesthesiologists often provide important expertise during long complex procedures or those requiring precise instrumentation. Anesthesiologist-delivered sedation has become increasingly common in endoscopy centers and is projected to grow substantially [186]. However, the use of anesthesia-assisted sedation for ASA class I and II patients for endoscopy is cost-ineffective [187]. Anesthesia involvement significantly increases the cost [188,189]. Cost doubles in Medicare patients and quadruples in commercial insurance [190].

Despite the cost-ineffectiveness of using anesthesiologists and anesthetists for routine endoscopic procedures, financial incentives in the US, at least for the time being, are still aligned to increase their involvement in routine practice. The Center for Medicare and Medicaid Services (CMS) accelerated the use of anesthetists for routine procedure by issuing a policy stipulating that deep sedation should only be administered by anesthesia specialists [191]. The first policy issued by CMS stated that propofol could only be administered by anesthesia specialists [191]. Subsequently, the policy was changed so that propofol was no longer mentioned but deep sedation remained the domain of anesthesia specialists [192]. Since the ASA considers propofol to be synonymous with deep sedation (despite the extensive evidence that BPS can be targeted to moderate sedation) [95,151–153,193–195], this impedes the expansion of EDP in the US [196]. However, EDP continues to expand in certain European countries [197], particularly Germany [198] and Switzerland [199–201].

General anesthesta

General anesthesia may be appropriate in patients with paradoxical agitation to benzodiazepines, for difficult to sedate patients, for children [202], for emergency therapeutic procedures [203], and for procedures which are anticipated to be long and complicated (e.g., double-balloon enteroscopy) [204,205]. It is also an option for patients who are obtunded, or have high aspiration risk including those with active hematemesis.

Pregnancy and lactation

Meperidine alone is preferred with small doses of midazolam if needed. Fentanyl is preferred over meperidine for breast feeding mothers [177,206]. Breast milk should be expressed and discarded for several hours before resuming breast feeding (at least 4 h after midazolam administration and for 24 h after propofol exposure).

Cardiac comorbidity

Endoscopy <1 month after myocardial infarction (MI) is associated with a 1.5% risk of major cardiopulmonary complications [207]. Patients with an MI in the previous 30 days, an Acute Physiology and Chronic Health Evaluation (APACHE) score of ≥16 is associated with a major complication rate of 21% compared with 2% in those with low APACHE scores [208]. Colonoscopy after MI is associated with a higher rate of minor cardiovascular complications [209]. Endoscopy should thus be avoided if possible in the first month after an MI.

Procedural monitoring

Careful patient monitoring is mandatory because of the potentially dangerous cardiopulmonary complications associated with sedation [210–212]. In addition to the endoscopist, another qualified individual must be assigned to monitor the patient. This person can perform brief interruptible tasks without leaving the room if the patient is moderately sedated. If deep sedation is achieved, this person must direct full attention to observing the patient and monitoring the respiratory effort [11]. Hemodynamic parameters can also be affected by the procedure itself, e.g., tachycardia and hypertension because of painful intervention like papillotomy and vasovagal reaction during colonoscopy. Periodic blood pressure monitoring, continuous pulse oximetry, and pulse measurements are mandatory. Vital signs, oxygenation, and level of consciousness should be assessed before the beginning of the procedure, after administration of sedatives, at regular intervals during the procedure, during initial recovery, and just before discharge. Depth of sedation should be continuously monitored clinically in all patients.

Oxygen tanks, oral suction devices, oral airways, reversal agents, and fully equipped code carts must be available. Cardiac defibrillators should be immediately available for patients with cardiovascular disease undergoing moderate sedation and for all patients undergoing deep sedation [213].

Oximetry

Respiratory depression is a major cause of sedation-associated morbidity. Hence pulse oximetry is an established standard protocol for procedural monitoring [13,214,215]. Early detection of hypoxemia decreases adverse events like cardiopulmonary arrest and death. The pulse oximeter is a spectrophotometric device that detects and calculates the differential absorption of light by oxygenated and reduced hemoglobin to produce an estimate of oxygen saturation. Pulse oximetry does not substitute for clinical monitoring of respiratory rate and effort [7,216,217]. There is no evidence that routine administration of
supplemental oxygen reduces the incidence of cardiopulmonary complications. Several studies have demonstrated that it delays the recognition of hypoxemia and apnea. Despite these reservations, many practitioners use supplemental oxygen routinely and in all cases. Routine use of supplemental oxygen for average risk patients should be based on local institutional policy and prevailing standards. It is recommended for elderly patients and those with significant comorbid disease (ASA IV and V) [11]. Motion may cause false alarms due to probe dislodgement. A waveform is essential to distinguish true desaturations from motion artifact. Readings may be inaccurate if shock or vasoconstriction is present.

**Capnography**

Capnography may be masked in patients who are receiving supplemental oxygen and may lead to carbon dioxide (CO₂) retention and respiratory acidosis. Capnography is continuous measurement of inhaled and exhaled CO₂ concentration, typically displayed as a numeric value and a graphical tracing. CO₂ absorbs light in the infrared region of the electromagnetic spectrum and quantification of the absorption generates a curve. Capnography provides breath-to-breath feedback and generates a respiratory rate that is measured at the airway [218]. There is evidence that capnography may detect ventilatory compromise that would otherwise not be detected by routine monitoring [219–221]. It is superior to oximetry for evaluation of ventilation [222–224] and it accurately detects apnea [225]. When apnea occurs, 60–120 s may elapse before arterial oxygen saturation begins to drop. It also improves safety during ERCP/EUS [226]. ASA standards per revision in 2011 recommend the use of capnography in moderate and deep sedation [227]. Hence capnography is being advocated as a standard of care in sedation [228], but evidence of improved outcomes is lacking and the need for routine capnography is not yet widely accepted.

**Bispectral monitoring**

Bispectral monitoring (BIS) is a processed encephalogram. It expresses brain activity as a value on a linear scale from 100 (fully awake) to 0 (no cortical activity). Values below 60 correlate with general anesthesia. BIS values, when used for benzodiazepine and/or opiate sedation, have been shown to track the sedative effect (parallel to OAA/S) and correlate with patient's recovery and endoscopist satisfaction [229–231]. It discriminates between moderate and deep sedation better than the auditory evoked potential index [232]. During propofol sedation, the BIS scores lag behind the actual sedation level during both induction and recovery, but correlate fairly well with sedation level during the maintenance phase [233,234]. Currently, BIS is not a standard monitoring tool in routine endoscopy and its use remains experimental [235–237]. There is controversial evidence regarding the use of BIS during ERCP [238,239] and it may be useful when deep sedation with propofol is used [240]. EEG monitoring can have a propofol sparing effect during lengthy procedures [241].

**Hemodynamic monitoring**

Blood pressure should be measured before and after the procedure and at 5–10 min intervals during the procedure. More frequent monitoring may be necessary (every 3–5 min) in patients with acute gastrointestinal bleeding and if hemodynamic disturbances are anticipated and in patients with underlying cardiopulmonary disease. EKG monitoring is recommended during deep sedation [110,242] and in patients with significant cardiovascular or pulmonary disease undergoing moderate sedation. It is also recommended in elderly patients, those with acute gastrointestinal bleeding and those in whom prolonged procedures are anticipated [13].

**Postprocedure monitoring**

Because of the duration of action of sedatives, patients are at risk for complications during recovery. Therefore, continuous monitoring is recommended in an appropriately staffed and equipped area until patients recover to a baseline level of consciousness and achieve pre-sedation vital signs [243]. Resuscitation equipment personnel with appropriate skills should be readily available in the recovery area. The clinician should be in proximity until the patient is hemodynamically stable and readily arousable [242]. Monitoring and predefined criteria should be developed and utilized within all endoscopy units to avoid adverse events following the administration of sedation [244].

Sedatives may cause a prolonged period of impaired cognition, so patients should be advised against driving, operating heavy machinery, and making important decisions until the following day. Discharge instructions must be written because of the amnesic effects of the medicines. Patients should be accompanied by a responsible adult at the time of discharge. Psychomotor recovery is much faster with propofol than with benzodiazepines/opioids [245]. Patients with sleep apnea who receive large doses of either opioids or benzodiazepines (but not short-acting agents such as propofol) are at risk of airway obstruction after leaving the unit if they fall asleep. They may require prolonged monitoring before discharge.

**Complications of sedation and their management**

Hemodynamic changes during endoscopy are common [246,247]. Risk factors for sedation-related complications include older age [24,248], comorbid conditions [249] (particularly pulmonary disease), higher ASA grade [23,250], emergency and therapeutic procedures [13,251–254], upper gastrointestinal bleeding [255–257], compromised airway [258], obesity [258], dementia, and anemia [251]. Obstructive sleep apnea does not clearly increase the risk of cardiopulmonary complications [259,260].
Cardiopulmonary complications constitute about 40–50% of all endoscopic complications. The overwhelming majority are pulmonary and include aspiration, oversedation, hypoventilation, vasovagal episodes, and airway obstruction [261–263]. Clinical Outcomes Research Initiative (CORI) data show that inpatient status and trainee participation are associated with a higher incidence of cardiopulmonary events [23]. The incidence of cardiopulmonary events with opioids and benzodiazepines ranges from of 2/1000 [171] to 5.4/1000 procedures [264]. However, only 0.01%–0.03% of these events are significant such as MI or life-threatening arrhythmias [216,265,266]. The incidence of sedation-related fatalities with opioids and benzodiazepines ranges from 1/3000 to 1/11 000 cases [171,264,267,268]. The risk of death associated with EDP has been <1 in 150 000 cases [53,59,60,85,95,100–102,141,269–279].

Emergency equipment including a crash cart that stores reversal agents, CPR drugs, advanced airway equipment, as well as a functional defibrillator should be immediately available to manage sedation-related complications.

Respiratory depression

Respiratory depression and airway obstruction are the primary causes of drug-induced morbidity and may manifest as hypoxemia or CO₂ retention, usually but not always together [223,252]. Hypoventilation risk is increased in patients receiving high doses of benzodiazepines and opiates [252], not only because of their sedative effect but also depression of respiratory drive due to decreased central responsiveness to CO₂.

Hypoxia

For EGD, the physical presence of the endoscope may contribute to hypoxemia [280,281], higher degrees of desaturation occur with large-diameter endoscopes [249] and in procedures performed by inexperienced endoscopists [282]. The need for bag mask ventilation during nonanesthesiologist administration of propofol is substantially more frequent during upper endoscopy than colonoscopy [82]. Looping during colonoscopy may cause transient desaturation [265]; however, it is generally mild and transient. Concomitant administration of midazolam, fentanyl, and propofol does not cause arterial desaturation [283]. Sustained desaturation to less than 90% can be dangerous in elderly people and those with ischemic heart disease [284]. It can lead to cardiac ischemia [285–287] and both atrial and ventricular arrhythmias [249,288]. In ASA I and II patients, high BMI and age >60 years correlate with hypoxemia [104]. Total drug dose is a major predictor of apnea [289]. In patients with known or suspected OSA, supine position and combination of long-acting sedatives should be avoided.

Carbon dioxide retention reflects alveolar hypoventilation and may occur during endoscopy [223,252]. Although, oxygen supplementation readily corrects hypoxemia, it does not correct underlying hypoventilation. Severe hypoventilation may go undetected by pulse oximetry once supplemental oxygen is applied [290,291].

Patients with respiratory depression and hypoxia should be given supplemental oxygen by increasing the amount of oxygen delivered or changing the delivery route from nasal cannula to face mask. If the patient is snoring and breathing is labored, head tilt and jaw lift will usually open the airway. The oropharynx should be suctioned and an oral airway inserted if necessary. If these maneuvers do not help or if the patient is apneic or hypoventilating, breathing should be assisted with a bag valve mask device.

Cardiac and hemodynamic complications

Myocardial ischemia and infarction can occur during endoscopy, particularly in patients with cardiac disease [286,287]. Vasovagal reactions usually manifest as diaphoresis and bradycardia and frequently are a result of overinsufflation and pain during colonoscopy. Atropine is effective in treating bradycardia. Significant increases or decreases in blood pressure occur commonly during endoscopy [265,292,293]. Hypotension should respond to fluid administration if the underlying cause is hypovolemia. Most hypotension during endoscopy is well tolerated, but prolonged or severe hypotension should lead to consideration of reversal agents and vasopressor agents such as ephedrine or dopamine. Hypertension may be treated with giving more sedatives or analgesics if the patient is underdosed or by decreasing pain (e.g., reducing endoscope loops or by suctioning air).

Aspiration

Massive pulmonary aspiration should be the most feared complication of endoscopy, since it can be fatal. Aspiration may result in pneumonia and adult respiratory distress syndrome as well as cardiopulmonary arrest and carries a high risk for mortality [171]. The risk is increased with obtundation, dementia, excessive esophageal or gastric contents, and in those with active upper gastrointestinal bleeding. Propylactic endotracheal intubation is indicated with active hematemesis, especially from variceal bleeding [294] or those who are unstable, obtunded, or uncooperative. When excessive gastric contents are encountered, excessive insufflation should be avoided and the procedure should be terminated if the material cannot be readily cleared by suction. Elderly patients are at greater risk for aspiration as a result of an increase in the sensory stimulus threshold required for reflexive glottic closure. It is advisable to avoid topical inhibition of the gag reflex in high-risk patients. A catheter for oropharyngeal suction should be by the bedside at all times. A recent report found that aspiration was the most common complication after colonoscopy [295]. The use of anesthesia specialists, which is a surrogate for deep sedation and propofol use, has also been associated with an increased risk of aspiration pneumonia [16].

Cardiac arrhythmias

The risk of arrhythmias increases with advanced age, underlying cardiovascular disease, arterial desaturation, and, in the case of
EGDs, the diameter of the endoscope used [249]. The most common arrhythmia is sinus tachycardia as a result of hypoxemia or painful stimuli.

**Procedure termination**

Procedure termination due to inadequate or excessive sedation may result in morbidity due to delayed therapy, extended hospitalization, repeat or alternative procedures such as surgery, and increased cost. In a prospective multicenter study, 4.1% of all ERCPs had to be terminated prematurely due to difficulty with sedation [223].

**Training for use of sedatives**

Several guidelines have been published regarding training for personnel-administering sedatives [11,13,54,251,261,296–299] (Box 131.1). Properly trained nursing personnel are essential and should have a good understanding of the pharmacology of the sedation agents and ability to recognize complications and initiate appropriate interventions. They must also understand their institutional policies and procedures pertaining to procedural sedation [300]. Training should include didactic as well as practical teaching and competency should be formally assessed and documented. Simulation technology has been shown to enhance training [301]. Proper training is mandatory for the safe practice of nonanesthesiologist-administered propofol sedation. Successful training programs for nonanesthesiologist administered propofol sedation incorporate didactic training [302], testing, and typically 2 weeks of observation and supervised administration [100,242]. Airway skill competency (identification and management of inadequate ventilation) is a major part of training. For moderate sedation, the practitioner should be capable of placing an oral and/or nasal airway as well as performing bag mask ventilation. When deep sedation is targeted, he/she should be skilled in the use of extraglottic devices like the LMA. The practitioner should also be able to provide basic life support, with immediate availability of a provider with advanced life support skills (within 1–5 min) for moderate sedation and within the procedure room for deep sedation [11,297–299,303].

References are available at www.yamadagastro.com/textbook

**Further reading**


Vargo J.J. Propofol may be safely administered by trained nonanesthesiologists. Pro: propofol demystified: it is time to change the sedation paradigm. Am J Gastroenterol 2004;99:1207; discussion 11.

Upper gastrointestinal (GI) endoscopy is the method of choice for examining the upper GI system. It not only achieves the diagnosis of many upper GI diseases, but also gives opportunity for therapeutic interventions with minimally invasive options. This chapter reviews the background and techniques of diagnostic upper endoscopy, including standard and advanced imaging methods. Therapies applied during upper GI endoscopy will be examined, but will not be described here in detail. Finally, safety of upper GI endoscopy will be reviewed to help the reader understand the risks of the procedures and compare with alternative diagnostic or therapeutic approaches.

**History and background**

Rudolf Schindler, the father of modern endoscopy, pioneered the use of gastroscopy through the use and development of a semirigid gastroscope [1]. The first endoscopic device was introduced in 1806 by Philip Bozzini, who developed a “Lichtleiter” (light conductor) “for the examinations of the canals and cavities of the human body.” However, the Vienna Medical Society disapproved of such a device, and the development stalled. An endoscope was apparently first introduced into a human in 1853.

The use of an electric light was a major step in the improvement of endoscopy; these lights were at first external. Later, smaller bulbs became available, making internal light possible. Jacobeus has been credited with early endoscopic explorations of the abdomen and the thorax with laparoscopy (1912) and thoracoscopy (1910). One of the major developmental milestones for endoscopy was the invention of a superior glass fiber, which Basil Hirschowitz applied to the development of flexible endoscopes. The technology not only resulted in the first useful medical endoscope, but revolutionized endoscopic uses and led to practical fiberoptics.

**Videoendoscopes**

Videoendoscopy, introduced in the mid-1980s, has dramatically improved and expanded the field of endoscopy. The endoscopic image is generated electronically, using a charge-coupled device (CCD) located in the tip of the endoscope [2]. Endoscope processors manage the images and display them on video monitors. Prior to videoendoscopy, fiberoptics generated the images on small hand-held eye-pieces. The first videoendoscopes used black and white CCDs that required a color wheel. Green, red, or blue light was sequentially sent down the illumination bundle of the endoscope and activated the CCD at the tip [3]. A color image was reconstructed using the three sets of images generated by the colored lights. The videoprocessor displayed a full-color image of the GI tract lining, although with apparent image flickering during rapid movement.

Most current videoendoscopes use a color CCD that obtains the image in color on the tip of the endoscope. These devices provide 30,000–850,000 pixels of resolution. By incorporating high-pixel-density charged-coupled devices, high-resolution endoscopes provide images that display vivid mucosal detail.
High-resolution endoscopes are capable of discriminating objects 10–70 μm in diameter; in comparison, the naked eye is capable of discriminating objects 125–165 μm in diameter. The videendoscope has controls for introducing air, water, and suction as well as knobs for moving the endoscope tip up, down, and to the right and left. The right hand is used to advance the instrument and to manipulate the tip control knob. Torque of the endoscope is accomplished by rotating the instrument control handle with the right hand, which results in rotation of the entire shaft and tip of the endoscope. The instrument channel is shared for the passage of accessories and suction. The instrument channel is variable in diameter and some instruments have two instrument channels.

There are also buttons on the videendoscope control handle to activate digital video recording, image capture, and recording of video images. Videendoscopy has greatly expanded the viewing capabilities of procedures. Multiple monitors in the procedure room provide bright vivid images that enable many personnel to participate in procedures. The live video images can also be distributed remotely to sites within an institution, or beyond, for teaching, research, and demonstration [4].

Endoscopy training has improved dramatically with the use of videendoscopy. Documentation of procedures is provided by the saving, retrieval, and reviewing of stored digital images [5]. Stored images can be recalled from a central image storage system and sent to any location in the endoscopy service. The storage drives can be used for image processing and management, as well as enabling reliable storage of endoscopic images and information on PACS (picture archiving and communication system) [6]. Hardware and software are now available for the capture, editing, and storage of video clips.

**Technical considerations**

Upper GI endoscopy is a highly technical procedure that requires a close cooperative arrangement between physicians and nurses. The formal establishment of an endoscopy unit in an institution is essential to provide high-quality exams in a safe environment [7]. With only a few exceptions, upper GI endoscopy should be performed in a hospital or a medical care facility that can reliably provide highly trained personnel and specialized equipment. In addition to an array of endoscopes and processors, the procedure unit should be equipped with the appropriate accessories, suitably organized. In addition to procedure rooms, it is critical to have a travel cart that will enable endoscopists to carry out endoscopic procedures at sites remote from an endoscopy unit as necessary.

Well-maintained, controlled-access storage is essential for the endoscopic accessories. There must be a suitable area for endoscope disinfection and preparation of accessories for sterilization. It is also critical to have preparation and recovery areas for the evaluation and monitoring of patients before and after endoscopy. Electrocautery devices are necessary for the performance of many endoscopic procedures. As these devices are frequently used, it is essential that they be readily available during procedures and properly maintained by qualified personnel.

**Before starting**

The need for diagnostic and interventional endoscopy should always be carefully evaluated and contraindications should be excluded (Box 132.1). Attention must be given to all quality indicators (Box 132.2). Before endoscopy is performed, a thorough history should be obtained from the patient. The history should include previous surgery, endoscopic procedures, and anesthesia history. A list of the patient’s medications should be generated. A review of active medical problems will help the endoscopist assign an ASA (anesthesia risk) score and decide whether the patient will safely tolerate conscious sedation.

Most patients begin fasting after midnight the evening before the procedure. The patient should have no liquids for 4 h before endoscopy and no solids for at least 6–8 h beforehand. Patients with gastric outlet obstruction may be kept on a clear liquid diet for 24–48 h, and lavage of the stomach with a large-bore tube may be necessary to remove retained stomach contents. Meaningful informed consent is an ethical imperative and should be obtained by a physician prior to every procedure. The physician should provide a realistic assessment of the risk of the procedure and the consequences of the complications as well as alternatives. A discussion of risks should include a statement of the risks of conscious sedation. The patient or their advocate should have the opportunity to have questions answered. Topical anesthesia to the pharynx is often provided in order to minimize the gag reflex during endoscopy. If sedation is provided by anesthesia, separate personnel will be needed for a timely procedure and consent (see Chapter 131).

**Introducing the endoscope**

Most small-diameter videoendoscopes can be easily passed under direct vision through the upper esophageal sphincter. The tip of the instrument is advanced in the midline into the direction of the closed cricopharyngeal sphincter. The patient is asked to swallow and, under direct vision, the tip of the instrument is passed from the epiglottis and larynx into the proximal esophagus. In the past, endoscopes were passed blindly, aided by the swallowing action. The direct vision technique allows an inspection of the pharynx, epiglottis, and vocal cords prior to insertion. Furthermore, direct imaging may decrease the risk of the inadvertent passage of the endoscope into a proximal esophageal diverticulum. Small-diameter videoendoscopes can also be passed transnasally and may provide the opportunity to perform unsedated endoscopy [8].

**The normal upper gastrointestinal endoscopic examination**

The endoscopic examination of the upper GI tract begins with an examination of the upper esophagus as the endoscope is
Box 132.1 Indications and contraindications for esophagogastroduodenoscopy.

**EGD is generally indicated for evaluating:**

- Upper abdominal symptoms that persist despite an appropriate trial of therapy
- Upper abdominal symptoms associated with other symptoms or signs suggesting serious organic disease (e.g., anorexia and weight loss) or in patients >45 years old
- Dysphagia or odynophagia
- Esophageal reflux symptoms that are persistent or recurrent despite appropriate therapy
- Persistent vomiting of unknown cause
- Other diseases in which the presence of upper GI pathological conditions might modify other planned management (examples include patients who have a history of ulcer or GI bleeding who are scheduled for organ transplantation, long-term anticoagulation, or long-term nonsteroidal antiinflammatory drug therapy for arthritis, and those with cancer of the head and neck)
- Familial adenomatous polyposis syndromes
- For confirmation and specific histological diagnosis of radiologically demonstrated lesions
  - suspected neoplastic lesion
  - gastric or esophageal ulcer
  - upper tract stricture or obstruction
- GI bleeding
  - in patients with active or recent bleeding
  - for presumed chronic blood loss and for iron deficiency anemia when the clinical situation suggests an upper GI source or when colonoscopy results are negative
- When sampling of tissue or fluid is indicated
- In patients with suspected portal hypertension to document or treat esophageal varices
- To assess acute injury after caustic ingestion
- Treatment of bleeding lesions, such as ulcers, tumors, vascular abnormalities (e.g., electrocoagulation, heater probe, laser photocoagulation, or injection therapy)
- Banding or sclerosis of varices
- Removal of foreign bodies
- Removal of selected polypoid lesions
- Placement of feeding or drainage tubes (peroral, PEG, percutaneous endoscopic gastrostomy)
- Dilatation of stenotic lesions (e.g., with transendoscopic balloon dilators or dilation systems using guidewires)
- Management of achalasia (e.g., botulinum toxin, balloon dilatation)
- Palliative treatment of stenosing neoplasms (e.g., laser, multipolar electrocoagulation, stent placement)

**EGD is generally not indicated for evaluating:**

- Symptoms that are considered functional in origin (there are exceptions in which an endoscopic examination may be done once to rule out organic disease, especially if symptoms are unresponsive to therapy)
- Metastatic adenocarcinoma of unknown primary site when the results will not alter management
- Radiographic findings of:
  - asymptomatic or uncomplicated sliding hiatal hernia
  - uncomplicated duodenal ulcer that has responded to therapy
  - deformed duodenal bulb when symptoms are absent or respond inadequately to ulcer therapy

**Sequential or periodic EGD may be indicated for:**

- Surveillance for malignancy in patients with premalignant conditions (i.e., Barrett esophagus)

**Sequential or periodic EGD is generally not indicated for:**

- Surveillance for malignancy in patients with gastric atrophy, pernicious anemia, or prior gastric operations
- Surveillance of healed benign disease such as esophagitis or gastric or duodenal ulcer
- Surveillance during repeated dilations of benign strictures unless there is a change in status

EGD, esophagogastroduodenoscopy; GI, gastrointestinal; PEG, percutaneous endoscopic gastrostomy.

passed through the upper esophageal sphincter. Because the proximal esophagus is best examined on withdrawal, the endoscope is usually passed to the midesophagus, where the formal examination begins. At 40 cm lies the ora serrata, which is the junction between the pearly stratified squamous mucosa and the gastric columnar epithelium. The esophageal folds can be seen to change with air distention. It is possible to recognize extrinsic pressure on the esophagus from adjacent structures, such as the aorta and the left main stem bronchus. The impingement by the diaphragm is apparent in the upper stomach and defines the presence of a hiatal hernia.

With slight angulation to the left and anteriorly, the endoscope is passed into the stomach. Air is insufflated to distend the stomach. It is important to notice the presence of food, bile, or blood in the gastric lumen. Gastric fluid in the cardia should be aspirated to improve endoscopic inspection and to reduce the likelihood of regurgitation and aspiration during the procedure. The gastric mucosa is inspected, and observations are made about the color, texture, and size of folds. The gastric folds begin in the upper portion of the stomach and extend down to the entrance into the antrum. With gentle distention of the stomach, these folds often flatten. The size, number, and depth of mucosal defects are noted. Indentation of the lumen by mural lesions, or extrinsic compression by extrinsic organs, can be observed.

A complete examination of the stomach requires a retroflexed view of the stomach. The maneuver takes place in the antrum with a 180° flexion of the endoscope in an inflated stomach. The gastroesophageal (GE) junction, cardia, and fundus can be examined by pulling the endoscope. Retroflexion also permits inspection of a hiatal hernia. Lesions in a hiatal hernia and the GE junction are best viewed in a retroflex position. The entry into the antrum of the stomach is marked by the incisura, a fold on the lesser curve of the stomach. The antrum can be easily
Box 132.2 Summary of proposed quality indicators for esophagogastroduodenoscopy

1. Accepted indication(s) is provided before performance of EGD.
2. Informed consent is obtained, including specific discussion of risks associated with EGD.
3. Prophylactic antibiotics are given in patients with cirrhosis with acute upper GI bleeding who undergo EGD.
4. Prophylactic antibiotics are given before placement of a PEG.
5. Complete examination of the esophagus stomach and duodenum, including retroflexion in the stomach.
6. Biopsy specimens are taken of gastric ulcers.
7. Barrett esophagus is measured when present, with the location of the gastroesophageal junction and squamocolumnar junction in centimeters from the incision being documented.
8. Biopsy specimens are obtained in all cases of suspected Barrett esophagus.
9. Type of upper GI bleeding lesion is described and location is documented. For peptic ulcers, at least one of the following stigmata is noted: active bleeding, nonbleeding, nonbleeding visible vessels (pigmented protuberance), adherent clot, flat spot, cleaned based.
10. Unless contraindicated, endoscopic treatment is given to ulcers with active bleeding or with nonbleeding visible vessels.
11. In cases of attempted hemostasis of upper GI bleeding lesions, whether hemostasis has been achieved is clearly documented.
12. When epinephrine injection is used to treat nonvariceal upper GI bleeding or nonbleeding visible vessels, a second treatment modality is used (e.g., coagulation or clipping).
13. Variceal ligation is used for endoscopic treatment of esophageal varices.
14. Written instructions, which include particular signs and symptoms to watch for after EGD, are provided to the patient on discharge.
15. In patients undergoing dilation for peptic esophageal strictures, PPI therapy is recommended.
16. Patients diagnosed with gastric or duodenal ulcers are instructed to take PPI medication or an H2 antagonist.
17. Patients diagnosed with gastric or duodenal ulcers have documented plans to test for the presence of H. pylori infection.
18. Rebleeding rates after endoscopic hemostasis are measured.

EGD, esophagogastroduodenoscopy; GI, gastrointestinal; PEG, percutaneous endoscopic gastrostomy; PPI, proton pump inhibitor.

Identified by the lack of folds and a conical shape. The antrum is the site of the initiation of peristalsis. Vigorous contractions begin in the proximal antrum and progress through the antrum at a frequency of approximately three per minute. Antral peristalsis terminates in the pylorus. The viewing of peristalsis enables the endoscopist to examine the antral mucosa in detail, particularly for infiltrating lesions. Peristalsis may be weak or absent in a heavily sedated patient; in any case, quantification of peristalsis is not possible.

Once the examination of the body and antrum has been completed, the endoscope is advanced to the pylorus. It is sometimes necessary to create a loop along the greater curvature before the tip of the endoscope can progress through the pylorus. With a small-caliber endoscope, it is possible to inspect the duodenal bulb in detail. The endoscope is passed beyond the apex of the bulb into the second descending portion of the duodenum. Passage from the tip of the bulb into the descending duodenum is readily performed with a turn of the endoscope to the right. The duodenal bulb is usually free of folds; duodenal Kerckring folds begin in the descending portion of the duodenum. A tangential view of the ampulla is usually appreciated.

After completion of the examination in the duodenum, the endoscope is withdrawn, during which time the endoscopist can examine the mucosa of the duodenum, stomach, and esophagus. If there is any suspicion of a lesion in the stomach, it is important to inflate the stomach, flattening the folds and allowing a detailed examination of the gastric mucosa for small ulcers, angioectasia, and early gastric cancer. After completion of the examination of the stomach, air is withdrawn. During the withdrawal of the endoscope through the esophagus, it is important to examine the upper esophagus, the upper esophageal sphincter (UES), and the larynx because these may not have been examined in detail during the initial introduction [9].

In transnasal esophagogastroduodenoscopy (EGD), a small-caliber endoscope is passed via the most patent side of the nasal cavity after local application of lidocaine gel and a nasal decongestant [10]. After inspection of the pharynx, the scope is introduced into the esophagus after traversing the UES under direct vision. Following evaluation of the esophagus, the stomach and duodenum are entered and evaluated.

The use of endoscopic accessories

The use of endoscopic accessories has greatly expanded the number of procedures that can be performed. Accessory devices are used to obtain tissue, inject agents, direct cautery, deliver diagnostic and therapeutic light, and provide additional imaging probes.

Biopsy forceps

Biopsy forceps are used to retrieve specimens of mucosa for histology or culture (Table 132.1). The size of the forceps, as permitted by the size of the instrument channel, will determine the size of the specimen obtained. The standard forceps used in a 2.8-mm biopsy channel have a span of 8 mm and can retrieve a full-thickness biopsy of the mucosa. Large cup forceps provide larger specimens with less crush artifact. Forceps are available for single or multiple biopsies. A small central knife, an optional feature, is used to hold multiple specimens. “Hot forceps” (with cautery) should not be routinely used as they provide inferior histological specimens and higher complication rates [11]. Reusable and disposable forceps are available and adequacies of samples are generally excellent for both [12]. A 1.8-mm diameter biopsy forceps are available for the 2-mm working channel of transnasal endoscopes. Biopsy specimens, obtained by such forceps, are suitable for histological examination [13].

Biopsy specimens are retrieved with tweezers or by flushing, but care should be taken to avoid fragmentation of the specimen. It is not necessary to orient mucosal specimens; this is
usually performed in the pathology laboratory. Large biopsy forceps should be used to obtain mucosal specimens for the detection of malignancy, in order to maximize the quality and quantity of tissue. The risk of bleeding from biopsies is negligible even in patients using antithrombotic agents [14]. Most endoscopic forceps obtain mucosa and, occasionally, a small amount of submucosa. To sample more deeply into a lesion, such as a submucosal tumor, needle cytology may be applied, or repetitive sampling with large biopsy forceps should be made in the same area (“well biopsy”).

The acquisition of diagnostic material from the esophagus is more difficult than from the stomach because of the orientation of the esophagus. Angled forceps have been suggested to improve the biopsy of the esophagus, but their superiority to standard forceps are not clear [15,16]. As an alternative to pinch biopsies, a snare may be used to obtain a large sample of tissue from abnormal mucosa (Table 132.1) [17]. The snare is placed over the fold or polypoid area, tightened, and gently pulled away from the wall. Prior injection of saline or diluted epinephrine in the submucosa may lift the mucosa to facilitate snaring and to prevent deep mural damage. As the snare is pulled through the lesion, the electrosurgical current aids in the cutting through the tissue and prevents bleeding. The snare biopsy technique can be extended by lifting the targeted mucosa prior to snaring similar to grasp-and-snare endoscopic mucosal resection technique [18]. In this technique, a two-channel endoscope is used with the snare in one channel and lifting forceps in the second channel. The snare is opened and the forceps are directed through the snare. The tissue is grasped by the forceps and pulled up into the snare. As the snare is tightened, the tissue can be excised with electrocautery. This technique may result in unexpectedly large, deep biopsy specimens and is not recommended for the inexperienced endoscopist (see Chapter 140).

Cytology brushes
Retrieval of specimens for cytological evaluation is easier than using biopsy forceps for tissue acquisition (Table 132.1) [19]. Brushing of mucosal lesions is usually performed for the diagnosis of infectious processes in the upper GI tract. However, cytology brushing is also important in lesions that are inaccessible for biopsy, such as tight strictures in the esophagus. Cytology brushes are often protected by a plastic sheath, which aids in the retrieval of diagnostic material. After removal of the cytology brush from the endoscope biopsy channel, the specimen is placed on a glass slide and into preservative solution. For the diagnosis of *Candida* infections, a simple smear can be submitted for fungal staining. Cytological material from the upper GI tract can also be retrieved with the use of an aspiration needle. Aspiration cytology is usually performed for cystic lesions, submucosal tumors, or infiltrating malignancy in the gastric wall. A small-gauge needle is used to obtain small amounts of tissue or fluid from the lesion using suction. Needle aspiration cytology is usually performed with endoscopic ultrasonography (EUS) guidance because of the ability of EUS to direct the needle into areas rich in cytological material [20].

Measuring mucosal blood flow
Endoscopic imaging of the upper GI mucosa is not a reliable method for the measurement of mucosal blood flow or the detection of abnormal blood vessels. The measurement of blood flow may be used in accessing focal lesions or for a mucosal process. Doppler ultrasound probes can detect the flow in abnormal blood vessels below the mucosa, such as varices, or in an artery in the base of an ulcer [21]. Doppler devices can be used before and after endoscopic hemostatic therapy, such as injection or thermal therapy for an artery in the base of an ulcer [21,22]. It is also possible to use a laser Doppler device to measure mucosal red blood cell velocity, a parameter thought
to correlate with mucosal blood flow [23]. The assessment of mucosal blood flow may be predictive of ulcer healing. Mucosal blood flow is normally increased in the mucosa adjacent to ulcers and attenuated periulcer blood flow may predict healing of a benign gastric ulcer [24]. Paradoxically, it appears that blood flow is decreased in areas of portal hypertensive gastropathy [25].

**Advanced imaging techniques**

**Endoscopic ultrasonography**
Upper GI endoscopy provides an opportunity to guide the passage of imaging instruments in close proximity to lesions or areas of interest. Coupling of ultrason with endoscopy (endoscopic ultrasound or EUS) was a major advance in endoscopy. Endoscopic ultrasound is the most commonly performed advanced imaging procedure [26]. There are two approaches to combining these technologies. In the first approach, the endoscope has an ultrasound device built into the tip of the endoscope. The ultrasound transducer can be oriented radially, and provide cross-sectional images of the GI tract, or in a linear orientation. In the linear orientation, fine-needle aspiration can be directed with ultrasound imaging of the GI tract and for the major organs adjacent to the esophagus, stomach, and duodenum.

Alternatively, small ultrasound probes can be passed through the instrument channel. Probe endosonography provides high-resolution radial images of wall lesions. Using water as a medium, the high-frequency probe offers a detailed examination of mucosal and subepithelial lesions and their relationship to the wall structure of the GI tract. Probe endosonography may provide staging of early malignancy as well as differentiate between cystic, solid, and lipomatous lesions (Table 132.2). Disadvantages of probe endosonography include the need for water immersion and the inherent inability to provide imaging of structures adjacent to the wall.

EUS imaging has dramatically improved tumor staging, acquisition of tissue from the pancreas, and ability to provide injection therapies [27]. See Chapter 146 for more on EUS.

**Chromoendoscopy**
Chromoendoscopy is an in vivo technique in which the mucosa or a lesion is washed with an agent designed to enhance mucosal imaging [28]. Chromoendoscopy agents include those that enhance the mucosal detail (contrast chromoendoscopy) or in which the agent is absorbed by certain cell types (vital staining) (Table 132.3). The dye agent is usually sprayed against the mucosa using a specially designed catheter passed down the biopsy channel of the endoscope. Various dyes are used for particular clinical settings and provide specific information regarding mucosal abnormalities. Before using any of these dyes, it is necessary to wash away adherent mucus [29]. This is often accomplished using a solution of dimethyl polysiloxane, sodium bicarbonate, and pronase. A 10% solution of N-acetylcysteine can also be used before spraying the dye.

“Contrast agent” dyes are used to accentuate minute alterations in mucosal architecture by accumulating in normal or abnormal mucosal structures and accentuating small lesions. This is best achieved using indigo carmine, which pools between mucosal grooves and provides a three-dimensional image of the mucosa (Table 132.3). Similar effects have been reported with

**Table 132.2** Radiological and endoscopic imaging used to stage gastrointestinal malignancies.

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Device used</th>
<th>Agent used</th>
<th>Detection of malignant tissue</th>
<th>Availability</th>
<th>Clinical applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUS</td>
<td>Dedicated echoendoscope; high frequency ultrasound probes can be used through the instrument channel; fine needle aspiration device can be used with linear EUS</td>
<td>Water is used as a coupling agent. Levovist or Definity are intravenous ultrasound contrast agents rarely used in EUS</td>
<td>The vast majority of malignancies are relatively less echogenic (hypoechoic) compared to normal tissue</td>
<td>Widely available</td>
<td>Frequently used to stage esophageal, gastric, pancreatic, and rectal cancer</td>
</tr>
<tr>
<td>OCT</td>
<td>Laser infrared light source, semiconductor optical amplifier, catheter probe</td>
<td>None</td>
<td>Changes architecture of tissue (e.g., loss of goblet cells) is used as a sign of malignancy</td>
<td>Not widely available</td>
<td>Staging of superficial malignancies</td>
</tr>
<tr>
<td>CT</td>
<td>An X-ray beam is emitted in a fan shape as the rotating frame spins the X-ray tube and detector around the patient. Multidetector CT with computer generated images</td>
<td>Intravenous and oral iodine-based contrast agents</td>
<td>Using ionized radiation, the vast majority of malignant tissue have a different attenuation, accentuated by the use of intravenous contrast</td>
<td>Helical CT is widely available MDCT will become widely distributed</td>
<td>Broad applications in staging of advanced GI malignancies</td>
</tr>
</tbody>
</table>

CT, computed tomography; EUS, endoscopic ultrasound; GI, gastrointestinal; OCT, optical coherence tomography; MDCT, multidetector computed tomography.
Lack staining. The double staining with Lugol and methylene blue significantly improved the detection and diagnosis of early esophageal squamous cell carcinoma and precancerous lesions in a study [34]. Congo red is a reactive stain that maps the acid-producing parietal cell mucosa, staining from red to dark blue in the presence of acid secretion. Lesions associated with hereditary diffuse gastric cancer can be detected by Congo red and methylene blue staining [35].

Magnification endoscopy

Magnification endoscopy provides higher-resolution images of the epithelium in concert with chromoendoscopy (Table 132.3). Absorptive staining takes place over a few minutes after application of the dye to the tissue. Once staining is achieved, the excess solution is washed away. Lugol solution stains intracellular glycogen in nonkeratinized squamous epithelium and therefore normally stains the entire esophageal mucosa (Table 132.3). Early esophageal cancer and high-grade squamous dysplasia do not stain with Lugol solution [32]. Lugol staining is useful in looking for plaques overlying varices, evaluating high-risk patients, or to precisely map a neoplasm of the esophagus. Methylene blue dye is used to enhance the detection of dysplastic tissue arising from Barrett epithelium as the dye is not absorbed by the dysplastic tissue [33]. Biopsies are directed to areas of Barrett mucosa that lack staining. The double staining with Lugol and methylene blue significantly improved the detection and diagnosis of early esophageal squamous cell carcinoma and precancerous lesions in a study [34]. Congo red is a reactive stain that maps the acid-producing parietal cell mucosa, staining from red to dark blue in the presence of acid secretion. Lesions associated with hereditary diffuse gastric cancer can be detected by Congo red and methylene blue staining [35].

### Table 132.3 Summary of endoscopic image enhancement techniques used for detection of gastrointestinal malignancy.

<table>
<thead>
<tr>
<th>Endoscopic technique</th>
<th>Agent or device used</th>
<th>Mechanism</th>
<th>Clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-resolution endoscopy</td>
<td>High-resolution endoscope with high pixel density (e.g., 850,000)</td>
<td>Increased resolution by the coupled chip device (CCD) on the endoscope</td>
<td>Endoscopic identification of surface details such as crypts, glands, and pit pattern</td>
</tr>
<tr>
<td>Magnification endoscopy</td>
<td>Magnification endoscope with manual (lens change) or electronic control</td>
<td>Magnification of the endoscopic image</td>
<td>Endoscopic identification of surface details enhanced with dyes</td>
</tr>
<tr>
<td>Combined high-resolution and magnification endoscope</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>Chromoendoscopy</td>
<td>Topical agents often used in conjunction with magnification endoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lugol solution</td>
<td>Contrast dye, staining glycogen in squamous epithelium</td>
<td>Detection of early squamous cell carcinoma of the esophagus</td>
<td></td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Absorptive dye, staining absorptive epithelium (small intestine and colon) including Barrett</td>
<td>Detection of Barrett esophagus and early malignancy arising from Barrett (lack of staining)</td>
<td></td>
</tr>
<tr>
<td>Indigo carmine</td>
<td>Contrast dye, outlining mucosal surface</td>
<td>Detection and mapping of gastroduodenal malignancies</td>
<td></td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Reversible intracellular protein denaturation</td>
<td>Detection of Barrett epithelium</td>
<td></td>
</tr>
<tr>
<td>Narrow band imaging</td>
<td>Electronic light source with narrow-band filters</td>
<td>Enhancement of surface capillary patterns, pits and villi</td>
<td>Detection and mapping of early gastric and esophageal cancer</td>
</tr>
<tr>
<td>Fluorescence endoscopy</td>
<td>Image-processing module that provides real-time fluorescence images 5-aminolevulinic acid (topical or systemic), hexaminolevulinate (HAL)</td>
<td>Sensitzers accumulate selectively in malignant lesions and induce fluorescence upon illumination with light of the appropriate wavelength</td>
<td>Detection of early gastric and colonic adenomas and malignancies</td>
</tr>
<tr>
<td>Confocal microscopy</td>
<td>Dedicated combined endoscope and microscope image processing unit Acriflavine hydrochloride or fluorescein sodium</td>
<td>Fluorescent agents are absorbed by tissue and provide cellular and histological details</td>
<td>Broad applications in detection of mucosal neoplasia</td>
</tr>
</tbody>
</table>

CCD, coupled chip device; HAL, hexaminolevulinate.
accurately diagnose sprue (Table 132.3) [36]. Similar techniques have been applied to the diagnosis of Barrett esophagus. The finding of villi arising from the esophageal epithelium is diagnostic of intestinal metaplasia. Furthermore, esophageal papillary squamous cell islands surrounded by glandular Barrett epithelium have been visualized by high-power magnifying endoscope in a study [37]. Changes in the vill morphology have enabled endoscopists to diagnose early gastric cancer [38].

Narrow band imaging
Narrow band imaging (NBI) involves the use of interference filters to illuminate a target in narrowed red, green, and blue (R/G/B) bands of the spectrum (Table 132.3). The imaging modality is built into commercial endoscopy processors and no catheters or probes are necessary. NBI provides imaging of the surface of epithelium, particularly of the surface vascular pattern. Many early malignancies have surface pattern changes in vascularity, such as the corkscrew pattern seen in early gastric cancer [39]. When NBI is used in conjunction with magnification endoscopy, the diagnosis of intestinal metaplasia of the esophagus can be secured with a high degree of accuracy [40]. In trials, NBI has produced results similar to high-resolution chromoendoscopy [41]. Fuji Intelligent Color Enhancement (FICE) (Fujifilm Corporation) technique and i-scan (Pentax Medical) are other methods of virtual chromoendoscopy developed by different manufacturers. Both methods use a postimage acquisition software to reconstruct endoscopic images for enhanced mucosal surface contrast [42,43]. The superiority of these systems to standard endoscopes for detection of mucosal abnormalities is under investigation.

 Optical biopsy
Advances in fiberoptics, light sources, and detectors have led to the development of several novel methods for tissue evaluation in situ [44]. The term “optical biopsy” refers to advanced mucosal visualization techniques that enable the endoscopist to make a real-time endoscopic optical diagnosis, which has previously been possible only by using histological or cytological analysis. Optical coherence tomography, confocal microendoscopy, fluorescence endoscopy, and molecular imaging techniques are still under investigation and development for tissue evaluation in situ (Table 132.2). Endoscopic imaging can be expanded through the use of spectroscopy probes that can be placed through the instrument channel to image the mucosa. It is hoped that these techniques will permit in situ detection of dysplasia arising in Barrett esophagus [45]. A newly developed system, called endoscopic polarized scanning spectroscopy, performs rapid optical scanning and multispectral imaging of the entire esophageal surface and appears to provide real-time diagnosis of dysplasia with high sensitivity and specificity [46].

Optical coherence tomography
Optical coherence tomography (OCT) is an infrared-based imaging technique that provides high-resolution imaging of mucosal details (Table 132.2). Although OCT is used clinically in cardiology and ophthalmology, it is not a standard imaging technique in endoscopy. OCT is ideally equipped to differentiate between the basic epithelial structures, such as squamous and columnar epithelia [47]. Extensive testing has demonstrated the ability to diagnose Barrett esophagus [48]. Furthermore, OCT may be able to detect early changes of dysplasia and guide mucosal biopsies [49]. It might also be useful for the preoperative staging of superficial esophageal squamous cell carcinomas with a high degree of accuracy [50]. Advanced OCT systems, such as confocal laser endomicroscopy and optical frequency domain imaging, have potential to accurately detect advanced histology [47,51,52].

Endoscopic confocal microscopy
Endoscopic confocal microscopy provides the highest resolution images of the GI tract of any imaging modality (Table 132.3) [53]. There are two types of instruments available for clinical use, a dedicated endoscope and a probe that can be placed through the channel of an endoscope. Confocal endomicroscopy uses blue laser light, often in conjunction with an intravenous and a topical fluorescent agent. The images obtained from this technique provide near real-time cellular details, including individual epithelial cells to a depth of 1–2 mm. The crypts of the colonic mucosa, the villi of the terminal ileum and duodenum, the gastric pits of the stomach, and the squamous epithelium of the distal esophagus can be clearly visualized. The technique has been demonstrated to improve the detection of dysplasia arising from the colonic mucosa in patients with inflammatory bowel disease [54]. The high-resolution imaging has demonstrated Helicobacter pylori organisms in the gastric mucosa [55].

Therapeutic upper endoscopy
Removal of foreign bodies
In removing a foreign body, the endoscopist should carefully evaluate the patient for any possible evidence of airway obstruction or perforation prior to the endoscopic procedure. During removal of a foreign body, an overtube provides a degree of protection of the airway but the only way to ensure complete airway patency is to first place a cuffed endotracheal tube prior to extracting the foreign object. The mucosa can be protected, especially in the removal of sharp objects, by using an overtube to protect the intestinal lining during removal of a sharp foreign body [56]. The endoscope can be withdrawn into the overtube while grasping the foreign body, which protects the mucosa from injury by the sharp foreign body (Figure 132.1). The overtube is also useful if the endoscope must be passed several times for removal of a foreign body, such as a piece of meat. An alternative to a plastic overtube is a simple latex protector hood fastened to the tip of the endoscope.
It is possible to remove foreign bodies with rigid or flexible endoscopes. Foreign bodies in the area of the hypopharynx and very proximal esophagus are often best removed with an open laryngoscope and grasping forceps. For other foreign bodies, flexible endoscopes are used, preferably with a large instrumentation channel (2.8–3.5 mm). The larger channel allows a variety of instruments to be used to grasp and secure the foreign body. These include baskets of the Dormia type, forceps for grasping the foreign body, and polypectomy snares. Alligator forceps with teeth are useful for grasping coins and other types of smooth objects. If an object is irregular or soft, other devices, such as baskets, snares, and graspers with three prongs, can be used. The net retrieval catheters are capable of extracting a variety of foreign bodies safely [57]. An irregular, sharp object, an object with a ragged surface, or an object that is impacted in the wall (e.g., dental plate) may require a rigid laryngoscope or esophagoscopy to be passed under general anesthesia for removal of the foreign body [58].

**Endoscopic control of upper gastrointestinal bleeding**

Upper GI bleeding is one of the most common indications for upper GI endoscopy. For approximately 85%–95% of these patients, a precise diagnosis of the cause of the bleeding can be obtained. In most patients with bleeding, endoscopy can be performed as soon as the patient is stabilized hemodynamically. For a few patients with massive hemorrhage, endoscopic control of bleeding may not be possible. Endoscopic treatment of nonvariceal and variceal bleeding is discussed in Chapters 138 and 139.

**Polypectomy**

Although polyps in the upper GI tract are relatively common, removal is often not necessary. The most frequent type of gastric polyps are fundic gland polyps that result from use of proton pump inhibitors [59]. These polyps rarely bleed significantly and have no malignant potential. They do not need treatment or surveillance. Hyperplastic polyps are the second most common type of gastric polyps. Although rare, the malignant transformation is well documented and total excision is suggested if the diameter is more than 5 mm [60]. Removal of a polyp or polypoid lesion is indicated in neoplastic lesions or those lesions that cause bleeding or symptoms [61]. Polypectomy is accomplished using a wire snare placed over the polyp in a fashion similar to colonoscopy (Figure 132.2). Snares of a variety of sizes and shapes are available, including a symmetric ellipse, a hexagon, and a slightly hooked configuration. After the handle is closed, the tip of the snare should retract at least 1 cm into the plastic overtube. As the snare is tightened on the lesion, an electrocoagulative current is applied, alone or in
combination with a cutting current, during the transection of the polyp. The complications of gastric polypectomy include hemorrhage and perforation. Because of the thickness of the gastric wall, perforation is rare, but hemorrhage may be a significant problem. The risk of bleeding is probably greater in large polyps with thick stalks. Injection of the stalk with epinephrine is recommended, but may not always prevent bleeding. Mechanical hemostatic devices, such as endoloops or clips, can prevent bleeding after polypectomy. Endoscopic treatment of polyps is discussed in detail at Chapter 140.

**Mucosal resection**

Endoscopic mucosal resection (EMR) is a group of techniques designed to remove superficial malignancies of the GI tract. The lesions are most commonly located in the stomach, but an increasing number of dysplastic lesions are being discovered in Barrett esophagus. Usually, the lesion is first examined with endosonography to confirm its superficial nature. In principle, the lesion should be limited to the mucosal layer, but lesions involving the submucosa can also be resected. After proper localization with chromoendoscopy or fluorescence endoscopy, the lesion is lifted after submucosal injection of an agent designed to separate the mucosa from the deep layers [62]. Epinephrine diluted with saline is a commonly used injectant because it provides transient hemostasis as well as separation of the wall layers.

The most commonly performed method for EMR is cap-assisted EMR. In this technique, a translucent plastic cap is placed on the tip of an endoscope and the target tissue is aspirated into the cap. A small snare placed inside the rimmed cap provides the ability to resect a considerable amount of tissue. The lesion is suctioned into the cap and the snare tightened around the lesion. The snare is then advanced out of the cap to enable the extent of the captured mucosa to be confirmed prior to transection. The size, shape, and flexibility of the cap will determine the amount of tissue that is resected [63]. Large surface area mucosal malignancies can be resected using endoscopic knives. Transection is performed with cautery, allowing the specimen to be retrieved for histopathological examination. Although the primary purpose of EMR is resection of malignancy, the procedure also provides detailed histological evidence of the tumor stage (Table 132.1). Mucosal specimens obtained with EMR techniques provide higher accuracy for the detection of mucosal malignancy [64]. When used for the resection of mucosal adenocarcinoma in Barrett esophagus, cap-assisted EMR provides high rates of remissions [65]. Current EMR techniques and complications are discussed in Chapter 140.

**Dilation**

Esophageal stricture dilation may be performed using Maloney (bougie) dilators, wire-guided dilators, or balloons (Table 132.4) [66]. Semirigid esophageal dilating devices are passed through strictures using a guidewire placed endoscopically. The guidewire with a spring tip is passed through an instrument channel across the stricture. With the guidewire in place, the endoscope is removed. Confirmation of the positioning of the guidewire below the stricture can be obtained by fluoroscopy, but is rarely needed. Dilators of increasing diameter are successively passed over the guidewire and across the stricture. The guidewire and the spring tip should remain below the area to be dilated throughout the procedure. Thermoplastic Savary dilators are the most commonly used wire-guided dilator [66].

Flexible endoscopy has an increasingly important role in dilating strictures with the use of through-the-scope (TTS) balloons or placement of a guidewire. However, the overall need for esophageal stricture dilation has decreased with the increasing use of proton pump agents limiting the frequency of strictures due to peptic injury associated with gastroesophageal reflux disease (GERD) [67]. TTS or controlled radial expansion (CRE) balloon dilation of esophageal strictures is highly successful and safe [68]. The radial force provided by a CRE balloon is greater than the radial force generated by bougie dilation. Stricture dilation has been facilitated by the use of CRE balloons, dramatically improving patient tolerance. In a complex stricture, the balloon should be directed with a guidewire. However, in most strictures, the balloon is easily placed in the stricture and held in place during pneumatic dilation. Balloons used for CRE vary from 4 to 20 mm in diameter when fully inflated with a liquid, and many provide graduated dilation over 3 mm. The risk of perforation is low in benign strictures, but malignant strictures can only be safely dilated to 14 mm [69].

---

**Table 132.4 Methods for esophageal stenosis dilation.**

<table>
<thead>
<tr>
<th>Method</th>
<th>Maloney dilation</th>
<th>TTS-CRE balloons</th>
<th>Insight dilator</th>
<th>Catheter-based balloon dilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign esophageal stenosis</td>
<td>Highly effective</td>
<td>Highly effective</td>
<td>Not well tested</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Malignant esophageal stenosis</td>
<td>Transient effect</td>
<td>Transient effect</td>
<td>Not well tested</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Achalasia</td>
<td>Not effective</td>
<td>Transient effect</td>
<td>Not tested</td>
<td>Effective</td>
</tr>
<tr>
<td>Benign pyloric channel stenosis</td>
<td>Not indicated</td>
<td>Effective</td>
<td>Effective</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Malignant duodenal stenosis</td>
<td>Not indicated</td>
<td>Transient effect</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

TTS-CRE, through-the-scope controlled radial expansion.
Ultrathin endoscopy may provide a complete evaluation of lesions in advanced esophageal strictures and gives a better opportunity for dilation [70].

Using the same principles for esophageal stricture dilation, TTS balloons can be employed for strictures in the pylorus and duodenum. Benign strictures of the pylorus are easily dilated with lasting benefit [71]. Passage of the balloon and its inflation can be monitored with fluoroscopy to be certain that the waist of the balloon, representing the stricture, has been obliterated.

**Stents**

Esophageal stent placement is a highly effective procedure for the palliation of malignant dysphagia. The timing of stent placement is very important in order to provide optimal benefit to the patient and avoid complications, such as stent migration. Prior to stent placement, endoscopy is used to evaluate the degree of narrowing, measure the length of the tumor narrowing, and determine the distance from the top of the tumor to the incisor teeth, an important factor in placing the prosthesis. As in all procedures, patients and family should be fully informed of the risks and complications of esophageal stent placement. Prior to the placement of an esophageal stent, the esophageal lumen must be large enough to accommodate a stent. Dilatation of the malignant stricture can be accomplished with CRE balloons or bougies. After the length of the stricture is determined, the stent length should be long enough to include 2.5–3 cm proximal to the narrowing and the same distance distal to the narrowing to prevent early restenosis by overgrowth of tumor. The proximal and distal sites of the stricture should be marked with an injection of contrast or the placement of a clip. Stent placement is usually performed with fluoroscopic guidance; however, stent insertion under direct endoscopic vision and without fluoroscopy is also possible [72].

Expandable esophageal stents that are placed across a malignant stricture readily provide luminal patency. Self-expanding esophageal stents are provided in a covered or a noncovered format. These devices are passed over a guidewire through the malignant narrowing, within a sheath covering the compressed stent. After the constraining sheath is released, the stent is left in place and expands. The expanding stents have the advantage of producing a wide lumen through the stenosing tumor mass. However, these stents are difficult to remove. Stents covered by a silicone membrane may prevent tumor ingrowth and offer relief from symptoms associated with fistulas and leaks [73]. Polyflex-covered self-expanding plastic stents are designed to be used in benign strictures and be removed. They provided satisfactory palliation of benign esophageal strictures; however, migration to stomach and dysphagia recurrence were common after stent removal [74]. Biodegradable esophageal stents have been suggested as an alternative for refractory esophageal strictures without need for removal. The stents were found effective in preliminary studies; however, larger studies with longer follow-up are needed [75].

**Laser tumor ablation**

An endoscope can be used to guide a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser to establish patency of a malignant esophageal stricture [76]. Repeated ablative sessions are required in order to eliminate sufficient malignant tissue for symptomatic relief. Long-term success, in terms of relief of dysphagia, is relatively modest, about 66% [76]. This approach has largely been replaced with the placement of self-expanding metal stents [77]. Stenting can provide rapid relief from dysphagia in a single endoscopic procedure and is associated with low risk. Endoscopic laser therapy with homogenatise oxidase (HGD) has been used in small numbers of patients with Barrett esophagus [78]. Argon plasma coagulation (APC) is an alternative method for laser photocoagulation of Barrett epithelium and dysplasia (Table 132.5) [79]. APC shortened the length of Barrett’s esophagus but complete regression rate was just 50% and the long-term recurrence rate was high [80,81]. APC can be used in conjunction with EMR for the elimination of residual tissue in the base of mucosectomy sites.

**Endoscopic radiofrequency ablation**

Radiofrequency ablation (RFA) is another technique for treatment of low- and high-grade dysplasia which uses a balloon-based bipolar electrode array in patients with Barrett esophagus. The method aims to destroy the dysplastic and metaplastic epithelium with RF energy and allow regrowth with the squamous epithelium that normally lines the distal esophagus. RFA is usually applied initially with a circumferential balloon catheter and then focally for residual areas with a catheter system consisting of an electrode array mounted on the tip of the endoscope. Barrett with high- and low-grade dysplasia, and intestinal metaplasia, as well, were completely eradicated in 81%, 90%, and 77% of patients, respectively, in a multicenter sham-controlled trial [82]. Patients in the ablation arm had less disease progression (3.6% vs 16.3%) and fewer cancers (1.2% vs 9.3%) compared to controls at the end of 12 months. A long-term follow-up study for durability of RFA showed dysplasia remained eradicated in 85% of patients at the third year without maintenance treatment [83]. Endoscopic RFA is a well-tolerated and safe method compared to other ablation methods but 2%–14% esophageal stricture rates have been reported in studies [84,85].

**Safety of upper gastrointestinal endoscopy**

**Medical history**

Obtaining a complete medical history, including previous surgery, allergy, anesthesia, and medications, is the first step for a safe endoscopy. This information will also help the endoscopist to decide whether the patient can tolerate intravenous conscious or deep sedation safely. Knowledge of a history of airway or upper esophageal surgery, procedures, or of radiation, will help decrease the risk of perforation. Knowledge of bleeding tendencies in the patient or the patient’s family and
For gastrointestinal endoscopic procedures, the standard regimen is 2 g of ampicillin, administered intravenously or intramuscularly, plus gentamicin (1.5 mg/kg, not to exceed 80 mg), administered intravenously or intramuscularly 30 min before the procedure, followed by 1.5 g of amoxicillin taken orally 6 h after the initial medication. Alternatively, the parenteral regimen may be repeated once 8 h after the initial dose.

### Procedure-related complications

Diagnostic upper endoscopy is generally safe and significant complications are uncommon [88]. However, therapeutic endoscopy increases the risk of complications due to underlying conditions, type of intervention, endoscopists’ experience, and patient-related factors. Perforation is the most directly assignable complication of upper GI endoscopy, but this occurs in less than 0.1% and is increasingly rare. The most common cause of perforation is the passage of the blind tip of the endoscope into a malignant stricture. If these perforations are recognized early, immediate surgery and repair will provide closure with a minimum of morbidity. The performance of EMR and resection of a subepithelial malignancy is also associated with esophageal perforation. However, in the case of EMR, perforations are usually small and may be managed with endoscopic clipping. The third most common cause of perforation is the performance of large-balloon dilation of a stricture or achalasia. These types of perforations are more accurately referred to as tears, and their management is much more difficult. Uncomplicated, small perforations may be managed endoscopically and with supportive care. Large tears require urgent surgical resection and/or repair [89].

References are available at [www.yamadagastro.com/textbook](http://www.yamadagastro.com/textbook).

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Table 132.5 Endoscopic methods for ablation of malignancy.

<table>
<thead>
<tr>
<th>Method of application</th>
<th>Argon plasma coagulation</th>
<th>Photodynamic therapy</th>
<th>Radio frequency ablation</th>
<th>Ethanol</th>
<th>Laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary clinical indication</td>
<td>Ablation of vascular lesions</td>
<td>Barrett esophagus with dysplasia</td>
<td>Ablation of hepatocellular carcinoma, Barrett esophagus with dysplasia</td>
<td>Ablation of hepatocellular carcinoma</td>
<td>Ablation of esophageal malignancy</td>
</tr>
<tr>
<td>Method of application</td>
<td>Topical application via catheter</td>
<td>Intravenous photosensitizer and catheter-guided light exposure</td>
<td>Percutaneous needle with RFA wire, Endoscopic balloon catheter</td>
<td>Needle injection</td>
<td>Catheter-directed laser light</td>
</tr>
<tr>
<td>Primary oncological application</td>
<td>Barrett esophagus with dysplasia</td>
<td>Barrett esophagus with dysplasia</td>
<td>Hepatocellular carcinoma, Hypernephroma</td>
<td>Hepatocellular carcinoma</td>
<td>Esophageal malignancy</td>
</tr>
<tr>
<td>Additional targets</td>
<td>Adenomas</td>
<td>Gastric malignancy</td>
<td>Hepatic metastases, pancreatic cancer</td>
<td>Pancreatic cystadenomas</td>
<td>Gastric malignancy</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Coagulation and heat</td>
<td>Cell death induced by singlet oxygen</td>
<td>Heat</td>
<td>Protein denaturation</td>
<td>Heat</td>
</tr>
</tbody>
</table>

RFA, radiofrequency ablation.
Table 132.6 Antibiotic prophylaxis for endoscopic procedures.

<table>
<thead>
<tr>
<th>Patient condition</th>
<th>Procedure contemplated</th>
<th>Antibiotic prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>Stricture dilation</td>
<td>Recommended</td>
</tr>
<tr>
<td>History of endocarditis</td>
<td>Variceal sclerotherapy</td>
<td>Recommended</td>
</tr>
<tr>
<td>Systemic pulmonary shunt</td>
<td>ERCP obstructed biliary tree</td>
<td>Recommended</td>
</tr>
<tr>
<td></td>
<td>Other endoscopic procedures, including EGD and colonoscopy (with or without biopsy/polypectomy), variceal ligation</td>
<td>Recommended</td>
</tr>
<tr>
<td>Synthetic vascular graft (&lt;1 year old)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex cyanotic congenital heart disease</td>
<td></td>
<td>Optional</td>
</tr>
<tr>
<td><strong>Moderate risk:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most other congenital abnormalities</td>
<td>Esophageal stricture dilation</td>
<td>Optional</td>
</tr>
<tr>
<td>Acquired valvular dysfunction (e.g. rheumatic heart disease)</td>
<td>Variceal sclerotherapy</td>
<td>Optional</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Other endoscopic procedures, including EGD and colonoscopy (with or without biopsy/polypectomy), variceal ligation</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Mitral valve prolapse with regurgitation or thickened cordae</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>Low risk:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cardiac conditions (CABG, repaired septal defect or patent duetus, mitral valve prolapse without valvular regurgitation, isolated secondum atrial septal defect, physiologic functional, heart murmurs rheumatic fever without valvular dysfunction, pacemakers, implantable defibrillators)</td>
<td>All endoscopic procedures</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Obstructed bile duct</td>
<td>ERCP</td>
<td>Recommended</td>
</tr>
<tr>
<td>Pancreatic cystic lesion</td>
<td>ERCP, EUS-FNA</td>
<td>Recommended</td>
</tr>
<tr>
<td>Cirrhosis acute GI bleed</td>
<td>All endoscopic procedures</td>
<td>Recommended</td>
</tr>
<tr>
<td>Ascites, immunocompromised patient</td>
<td>Stricture dilation</td>
<td>No recommendation</td>
</tr>
<tr>
<td></td>
<td>Variceal sclerotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other endoscopic procedures, including EGD and colonoscopy (with or without biopsy/polypectomy), variceal ligation</td>
<td></td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>Peroesophageal endoscopic feeding tube</td>
<td>Recommended (parenteral placement cephalosporin or equivalent)</td>
</tr>
<tr>
<td><strong>Prosthetic joints</strong></td>
<td>All endoscopic procedures</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Cardiac prophylaxis regimens (oral 1 h before, i.m. or i.v. 30 min before procedure).
Amoxicillin by mouth or ampicillin i.v.: adult 2.0 g; child 50 mg/kg.
Penicillin allergic: clindamycin (adult 600 mg, child 20 mg/kg), or cephalaxin or cefadroxil (adults 2.0 g, child 50 mg/kg), or azithromycin or clarithromycin (adult 500 mg, child 15 mg/kg), or cefazolin (adult 1.0 g, children 25 mg/kg i.v. or i.m.), or vancomycin (adult 1.0 g, child 10–20 mg/kg i.v.).
CABG, coronary artery bypass graft; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde choangiopancreatography; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; GI, gastrointestinal.

Further reading

CHAPTER 133
Capsule and small bowel endoscopy

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Introduction

Endoscopic imaging has progressed significantly over the past several years. These advances have mainly been in the field of small bowel enteroscopy, defined as direct visualization of the small bowel with use of a fiberoptic or wireless endoscope. During the past decade, these new modalities have facilitated both the diagnostic evaluation and the therapeutic management of small bowel disorders. Multiple enteroscopic tools are now available that differ in technique and capabilities.

Capsule endoscopy (CE) enables noninvasive visualization of the entire small bowel, but it is a purely diagnostic test. CE is currently recommended as the third test of choice for evaluation of obscure gastrointestinal bleeding (OGIB) after negative bidirectional endoscopy. The test can also facilitate the diagnosis of inflammatory small bowel disease and small bowel tumors and the surveillance of familial polyposis syndromes. It may also aid the management of patients with complicated celiac disease.

Deep enteroscopy devices, which include balloon-assisted enteroscopy (BAE) and spiral enteroscopy (SE), allow both diagnostic and therapeutic interventions in the deeper portions of the small bowel but are relatively invasive compared to CE and are often protracted procedures. The more appropriate test for an individual patient is determined by several factors, including clinical presentation of the patient and index of suspicion for a lesion, including its suspected location. Therapeutic deep enteroscopy techniques are mainly used for evaluation and management of CE findings, but they may also have a role in patients with a negative CE but a high clinical suspicion for a small bowel lesion. Because preliminary data suggest comparable diagnostic and therapeutic yields with double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), and SE, the enteroscope of choice should be based upon its availability and the experience of the endoscopist with each technique.

The development of CE and deep enteroscopy techniques over the past decade have led to a shift toward an endoscopic approach to the management of small bowel disorders. Whereas CE has enabled diagnostic evaluation of the entire small bowel, BAE (DBE and SBE) and SE have facilitated both diagnostic and therapeutic management deep within the small bowel, thereby avoiding surgery in many patients. This chapter is a review of CE and small bowel endoscopy techniques, including a description of these devices, their diagnostic and therapeutic utility, their advantages and limitations, and how they should be used in clinical practice to manage patients with OGIB and other suspected small bowel diseases.
Overview of capsule endoscopy

Capsule endoscopy has revolutionized our approach to evaluating the small bowel. Introduced in the year 2000, CE was the first endoscopic test that enabled visualization of the entire small bowel. There are four CE systems currently available worldwide: (1) the PillCam SB2 and SB3 (Given Imaging Ltd, Yoqneam, Israel); (2) the Endo Capsule (Olympus Medical Systems Group, Center Valley, Pennsylvania); (3) the OMOM capsule (Jinshan Science and Technology Co Ltd, Chongqing, China); and (4) the MiroCam (IntroMedic Co Ltd, Seoul, Korea) (Figure 133.1). The PillCam SB2 and SB3, the Endo Capsule, and the MiroCam are currently approved by the US Food and Drug Administration (FDA). The systems include a capsule, an eight-point sensory array, and a portable data recorder. The PillCam SB2 and SB3 and the Endo Capsule measure 11 × 26 mm, and they contain light-emitting diodes, silver oxide batteries, a lens, a radiofrequency transmitter, and an antenna. The PillCam SB2 contains a metal oxide semiconductor, whereas the Endo Capsule has a charged coupled device.

Capsule endoscopy can be performed in the outpatient ambulatory setting. The capsule is usually swallowed by the patient with water. It can also be delivered directly into the small bowel using endoscopic assistance in patients with dysphagia or risk factors for an incomplete study such as gastroparesis [1,2]. The capsule is propelled throughout the small bowel by peristalsis over an 8- to 12-h period. Images are captured by the camera at the rate of two to six frames per second and transferred by wireless technology to the data recorder, which is strapped to the patient’s waist. The images are then downloaded and viewed on a computer with the appropriate software. The average physician time for viewing the images ranges from 45 to 120 min, depending on the complexity of the study [3].

To prepare for the procedure, patients have several alternatives because an ideal practice has not yet been clearly identified. Acceptable approaches include either or both a 24-h fast and a clear liquid diet the day before the examination and the ingestion of 2 to 4 liters of a gut lavage solution. One study showed that gut lavage improves visualization but not necessarily diagnostic yield [4]. However, two metaanalyses have shown that gut lavage increases both the quality of preparation and diagnostic yield [5,6]. Lower-volume lavage preparations appear to be as efficacious as higher volumes. Some evidence also suggests that taking simethicone before or with ingestion of the capsule reduces intraluminal bubbles and improves visibility [7].

The capsule videos allow visualization of the entire small bowel in 79% to 90% of patients [8]. The test is FDA-approved for use in patients older than age 2 years for evaluation of OGIB, Crohn’s disease, celiac sprue, polyposis syndromes, small bowel abnormalities on imaging studies, and clinical symptoms.

Figure 133.1 Types of capsule endoscopes currently available. (a) PillCam SB2 (Given Imaging Ltd, Yoqneam, Israel); (b) the Endo Capsule (Olympus Medical Systems Group, Center Valley, Pennsylvania); (c) the OMOM capsule (Jinshan Science and Technology Co Ltd, Chongqing, China); and (d) the MiroCam (IntroMedic Co Ltd, Seoul, Korea). Source: (a) Given Imaging Ltd. Image reproduced with permission; (b) Olympus Corporation of the Americas. Image reproduced with permission; (c) Jinshan Science and Technology. Image reproduced with permission; (d) IntroMedic Co Ltd. Image reproduced with permission.
A systematic review identified the most common indications for CE as OGIB (66%), clinical symptoms (10.6%), Crohn’s disease (10.4%), neoplastic lesions (3.5%), and celiac disease (1.7%) [9].

The main disadvantage of CE is its purely diagnostic capability; therefore, patients with positive findings still must undergo additional therapeutic procedures. There is also a high rate of incidental findings in up to 23% of healthy controls [10], which may result in unnecessary invasive procedures. Capsule images may be limited by incomplete visualization of the small bowel in 15% to 20% of patients [11]. Other limitations include the inability to control the movement of the capsule, difficulty in localizing identified lesions, and the potential for missing single-mass lesions.

Cardiac pacemakers, defibrillators, and other electromechanical devices are a contraindication to the use of CE. However, some evidence suggests that CE is safe in these patients and that capsule-related electromagnetic interference is extremely unlikely [12,13]. Dysphagia is a relative contraindication to use of CE. Although the capsule is usually easily ingested, patients may have difficulty if they have severe dysphagia, difficulty swallowing large pills, or a Zenker diverticulum. Therefore, obtaining a detailed swallowing history is important before capsule ingestion. If there is a concern, further evaluation may be warranted first. In patients for whom ingestion is a problem or for those with gastroparesis, a capsule-loading device (AdvanCE, US Endoscopy, Mentor, Ohio) can be used to deliver the capsule directly into the small bowel.

The most important complication is small bowel retention because of an underlying stricture or obstruction. This risk ranges from less than 1% in patients who present with OGIB or suspected Crohn’s disease to as high as 13% in patients with known Crohn’s disease or 17% in patients with small bowel tumors [14,15]. Most cases of retention are clinically silent, and symptomatic obstruction is extremely rare. If the capsule does not reach the colon or the patient does not witness excretion after 2 weeks, a follow-up abdominal film should be obtained. If retention persists, endoscopic or surgical removal may be required [16].

In patients with a suspected small bowel stricture or obstruction, a patency capsule (Agile Patency System, Given Imaging) can help determine the risk of capsule retention. The patency capsule is a self-dissolving capsule that is useful in determining the patency of the small bowel. The use of a patency capsule before CE in such patients has led to a significant reduction in the incidence of capsule retention [17–19]. One study that compared the patency capsule to radiological tests showed similar sensitivity (57% vs 71%; \( P > 0.99 \)) and specificity (86% vs 97%; \( P = 0.22 \)) for detection of clinically significant strictures [20].

**Deep enteroscopy techniques**

**Double-balloon enteroscopy**

Balloon-assisted enteroscopy allows deeper intubation of the small bowel than that available with push enteroscopy or ileocolonoscopy. Introduced in 2001, DBE (FUJIFILMS Holdings America Corp, Tokyo, Japan) was the first BAE. The DBE system comprises an enteroscope, an overtube, and a balloon-pump system (Figure 133.2a). The DBE is available in both a diagnostic model (EN-450P5) and a therapeutic model (EN-450T5). The enteroscope has a working length of 200 cm and a polyurethane overtube 140 cm long. Both the enteroscope and the overtube have latex balloons at their distal ends. The therapeutic model (EN-450T5) has an external diameter of 9.4 mm and an accessory channel of 2.8 mm, compared to 8.5 mm and 2.2 mm, respectively, for the diagnostic model (EN-450P5).

Depending on the suspected location of the small bowel lesion, DBE may be performed via the oral or the rectal route.

![Figure 133.2 Types of balloon-assisted enteroscopes. (a) Double-balloon enteroscope; (b) single-balloon enteroscope. Source: Adapted from Leighton [21]. Reproduced with permission.](image-url)
Advancement through the small bowel is achieved with a series of cycles using a push-and-pull technique. This process facilitates pleating of the small bowel over the enteroscope, allowing for a greater depth of insertion into the small bowel than that available with push enteroscopy or ileoscopy [22]. General anesthesia or monitored anesthesia is often used for oral procedures, whereas retrograde procedures may be performed with the patient under conscious sedation, although this practice varies at many centers.

Double-balloon enteroscopy has the potential for deeper advancement with the oral approach than with the rectal approach. The depth of intubation with DBE ranges from 240 cm to 360 cm for the oral approach and from 102 cm to 140 cm for the rectal approach [23–26]. Targeted enteroscopy is performed when there is a preidentified lesion on prior CE or small bowel imaging, and the route of DBE is based on the suspected location of the lesion. On the basis of capsule transit times, the oral route is used for lesions located within the proximal 75% of the small bowel and the rectal route is used for lesions in the distal 25% [27].

Total enteroscopy with DBE is defined as complete evaluation of the small bowel, with either a single approach or a combined oral–rectal approach. Total enteroscopy should be considered in patients with multiple small bowel lesions, a negative initial DBE, or high clinical suspicion for a small bowel lesion after a negative capsule study. The success rate for total enteroscopy varies considerably, from 0% to 86%, and is highest in the Asian population [22,24,25,28]. The diagnostic yield of DBE ranges from 43% to 80% [24,29] and is comparable to that for CE. DBE enables the performance of therapeutic interventions, including biopsies, injections, polypectomy, stricture dilation, hemostatic techniques (argon plasma coagulation, electrocoagulation, and hemoclips), and retrieval of foreign bodies, including retained capsules [23,29,30].

The main limitations of DBE include its invasive nature, prolonged duration, and requirement for additional personnel. DBE appears to be a relatively safe procedure. However, risks do increase with therapeutic maneuvers. The overall complication rate of DBE is 0.8% for diagnostic procedures and 4.0% for therapeutic procedures [31]. The most common complications include bleeding and perforation, usually related to the removal of large polyps. Pancreatitis has also been reported, but its incidence appears to have decreased over time [32,33].

Single-balloon enteroscopy

Single-balloon enteroscopy has also been developed for the evaluation and management of small bowel disorders. The SBE (Olympus Optical, Tokyo, Japan) was introduced in 2007. In contrast to DBE, this device has only one balloon, which is at the distal end of the overtube. The enteroscope is 200 cm long, and the overtube is 140 cm long (Figure 133.2b). The outer diameter of the SBE is 9.2 mm, and the accessory channel is 2.8 mm. The overtube and balloon are made from silicon, which can therefore be used in patients with latex allergy. SBE is also performed by the push-and-pull technique, but the advancement cycles differ slightly from those for DBE [34].

The depth of intubation with SBE ranges from 133 cm to 256 cm for the antegrade approach and from 73 cm to 163 cm for the retrograde approach [35,36], with a success rate of 15% to 25% for total enteroscopy [36,37]. The diagnostic yield of SBE ranges from 47% to 60% [35,36,38], and endoscopic therapeutics can be performed with SBE as with DBE. SBE has a complication rate of 1%, which includes perforation and pancreatitis [39].

Spiral enteroscopy

Spiral enteroscopy is the newest CE system available for clinical use. The Endo-Ease Discovery SB (Spirus Medical LLC, Stoughton, Massachusetts) is a spiral overtube made of polyvinyl chloride. It measures 118 cm and has a 21-cm raised helix at the distal end. The spiral-shaped overtube has a working length of 130 cm (Figure 133.3). Any enteroscope can be used with the Endo-Ease Discovery SB. With SE, the overtube is placed over a pediatric colonoscope or a push enteroscope and the enteroscope is advanced through the small bowel by clockwise rotation and then withdrawn by counterclockwise rotation [21]. The distal end of the overtube is locked in place 25 cm from the tip of the enteroscope. The system is then advanced into the small bowel by gentle rotation to the ligament of Treitz, where the collar is unlocked and the SE is advanced past the ligament. The device is then rotated using clockwise movements to reach the farthest extent possible or until there is no more pleating of the small bowel over the enteroscope. This series of steps is repeated to achieve maximal intubation. The device is withdrawn using counterclockwise rotation [40]. With the exception of a pilot study using retrograde SE in six patients [41], all studies of SE have used the antegrade approach. The mean depth of intubation with SE ranges from 176 cm to 250 cm [42,43]. Complications with SE include minor mucosal tears and perforation, which has been reported in 0.3% of patients [44].

![Figure 133.3 Spiral enteroscope (Endo-Ease Discovery SB, Spirus Medical LLC, Stoughton, Massachusetts). Source: Spirus Medical Inc. Image reproduced with permission.](image-url)
Comparison of the diagnostic yield of deep enteroscopy techniques

Capsule endoscopy versus double-balloon enteroscopy

Comparison of CE and DBE in patients with suspected small bowel disorders has been challenging. Two metaanalyses compared CE and DBE in patients with suspected small bowel disorders [45,46]. The first metaanalysis included 11 studies with 375 patients, most of whom had OGIB [45]. There was no difference in the pooled overall yield of CE and DBE for all small bowel disorders (60% vs 57%, respectively; weighted incremental yield, 3%; 95% confidence interval [CI] −4%–10%; P = 0.42) or for vascular, inflammatory, and neoplastic lesions. The second metaanalysis of eight studies also found a comparable yield with CE and DBE (odds ratio [OR] 1.21; 95% CI 0.64–2.29) for small bowel disorders [46]. However, in patients with OGIB, the subanalysis showed that CE had a significantly higher yield than DBE using a single approach (OR 1.67; 95% CI 1.14–2.44; P < 0.01) but not in comparison to DBE using a combined oral–rectal approach (OR 0.33; 95% CI 0.05–2.21; P > 0.05).

A updated metaanalysis of 10 studies found no difference in pooled diagnostic yield between CE and DBE (62% vs 56%; OR 1.39; 95% CI 0.88–2.20) [47]. However, the diagnostic yield of DBE after a positive CE was 75% (OR 1.79; 95% CI 1.09–2.96; P = 0.02), which was significantly higher than the yield after a negative CE (27.5%; 95% CI 16.7%–37.8%) [47]. A study of 193 patients evaluated the concordance of CE and DBE in OGIB [48]. CE and DBE had good agreement for vascular and inflammatory lesions but not for polyps or neoplasia. For polyps or neoplasia, DBE provided additional useful information. In addition, in those patients where CE detected only blood, DBE was able to clarify the etiology in two-thirds. Given the comparable yield of these tests, these modalities should be viewed as complementary. However, the noninvasiveness and higher success rate of total enteroscopy with CE support the use of CE before DBE for evaluation of small bowel disorders. This approach allows one to direct the initial route of DBE. Because of the potential for missed lesions and tumors on CE [49,50], additional evaluation with DBE should be pursued in patients with recurrent bleeding or a high index of suspicion, despite a negative capsule study.

Double-balloon enteroscopy versus single-balloon enteroscopy

Comparing DBE and SBE has also been difficult. A prospective randomized study compared the two types of enteroscopy in 100 patients with suspected small bowel disease [51]. DBE had a significantly higher success rate of total enteroscopy (66% vs 22%; P < 0.001) and a higher diagnostic and therapeutic yield (72% vs 48%; P = 0.025) compared to SBE. However, the Fujinon DBE was used for all cases, and SBE was simulated by not using a balloon on the enteroscope. In contrast, a retrospective study comparing DBE and SBE found SBE to be superior [52]. The diagnostic and therapeutic yield was significantly higher with SBE (705 vs 51.25; P < 0.05), but this study did not report the rate of total enteroscopy for each technique. Another prospective single-center study comparing DBE and SBE was prematurely discontinued after interim analysis due to an obvious advantage of DBE over SBE for total enteroscopy (57.1% vs 0%; P = 0.002) [53]. However, there was no difference in diagnostic yield or therapeutic outcome.

More recently, a randomized, controlled study showed that there was no significant difference between SBE and DBE in procedure time, insertion depth, diagnostic yield, or therapeutic yield [54]. Currently, the decision to use DBE or SBE should be based on enteroscope availability and the experience of the endoscopist with either technique.

Balloon-assisted enteroscopy versus spiral enteroscopy

In a prospective study, 35 patients with suspected small bowel disorders were randomized to DBE or SE [55]. There was no significant difference between the procedures in either diagnostic yield (47% for DBE vs 33% for SE) or mean depth of insertion (265 cm with DBE vs 216 cm with SE). In another retrospective study, SBE and SE were compared in 92 patients with small bowel disorders [56]. No significant difference was found in diagnostic yield of SE vs SBE (56.9% vs 43.4%, respectively; P = 0.12) or in the duration of the procedures. However, the mean depth of small bowel intubation with SE was significantly higher than that for SBE (301 cm vs 222 cm; P < 0.001) [56]. On the basis of these preliminary data, there appears to be no difference in diagnostic yield between BAE and SE. However, larger prospective randomized trials are necessary to confirm these findings.

Obscure gastrointestinal bleeding

Obscure gastrointestinal bleeding is defined as bleeding from the gastrointestinal tract that persists or recurs after a negative initial evaluation with bidirectional endoscopy and small bowel radiographs [57,58]. Up to 10%–20% of patients who present with OGIB will have an underlying etiology that may not be evident on initial evaluation [59]. Half of these patients will have recurrent or persistent bleeding that can pose a major challenge to diagnosis and management. Most OGIB is caused by small bowel bleeding. The underlying etiology often remains elusive, despite extensive evaluations, resulting in recurrent hospitalizations and multiple transfusions. The newer enteroscopy techniques have led to improved evaluation and management of these patients, and they have led to a major paradigm shift in the clinical approach to OGIB. This, in turn, has led to fewer surgical procedures and a decline in the morbidity and mortality associated with OGIB.

Capsule endoscopy for obscure gastrointestinal bleeding

The guidelines of the American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy
recommend CE as the third test in patients with OGIB after negative bidirectional endoscopy [57,58]. This recommendation is based on the results of two metaanalyses that unequivocally showed CE to be superior to other diagnostic modalities [60,61]. A metaanalysis of 14 studies found an incremental yield of 30% for CE over push enteroscopy (56% vs 26%) and of 36% for CE over small bowel radiography for clinically significant findings within the small bowel [60]. In a subanalysis, CE had a higher yield than push enteroscopy for detection of vascular and inflammatory lesions. Another metaanalysis of nine studies showed CE to be superior to push enteroscopy and barium small bowel radiography, with a difference of 41% for all small bowel disorders and 37% for OGIB [61].

The yield of CE in OGIB ranges from 35% to 76% [62–66], and a pooled analysis of 24 trials with 691 patients found an overall diagnostic yield of 87% [67]. A European study surveyed 23 centers about their capsule practice over 7 years [68]. Of the 2921 CE studies, 43% had been performed for OGIB, with a diagnostic yield of 66%. In a prospective study of 47 patients with OGIB that compared CE to intraoperative enteroscopy as the preferred standard, CE was found to have a diagnostic yield of 74% [69]. Other studies utilizing CE in patients with OGIB have also found a positive predictive value of 94% to 97% and a negative predictive value of 83% to 100% [70,71]. CE has also shown a high diagnostic yield after negative imaging with computed tomographic (CT) enterography [72].

The yield of CE is increased in patients with overt bleeding compared to those with occult bleeding, and in patients who undergo the procedure within 2 weeks of a bleeding episode [73–75]. Other factors that have a favorable impact on the yield of CE are recurrent bleeding, longer duration of bleeding, and low hemoglobin (<10 g/dL) [76]. However, CE may still be useful in patients presenting with iron deficiency anemia, with most of the lesions detected being vascular in nature [77] (Figure 133.4). In contrast, another study of patients with iron deficiency anemia and no evidence of gastrointestinal bleeding found that CE, not surprisingly, had a low diagnostic yield (25.7%) [78]. There is also evidence of favorable outcomes in patients who have undergone CE for evaluation of OGIB [70]. The positive impact of CE on clinical outcomes in patients with iron deficiency anemia is less clear [79]. CE is associated with a high negative predictive value, and two studies have demonstrated favorable outcomes after a negative CE [80,81]. Additional invasive testing may therefore be avoided in such patients unless the initial examination was compromised by suboptimal preparation or incomplete small bowel examination [82]. Repeat capsule studies may also be helpful in patients who present with recurrent bleeding after a negative or nondiagnostic examination [83–85].

**Double-balloon enteroscopy for obscure gastrointestinal bleeding**

Double-balloon enteroscopy can aid in evaluation and management of OGIB. It is useful after a positive CE for biopsies or hemostasis, after a negative CE in patients with recurrent bleeding or high clinical suspicion for a small bowel lesion, in patients for whom CE is contraindicated, and in those with active bleeding.

Evidence indicates that DBE is clearly superior to push enteroscopy for evaluation of OGIB [86]. The diagnostic yield of DBE ranges from 50% to 80%, and endoscopic therapeutics can be successfully performed in up to 75% of patients [23,24,26,87,88]. On the basis of a systematic review of 13 studies with 906 patients with OGIB, the diagnostic yield for DBE was 66% and included predominantly angiectasias [89]. The yield is significantly higher in patients with ongoing overt bleeding than in those with prior overt bleeding or occult bleeding or with multiple episodes or prolonged duration of bleeding [90,91]. Due to its deeper intubation of the small bowel, the oral approach is the preferred route for lesions suspected of lying within the proximal 75% of the small bowel, whereas the rectal route is used for more distal lesions [87,92]. In some circumstances, it may be more feasible and cost-effective to proceed directly to DBE [93]. Emergent DBE has been shown to be technically feasible and to facilitate the diagnosis and management of acute bleeding. Favorable outcomes have been reported in patients after DBE [94–96].

**Single-balloon enteroscopy for obscure gastrointestinal bleeding**

Single-balloon enteroscopy was introduced after DBE, and it has been evaluated in several studies. Some have shown SBE to have results comparable to those of DBE [36–38]. The largest single-center study evaluated SBE in 161 patients with suspected small bowel disorders, of whom 59% had OGIB [35]. The
mean depth of intubation was only 133 cm with the oral approach and only 73 cm with the rectal approach. However, the yield was 58%, similar to that in prior reports on DBE, and it included predominantly angiectasias. The concordance between CE and SBE findings was 40%, and SBE detected new findings in 17% of patients.

**Spiral enteroscopy for obscure gastrointestinal bleeding**

Preliminary studies indicate that the diagnostic yield and depth of small bowel intubation with SE is comparable to that for BAE with DBE or SBE [42]. SE is currently performed in most centers using only the oral approach. Several studies also support its use in patients with OGIB [43,97]. A more recent prospective study evaluated long-term outcomes after SE in patients with OGIB [98]. Findings confirmed that SE is safe and effective in reducing the incidence of overt bleeding, as evidenced by increased hemoglobin values, a decrease in blood transfusions and iron supplementation, and a decrease in therapeutic procedures on long-term follow-up. Retrograde SE has been described only in a pilot study of six patients [41]. SE detected lesions in four patients and allowed the performance of therapeutics, including polypectomy and stricture dilation, in three patients.

**Comparison of deep enteroscopy techniques in obscure gastrointestinal bleeding**

A randomized multicenter trial comparing DBE and SBE in 130 patients showed a comparable depth of intubation, total enteroscopy rate, and diagnostic yield for the two techniques [99]. Studies have also shown that SE is comparable to DBE [55,56]. There is no evidence to suggest that the time of day (morning or afternoon) of the procedure influences diagnostic or therapeutic yield [100].

Capsule endoscopy and DBE have a comparable yield in patients with OGIB [45,46,48]. The yield of DBE was increased after a positive CE (75%), as compared to the yield after a negative CE (27.5%) [47]. CE is the preferred initial test of choice because it allows evaluation of the entire small bowel in a noninvasive manner, and it also provides information on location of small bowel lesions. Additional evaluation and therapeutics may then be pursued with any of the deep enteroscopy techniques, based upon the availability of the equipment and the experience of the endoscopist.

**Crohn’s disease**

Crohn’s disease is characterized by mucosal and transmural inflammation of the bowel wall and can involve any segment of the gastrointestinal tract, although the small bowel is most commonly affected. As many as 30% of these patients have disease confined to the small bowel [101]. In a subset of patients with inflammation proximal to the distal ileum, the diagnostic evaluation can be challenging with traditional ileocolonoscopy, resulting in delay to diagnosis [102]. In these instances, direct visualization of the entire small bowel mucosa may be necessary for a definitive diagnosis and to determine the extent and severity of disease.

Capsule endoscopy has the distinct advantage of allowing direct visualization of the small bowel mucosa and thus can detect the mucosal inflammation of Crohn’s disease that may be missed by other techniques. Early Crohn’s disease may be missed on cross-sectional imaging but can be easily detected with CE. Because of this capability, CE has the potential to play a unique role in the evaluation of patients with suspected or known Crohn’s disease. CE has been shown to be more sensitive than cross-sectional imaging for detecting superficial mucosal involvement. A metaanalysis showed an incremental diagnostic yield of 40% for CE versus small bowel follow-through (63% vs 23%; P < 0.001); of 15% for CE versus ileocolonoscopy (61% vs 46%; P = 0.02); and of 38% for CE versus CT enterography (69% vs 30%; P = 0.001) [103]. An updated metaanalysis showed that CE had an incremental yield of 42% over push enteroscopy, 37% over small bowel radiographs, 39% over CT enterography, and 15% over ileoscopy for diagnosis of nonstricturing Crohn’s disease [104]. CE was superior for diagnosis of patients with either suspected or established Crohn’s disease. The overall yield of CE has been reported to range from 43% to 71% [105–108]. A prospective study that compared CE with CT enterography, small bowel radiographs, and ileocolonoscopy for evaluation of Crohn’s disease showed that sensitivity of CE (83%) was comparable to that for CT enterography (83%), ileocolonoscopy (74%), and barium small bowel radiography (65%) [109].

**Capsule endoscopy for suspected Crohn’s disease**

Evidence suggests that CE is useful in patients with suspected small bowel Crohn’s disease after negative ileocolonoscopy and barium small bowel radiography. One study found that CE had sensitivity and specificity of 93% and 84%, respectively, in patients with suspected small bowel Crohn’s disease [110]. Perhaps more importantly, CE also has high negative predictive value of 96% for Crohn’s disease. The diagnostic yield in these patients is improved when other inflammatory markers are present or extraintestinal manifestations are expressed. When considering a diagnosis of Crohn’s disease, one should take into account the chronicity of symptoms, laboratory evidence of chronic inflammation, extraintestinal manifestations, and abdominal imaging.

One limitation of CE may be its perceived low specificity for the specific diagnosis of Crohn’s disease [109]. Although the yield for small bowel abnormalities may be high, many of these abnormalities may not be clinically relevant or specific for the diagnosis. For example, minor mucosal abnormalities may be observed in asymptomatic persons. Drug-induced adverse effects, especially those of nonsteroidal antiinflammatory drugs, can also cause mucosal changes that mimic Crohn’s disease [10]. Other causes include celiac disease, infection,
ischemia, radiation injury, autoimmune disease, and immunodeficiency. Thus the question arises of how best to interpret abnormalities found on CE.

For suspected Crohn's disease, a treatment and management algorithm is recommended. Although CE appears to have greater sensitivity for mucosal inflammation than other imaging modalities in patients with suspected Crohn's disease, there is concern about its lack of specificity, as well as the risk of retention. Because of its high negative predictive value, CE may actually be more useful for excluding Crohn's disease than for confirming it. Thus, the exact indication for CE in suspected Crohn's disease remains an area of debate and uncertainty.

**Capsule endoscopy for established Crohn's disease**

Imaging of the small bowel in patients with established Crohn's disease can often be challenging. CE has the potential to aid the evaluation and monitoring of patients with established disease, particularly when lesions are beyond the reach of ileocolonoscopy. To determine whether CE should be used for these patients, one should: (1) evaluate disease distribution and activity; (2) assess for postoperative recurrence; (3) evaluate for indeterminate colitis; and (4) assess for mucosal healing and response to medications.

**Evaluation of disease distribution and activity**

Capsule endoscopy may prove useful in evaluating the distribution and activity of inflammation in the small bowel. A validated scoring system of endoscopic activity would be beneficial. Two CE scoring systems have been published: the Lewis Score [111] and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) [112]. The CECDAI was developed and validated for use in patients with established disease to track progression and activity objectively. However, these scoring systems have not yet been incorporated into clinical practice [113].

Capsule endoscopy could also help evaluate patients who have overlapping Crohn's disease and irritable bowel syndrome. It might be used to assess for small bowel inflammation in patients with Crohn's disease who are not responding to medication, particularly if both radiology and ileocolonoscopy are negative for active disease [114–117]. If the capsule study is normal, its documented high negative predictive value may help alter patient management. However, it is unknown whether this approach is cost-effective and what its impact will be on clinical outcomes [111].

**Assessing for postoperative recurrence**

Assessing patients for postoperative recurrence of Crohn's disease can aid their long-term management. In some circumstances, CE may be beneficial in evaluating such patients, especially if lesions are not easily accessible by endoscopy. However, the use of CE in this scenario is still unclear. Some authors suggest a significant increase in the yield of CE for lesions proximal to the surgical anastomosis that may be out of reach of the endoscope [118,119]. In contrast, others suggest that CE has a lower sensitivity than ileocolonoscopy for detection of preanastomotic ulcers in the neoterminal ileum after ileocolonic resection [119]. Currently, ileocolonoscopy is generally the procedure of choice. CE may be a reasonable alternative when the anastomosis is not accessible by endoscopy or the patient wishes to avoid invasive testing.

**Evaluation of indeterminate colitis**

Capsule endoscopy may also be indicated in the management of patients with indeterminate colitis when a specific diagnosis of Crohn's disease versus ulcerative colitis cannot be made. Small, uncontrolled studies have shown that CE may detect small bowel inflammation, suggesting a diagnosis of Crohn's disease, in 29% to 40% of patients [103,120,121]. Additionally, small bowel lesions have been reclassified as Crohn's disease on the basis of capsule findings [122–125]. A negative capsule study should rule out small bowel involvement, helping to clarify the clinical picture. However, when significant inflammation in the small bowel is identified, many of these patients can be reclassified. Long-term clinical outcome studies are still needed to confirm this potential role of CE.

**Assessing for mucosal healing and response to medications**

Capsule endoscopy can be useful for monitoring Crohn's disease inflammation by helping to document mucosal healing after initiation of therapy. CE can detect subtle mucosal abnormalities in the small bowel that may be missed by conventional modalities [113]. Its high diagnostic yield may also influence disease management and outcomes; as a result of CE findings, Crohn's disease therapy has been reported to change in a substantial number of patients [111]. Symptom assessment can be a poor indicator of the severity and extent of disease, and clinical response does not always correlate with mucosal healing. There is also evidence that mucosal healing after 1 year of treatment is predictive of reduced subsequent disease activity and decreased need for active treatment [126]. If mucosal healing becomes a primary end point, CE may facilitate this assessment. Future studies are needed to evaluate the relationship between clinical response and mucosal healing as determined from CE.

**Risks and limitations of capsule endoscopy in Crohn's disease**

Potential adverse outcomes can arise when CE is used in patients with Crohn's disease. Capsule retention is the most feared complication. The risk differs by indication. At 1% to 2.5%, the incidence of capsule retention within the general population is considered low [127–130]. The risk is also low in patients with suspected Crohn's disease; this subset of patients does not seem to have a higher risk of capsule retention. The capsule retention rate in suspected Crohn's disease is 2.6%, comparable to that of
the general population [131]. The risk appears to be highest in patients with established Crohn’s disease. The single most common cause of capsule retention is a stricture [9], with retention rates as high as 13% [131]. Any patient with known Crohn’s disease who is undergoing CE should be informed of the risk of capsule retention, even in the setting of normal small bowel imaging [109,132,133].

**Deep enteroscopy techniques**
The exact indication for deep enteroscopy techniques in the evaluation and management of small bowel Crohn’s disease has yet to be determined. At this time, these modalities are not considered first-line tools in patients with small bowel Crohn’s disease. Studies suggest that they may be useful for histological confirmation of small bowel findings on CE or imaging studies. They may also be useful in the performance of therapeutic interventions. The overall yield for small bowel Crohn’s disease ranges from 5% to 13% in all patients undergoing deep enteroscopy but increases to 74% to 96% in patients with known Crohn’s disease [134,135]. Studies have shown that deep enteroscopy is useful for dilation of Crohn’s disease–related small bowel strictures and retrieval of retained capsules [136,137].

**Small bowel tumors**
The newer small bowel enteroscopy modalities have had a substantial impact on the detection and management of small bowel tumors. It is critical to diagnose tumors of the small bowel early, as most are malignant, with a poor prognosis due to their late presentation [138,139]. CE and deep enteroscopy techniques have largely replaced intraoperative enteroscopy for diagnosis of primary and metastatic small bowel tumors, although surgery is still the mainstay in the management of these patients once the diagnosis is made.

**Capsule endoscopy for small bowel tumors**
The documented incidence of small bowel tumors has increased since the introduction of CE [140,141]. The two largest studies on CE found an incidence of 2.4% for small bowel tumors in cohorts of 2000 [142] and 5129 patients [143]. The most common small bowel tumors detected on CE are gastrointestinal stromal tumors, adenocarcinomas, and carcinoid tumors [142,143]. Some authors suggest improved outcomes in patients after diagnosis of small bowel tumors on CE [69,140].

Some authors have also reported an appreciable miss rate with CE for small bowel tumors [49,67,144,145]. This limitation of CE may be related to several factors, including rapid movement of the capsule through the small bowel, inability to achieve a 360° view, and lack of insufflation of the lumen. Therefore, additional evaluation with cross-sectional imaging or deep enteroscopy should be pursued after a negative CE in patients for whom there is high suspicion for tumor.

**Small bowel polyps and polyposis syndromes**

**Capsule endoscopy for small bowel polyps**
In addition to diagnosis of small bowel tumors, CE may be helpful in the surveillance of patients with hereditary polyposis syndromes, including familial adenomatous polyposis and Peutz–Jeghers syndrome. Several series have examined the use of CE in evaluating patients with polyposis syndromes [146–151]. In two studies, CE was found to be superior to barium small bowel radiographs for detection of polyps [147,152]. Furthermore, the test was preferred by most patients because it was better tolerated than small bowel radiography. However, the usefulness of CE in the management of polyposis syndromes is not clear at this time. Patients with Peutz–Jeghers syndrome may benefit from CE rather than barium small bowel radiography, particularly for surveillance or OGIB [152,153]. However, CE is not as good as standard endoscopy for evaluating the periampullary region and duodenal polyps in the vicinity of the duodenal sweep [154].

**Deep enteroscopy**
Multiple case reports have demonstrated the utility of DBE for histopathological diagnosis of small bowel tumors [155–158]. In addition to biopsies, DBE allows for other therapeutic interventions, including polypectomy in familial polyposis syndromes, tattooing of lesions to enable their detection at surgery, palliative dilation and stent placement, and retrieval of retained CEs [159–161]. DBE also enables detection of small bowel tumors missed on prior tests, including CE [49].

In a prospective study evaluating 301 patients at a single center over 3 years, the incidence of small bowel tumors and polyps identified on DBE was 9.6% [162]. DBE enabled endoscopic resection of polyps and was useful for diagnosis and localization of endoscopically unresectable tumors. In a large multicenter study, 144 small bowel tumors were identified in 1035 patients who had undergone DBE over 5 years [163]. The most common tumors were lymphoma and gastrointestinal stromal tumors. The complication rate was 10%, with perforation as the most common adverse event. In a more recent retrospective study of 1106 patients, 12.1% had a small bowel tumor diagnosed with the aid of DBE [164].

**Celiac disease**

**Capsule endoscopy for celiac disease**
Although CE has not been studied extensively in celiac disease, growing evidence suggests that it is quite accurate in identifying changes such as villous atrophy; scalloping, layered, or stacked folds; and the characteristic mosaic appearance of the mucosa [165–171]. CE may also provide information on the extent of small bowel involvement, although its clinical significance is not clear [171]. A metaanalysis indicated that the overall pooled
sensitivity and specificity for CE was 89% and 95%, respectively [172]. CE may be helpful in elderly patients with iron-deficiency anemia, especially in those with a normal upper endoscopy [173]. Two studies confirm CE as a viable replacement for biopsy in the diagnosis of celiac disease when upper endoscopy is contraindicated or when biopsies are negative or equivocal, despite a high index of suspicion [174,175].

Less impressive findings were found in another study evaluating the correlation between CE results and the degree of villous atrophy at histology [176]. There was moderate agreement, with sensitivity ranging from 90.5% to 95.2%. However, specificity was low at 63.6%, and the positive predictive value was 100%; the negative predictive value ranged from 77.8% to 87.5%. The authors suggested that CE should not replace duodenal biopsies for diagnosis of celiac disease. This was also the recommendation of the authors of another study in which CE did not add to duodenal biopsies [177]. In a more recent study comparing endoscopy to CE, endoscopy with distal duodenal biopsies was found to be superior in detecting proximal, nonresponsive disease, although it sometimes missed more distal lesions [178]. In a metaanalysis of three studies, the overall sensitivity of CE was 83% (95% CI 71%–90%) and the overall specificity was 98% (95% CI 88%–99.6%) [179]. The authors concluded that their findings could not justify the routine use of CE as an alternative to small bowel biopsies. Other evidence suggests that CE may be useful in evaluating patients with complicated or refractory celiac disease [180–184]. In patients with refractory celiac disease, it can help detect lymphomas as well as ulcerative jejunitis [185].

Deep enteroscopy for celiac disease

There are few published reports of studies addressing deep enteroscopy in the evaluation of celiac disease. One study reviewed DBE in patients with refractory celiac disease [186]. Twenty-four procedures were performed in 21 patients. Enteropathy-associated T-cell lymphoma was found in five patients, and ulcerative jejunitis was found in two patients. Another study evaluated DBE in patients with malabsorption [187]. DBE in 12 patients with clinical malabsorption yielded a diagnosis in eight (67%), including a new diagnosis in four (33%). Duodenal biopsies in four patients yielded no diagnosis. DBE also excluded enteropathy-associated T-cell lymphoma and/or ulcerative jejunitis in patients with refractory celiac disease. Overall, DBE had a diagnostic value of 42% in patients with malabsorption of unclear origin and should be reserved for patients with unexplained malabsorption, especially when duodenal biopsies are normal.

Deep enteroscopy in endoscopic retrograde cholangiopancreatography

In patients with intestinal bypass surgery, Roux-en-Y gastrojejunostomy, Billroth II reconstruction, and/or cholecdochojejunostomy, BAE can be used to facilitate endoscopic retrograde cholangiopancreatography (ERCP) [188–194]. These studies suggest that both DBE and SBE are effective techniques. More recently, a study of 37 postsurgical patients requiring ERCP compared push enteroscopy to DBE in a stepwise approach [195]. DBE led to successful imaging in 23 of 31 patients (74.2%) compared to six by push enteroscopy (19.4%). SE has also been studied to a limited extent. Thirty-four consecutive patients with Roux-en-Y anatomy underwent 54 ERCP procedures with either SBE or SE. No significant difference was found in the diagnostic yield of SBE (48.3%) compared with that of SE (40%). The overall therapeutic yield was 93.8%, with a therapeutic yield of 100% for SBE and 87.5% for SE (P < 0.99). The mean procedure time did not differ between the two techniques. There was also no difference in complication rates [196]. In patients with altered anatomy, all deep enteroscopy techniques should be considered for facilitation of direct cholangiography.

New techniques and innovations on the horizon

A paradigm shift has occurred in gastrointestinal endoscopy with the development and use of wireless capsules that provide gastrointestinal imaging [21]. Over time, the areas of innovation in CE have included new types of capsules with improved optics and better propulsion that are capable of performing biopsies and therapeutics, facilitating targeted drug delivery, and evaluating small bowel motility.

Clinical trials are being conducted of the MiroCam capsule (Intromedic), which relies for imaging on a complementary metal oxide semiconductor chip and for image transmission on its proprietary Human Body Communication technology [197]. The human telemetry technology of the MiroCam, electric-field propagation, dramatically reduces the amount of power the capsule consumes and then uses that surplus energy for more image production, resulting in higher image resolution.

Another focus of CE research is improved optics. A new type of CE incorporates four cameras focused out the sides of the capsule (CapsoCam SV1; CapsoVision Inc, Saratoga, California). The goal of this design is to enhance diagnostic yield by circumferential inspection of the small intestine, regardless of capsule orientation.

Another advance is blue-light imaging, which uses the spectral image-processing technology known as Fuji Intelligent Chromo Endoscopy (FICE; FUJIFILMS Holdings America Corp, Saitama, Japan). As FICE is integrated into the PillCam CE system, disease recognition may be further improved.

A major disadvantage of CE technology is the inability to control the movement of the capsule through the gastrointestinal tract. Because of the large size and peristaltic movements of the stomach, it is particularly difficult to examine without a maneuverable system. Thus, some researchers are focusing on the magnetic forces that control CE movement and location within the gastrointestinal tract [198]. This approach might
result in several improvements in procedure time, real-time viewing of images, and back-and-forth navigation.

The most extensively tested navigational system involves external magnetic fields that use either a permanent magnet or an electromagnet. One maneuvering system that includes a hand-held magnet has been studied using CE in the esophagus and stomach [199,200]. Another recent prototype of a magnetically guided CE that appears feasible and accurate uses an electromagnet and joysticks; it has been tested in the stomach [201]. Also under discussion is a capsule with eight electromechanical legs for locomotion [202]. However, challenges remain in bringing these enhancements into clinical practice.

Even the latest CE technology lacks the capability of performing biopsies. To obtain mucosal biopsies via CE, some researchers have focused on the development of a spring-loaded device (similar to the Crosby capsule) guided by real-time imaging and remote manipulation [203]. Another possible CE device for microscale biopsy is a capsule with single-crystal silicon planar microspikes and protruding barbs; it uses microelectromechanical systems technology [203].

Targeted drug delivery should also be possible soon with CE. A medication-filled plastic capsule called the iPill (Intelligent Pill; Philips Research, Royal Philips Electronics, Eindhoven, the Netherlands) has been tested in animals; it has a tiny pump that can deposit medicine at a specific location in bursts or all at once. Sensors in the capsule can detect acidity and temperature, allowing the capsule to react to pH changes.

Capsule endoscopy technology may also eventually enable endoluminal analysis, so that patients with motility disorders can be evaluated more precisely [204]. With such technology, the endoscopist could detect contractile events and noncontractile patterns, contents, and parietal and endoluminal structures and their movement. The motor function of the small bowel could also be evaluated quantitatively, using computer algorithms to analyze various endoluminal features.

**Conclusion**

Significant advances have occurred in the field of small bowel enteroscopy over the past decade. CE and other deep enteroscopy techniques have enabled both diagnostic evaluation and therapeutic management of most small bowel disorders. Endoscopic tools are complementary in the evaluation of the small bowel, and their selection should be based upon clinical presentation and suspected location of the lesion, as well as therapeutic need.

Deep enteroscopy techniques are useful for evaluation and management of small bowel disorders, including OGIB, small bowel tumors, and inflammatory diseases. The noninvasiveness of CE and its ability to visualize the entire small bowel make it the preferred test for evaluating patients with small bowel disorders. Therapeutic deep enteroscopy techniques are useful in patients with abnormal CE findings and in those with high clinical suspicion for a small bowel lesion despite negative CE.

**Acknowledgment**

The authors have the following conflict of interest or financial involvement with this manuscript. Jonathan Leighton: Given Imaging Ltd, Yqoqanam, Isael: Research and Consulting; Olympus Medical Systems Group, Center Valley, Pennsylvania: Consulting; CapsoVision Inc, Saratoga, California: Research. Shabana Pasha: CapsoVision Inc, Saratoga, California: Research.

References are available at [www.yamadagastro.com/textbook](http://www.yamadagastro.com/textbook)

**Further reading**


CHAPTER 134

Colonoscopy and flexible sigmoidoscopy

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Flexible scopes for sigmoidoscopy and colonoscopy have been available since the 1960s, utilizing insertion tubes of 65 cm, 130 cm, or 165 cm in length, respectively. The flexible sigmoidoscope is used to evaluate the rectum, sigmoid, and sometimes, descending colon. The colonoscope is designed to traverse the entire colon and in many instances the distal ileum as well.

During the past five decades endoscopy has benefited from numerous technical advancements. Initially these instruments relied on fiber optics for both delivery of light and return of image. But for the past 15 years miniaturized video chips incorporated into the tips of the instruments have improved significantly the color and resolution of the images. As the view has become sharper the scopes have also become narrower with increased flexibility, and tip angulation up to 180 degrees. This has permitted navigation of tight flexures, strictures, entry to distal ileum, and retroflexed views of challenging areas like the rectum and right colon, as well as crevices between haustral folds. Other widely available improvements include variable stiffness controls for the insertion tubes, changing the color band width for better polyp detection, and foot-controlled pressurized water lavage for clearer visualization.

The range of endoscope accessories has continued to evolve as well, providing the endoscopist with a wide armamentarium for better diagnosis and therapy. Among these are spray catheters and delivery systems for dye-spraying (chromoendoscopy), larger forceps for biopsy sampling, rotatable polypectomy snares for difficult to reach polyps, electrocoagulating “hot biopsy” forceps for simultaneous tissue removal and cautery, nets and baskets for polyp retrieval, and dilating “through-the-scope” balloons. For better hemostasis there are heater probes, bipolar electrocoagulation, argon plasma coagulation, and metallic clips. Needle injectors, like the sclerotherapy instruments used in upper gastrointestinal endoscopy, are available for lifting polyps before resection, and for tattooing polyp and tumor sites for future surveillance or surgical resection. Guide wires can be introduced through the instrumentation channel and left in place after scope withdrawal so that larger balloons, or self-expanding stents can be deployed across strictures.

Colonoscopy anatomy

For the endoscopist the degree of difficulty in navigating the colon from anus to ileum can range from relatively straightforward to...
daunting. This is determined in part by such factors as the degree of mesenteric fixation of the colon that has occurred during fetal development, inherent redundancy, prior intestinal, abdominal or pelvic surgery, or colonic inflammation. The experienced endoscopist relies upon the recognition of certain anatomic landmarks. These include visualization of the spleen and liver through the colon wall at their respective flexures, the triangular configuration of the transverse colon due to the array of the three longitudinal taeniae coli, the crescent-shaped appendiceal orifice, the flattening of circular colon lumen by the ileocecal valve, and the granular, villiform, more opaque appearance of ileal mucosa, signaling a complete examination. The normal colonic mucosa is smooth and glassy, with interlacing delicate vascularity visible through the rather transparent epithelial surface. Loss of this transparency may be due to inflammation, edema, or scarification (Figures 134.1–134.4) [2].

Figure 134.1 Transverse colon. In the transverse colon the lumen typically takes on a triangular shape due to the anatomical location of the three bands of longitudinal muscle, the taeniae coli. This is a useful landmark for the endoscopist, signifying successful passage around the splenic flexure.

Figure 134.2 Hepatic flexure. The hepatic flexure is identified by the bluish tint seen through the colonic mucosa from the liver in its position on the serosal aspect of this area. Note also the arborization of the colonic vasculature visible through the healthy, glistening colonic mucosa.

Figure 134.3 Ileocecal valve. The ileocecal valve as seen by the colonoscope is identified by a central notch in the ileocecal fold just distal to the caput cecum. It is occasionally possible to see both “lips” of the valve, making intubation simpler.

Figure 134.4 Appendiceal orifice. The appendiceal orifice is a key landmark for the endoscopist, signifying intubation of the cecal caput. While there is some anatomical variation, it typically appears as a semi-lunar slit because the appendix lumen is always at an angle to the long axis of the ascending colon. The appearance is generally unchanged following appendectomy.
The position and progress of the colonoscope is assessed by identifying the anatomic features described previously. Additional secondary cues may be afforded by trans-illumination of the scope tip through the abdominal wall, the intra-colonic impression of the endoscopist’s or assistant’s palpating finger on the abdominal wall, and the length of scope inserted as indicated on the calibrated shaft of the instrument. The anatomic landmarks provide the most accurate information at the rectal and cecal extremities, whereas precise location is difficult to establish elsewhere in the colon [3]. That is why many endoscopists tattoo lesions that may require future surveillance or surgery [4].

**Preparation and medication use for colonoscopy**

**Bowel cleansing**

The quality of a colonoscopic or sigmoidoscopic examination is judged by not only having traversed the complete anatomic extent but also examining a colon that has been cleared of all fecal debris. Preliminary colon cleansing is absolutely crucial to a complete and thorough examination of the large intestine.

For sigmoidoscopy adequate preparation may require one or two enemas with hypertonic phosphate, saline, or water given within an hour of the examination. In patients with constipation, strictures, or diverticulosis adequate cleansing may not be achieved and laxatives by mouth may be required, just as for colonoscopy.

Preparing for colonoscopy usually includes a liquid diet for at least one day prior to the examination. Oral iron medications should be stopped for 5 days to remove the dark coloration of colonic contents. Constipating agents such as diphenoxylate, loperamide and narcotics should be discontinued the day before the examination. There are numerous cathartic preparations for colonoscopy, ranging from large to small volumes of hypertonic phosphate, saline, or water given within an hour of the examination. In patients with constipation, strictures, or diverticulosis adequate cleansing may not be achieved and laxatives by mouth may be required, just as for colonoscopy.

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**Sedation**

For sigmoidoscopy sedation is seldom necessary since, with proper technique, it causes minimal patient discomfort. On the other hand, colonoscopy is intrinsically uncomfortable. It involves stretching of peritoneal attachments and insufflation of air, or carbon dioxide. Pain can be minimized by meticulous
 technique on the part of the endoscopist, specifically avoiding undue insufflation of air or the creation of loops of colon during introduction of the instrument, and assiduously aspirating air upon withdrawal [2]. Despite these maneuvers, sedating medications are usually required.

There is considerable variability among patients, endoscopists and local practice customs with regards to endoscopic sedation. In some countries, routine sedation is not employed while in others anesthesia is common [9]. Depending on the circumstances, the endoscopist, an assistant, or an anesthesiologist may administer sedation. Some commonly employed agents for sedation and analgesia are intravenous meperidine, fentanyl, diazepam, midazolam and propofol. An anesthesiologist usually administers the latter agent although this may not be required in some countries [10]. It is considered standard of care to monitor patients’ blood pressure, pulse rate, and oxygenation repeatedly during colonoscopy and during recovery from the sedation.

Antispasmodics like glucagon or hyoscymamine have been utilized to reduce spasm and facilitate colonoscopy with variable success in clinical trials. Some studies have demonstrated reduced patient discomfort using these agents with the added benefit of improved colonic inspection [11,12].

**Antibiotics**

Antibiotics are often administered in the presence of a prosthetic heart valve, history of endocarditis or recent vascular graft but there is little data to support this practice. Guidelines from major GI societies and the American Heart Association do not consider routine endoscopy as a high-risk procedure requiring endocarditis prophylaxis [13]. Patients with heart murmurs, pacemakers, cardiomyopathies, or those taking immunosuppressive therapies do not routinely receive antibiotic prophylaxis.

**Colonoscopic technique**

The technique of flexible sigmoidoscopy is identical to the first stage of a total colonoscopy. The most common positioning of the patient is the left lateral decubitus. During difficult intubations it may be useful to rotate the patient to supine, prone, or even right lateral decubitus [14]. Before insertion of the scope a thorough digital rectal examination is performed. This introduces lubrication gel to ease scope passage and assesses the quality of cleansing. In addition, rectal examination can uncover prostate pathology in males, adjacent pelvic masses, distal strictures and anal sphincter defects.

Upon introduction of the scope tip air is introduced to inflate the lumen. If the tip of the scope abuts the mucosal surface the lumen will not be seen until the scope is pulled back a few centimeters. The bright light of the colonoscope affords excellent views of the walls and contents of the lumen and is reflected from the mucosal surface. The multiple twists and turns of the rectum and proximal colon require careful steering to avoid impaction of the scope tip into the colon wall. The direction in which the tip must be aimed can be gauged by maneuvering the tip of the scope away from the brightest light reflection, just as one would steer a car through a curve in a dark tunnel, heading away from where the headlight beams are reflected off the tunnel wall. Pushing the scope without knowing the direction of the lumen leads to patient discomfort from stretching of the mesentery, gives a false sense of advancement, and can lead to perforation. Looping can be suspected when the luminal view is not advancing concomitantly with the amount of scope introduced or if the scope tip actually retracts as the shaft is being advanced into the rectum. It is far preferable to pull back and reposition than to push ahead without a luminal view.

Diverticulosis often presents a technical challenge for complete sigmoidoscopy or colonoscopy since it is accompanied by haustral hypertrophy and luminal spasm, fixation of the sigmoid colon as well as false luminal openings at the diverticular orifices (Figure 134.5). Considerable finesse is required to navigate such a sigmoid colon, including pleating the lumen over the tip of the scope by the endoscopist “jiggling” the shaft of the instrument, torquing the scope, repositioning the patient, or changing to a smaller caliber scope with a more acute tip angling capability [15].

Completing the colonoscopic examination requires steering the scope around the splenic and hepatic flexures and assuring that the cecum has been reached (see Figure 134.2). The endoscopist is challenged by the tendency of the shaft of the scope to loop in the sigmoid or elsewhere in the tortuous colon. The experienced colonoscopist learns to reduce loops before attempting to introduce more scope. Additional maneuvers include twisting the shaft clockwise or counter-clockwise, withdrawing air, external pressure on the abdominal wall, and changing the patient’s position [14,16]. A sign of successful technique is to observe “one-to-one” movement, that is,
advancement of the tip of the scope equal to the amount of scope being introduced into the anus. If the patient is experiencing discomfort during the procedure the endoscopist should consider that a loop has formed or too much air has been introduced [17]. Lack of meticulous technique in the early part of the examination portends difficulty in reaching the cecum or terminal ileum. After each flexure has been passed it is useful to reduce any loops that have formed before pressing on.

One of the most common errors made in colonoscopy is to conclude that the cecum has been reached because there appears to be no luminal view ahead of the scope, or the light of the tip has trans-illuminated the right lower quadrant of the patient's abdomen. In fact the most reliable landmarks are visualization of the appendiceal orifice and the ileocecal valve, preferably with entry into the terminal ileum (see Figures 134.2–134.3). With current instrumentation it is routine to obtain photo documentation of these landmarks, as well as of any abnormalities or suspicious areas [18]. If the cecal landmarks cannot be identified reliably it is prudent to obtain a subsequent radiographic exam such as CT colonography or “virtual colonoscopy” in order to clear the right colon of any significant pathology [19].

Filling the colon with water rather than air or carbon dioxide has been reported to markedly increase the ease of intubation and to heighten patient comfort during the procedure, permitting colonoscopy to be performed without sedation. Further studies need to be conducted to assess the feasibility of water-infusion colonoscopy [1].

After confirming complete intubation the endoscopist slowly withdraws the instrument, examining the full circumference of each haustral segment. Since the right colon and rectum are the areas in which polyps may often be missed it is desirable to retroflex the tip of the scope in these areas to view the far side of the haustral folds and most distal rectum (Figure 134.6) [20].

As each section of colon is cleared air is removed and the scope withdrawn to the next segment. Some studies have correlated missing lesions with too rapid a withdrawal of the instrument and it has been recommended that a minimum of 6 minutes be devoted to that phase of the colonoscopy [21].

### Colonoscopy assistants

A quality colonoscopy requires a coordinated team of endoscopists and assistants. Among the assistant's duties are [2]:
- preparing the patient for the endoscopy suite with gowning and documenting preexam vital signs
- reassuring the patient and family
- preparing and testing the endoscopy and recording equipment, accessories, sedating medications, gloves, lubricants, gauze and absorbent pads, and fluid for lavage
- maintaining adequate and up-to-date medications for reversal of anesthesia and equipment for resuscitation
- documenting biopsy and polypectomy specimens for pathology examination
- monitoring patient comfort and vital signs during and after the examination
- assisting the endoscopist with passage of the scope; this may entail providing external abdominal pressure or temporarily holding the scope while the endoscopist manipulates the controls
- participating in performing biopsies and polypectomies by opening and closing the forceps and snare as well as injecting fluid to raise polyps for resection and to mark sites with carbon tattoos
- cleaning and disinfecting the instrument and any re-usable accessories
- monitoring the patient in the recovery area after the procedure.

Experienced assistants also can provide another set of eyes to spot small or elusive polyps, or tumors. Even the most experienced endoscopist cannot perform excellent colonoscopy without an expert supporting staff.

### Indications for colonoscopy

While the most common use of colonoscopy is to screen for colorectal cancer there are numerous indications for colonoscopy (Box 134.1).

### Screening for polyps

The initial “screening” colonoscopy is recommended for all by the age of 50. In patients with first-degree family members with polyps or cancer the initial examination should be performed by the age of 40. In families with polyposis syndromes such as Lynch or hereditary nonpolyposis colorectal cancer (HNPCC)
the initial colonoscopy is performed in the late teens or early twenties [22] (see Chapter 80).

**Polyp surveillance**

Follow-up colonoscopic “surveillance” algorithms depend upon the findings at the screening examination. A 10 year interval has been proposed for patients with screening examinations that were normal or revealed hyperplastic polyps. For those with adenomatous polyps the follow-up recommended is 3 to 5 years depending upon the number, size, and histology of the resected polyps: 3 years after removal of multiple adenomas or an adenomatous polyp with villous features, or high-grade dysplasia; 5 years after resection of one or two small adenomas. The interval is shortened if carcinoma is present in the polyp and meets criteria for nonoperative management, if there were multiple large, sessile adenomas, or in hereditary polyposis syndromes (Box 134.2) [23].

After surgical resection of colon cancer colonoscopy should be performed within the first year, especially if the cancer was obstructing and prohibited a preoperative complete colonoscopy. If this is normal subsequent surveillance colonoscopies are indicated every 3 to 5 years [24].

**Flexible sigmoidoscopy and colonoscopy: use in diagnosis**

Flexible sigmoidoscopy and colonoscopy are valuable diagnostic modalities. They provide direct vision of the colonic mucosa without the radiation exposure of barium enemas and CT scans. They also enable photo-documentation of findings and biopsies for microscopic analysis.

**Sigmoidoscopy**

Direct luminal visualization is the best diagnostic test for evaluation of the rectum and sigmoid. Bright red rectal bleeding, anal and left lower quadrant pain are common complaints for which flexible sigmoidoscopy may prove diagnostic. Hemorrhoids, anal fissures, strictures, proctitis, vascular anomalies, diverticulosis and left colon polyps and cancers can be definitively diagnosed by employing this relatively simple procedure, with easy preparation and usually no sedation [25,26]. Sigmoidoscopy can prove diagnostic in recent onset diarrhea after antibiotics due to *Clostridium difficile* by revealing characteristic “pseudomembranes”, although these findings may be present only in the higher portions of the colon and may require a full colonoscopy.

A limitation of flexible sigmoidoscopy (as well as colonoscopy) is the assessment of the anal canal. Even with careful examination and employing retrosision the anal canal can be difficult to see. The best diagnostic study for pathology here is the rigid, beveled anoscope.

**Colonoscopy**

Colonoscopy remains the gold standard for examination of the entire colon. It is widely employed for detecting polyps, tumors,
inflammatory bowel disease, diverticulosis, vascular anomalies, ischemic colitis and strictures. Colonoscopy can be useful in evaluating changes in bowel habits (constipation or diarrhea), rectal bleeding, occult blood in the stool, and iron deficiency anemia. It can identify and mark sites for surgical resection or future surveillance. In the presence of a documented malignancy of the colon it can survey for synchronous polyps. Colonoscopy does not require the prior performance of a flexible sigmoidoscopy [2].

It should be recognized that occasionally, bright red rectal bleeding originates from the upper gastrointestinal tract from varices, ulcers, or vascular anomalies of the esophagus, stomach, duodenum, or small bowel. Evidence of hemodynamic compromise is often seen in the setting of bright red rectal bleeding arising from the upper gastrointestinal tract. Upper endoscopy is the first diagnostic test in such patients and colonoscopy need not be performed in the patient who presents with red rectal bleeding when an upper GI source has been demonstrated [27].

Persistent diarrhea with negative cultures for *C. difficile* and other bacterial, amebic, and protozoal pathogens mandates colonoscopy. Infectious colitis may involve the entire colon or be segmental. Ileal as well as colon involvement may be seen in *Salmonella*, *Campylobacter*, *Yersinia*, or tuberculosis. Amebiasis may produce characteristic flask-shaped ulcers in the right colon. Colonic friability may accompany *Shigella*, *Entamoeba histolytica*, toxicogenic *Escherichia coli*, and *cytomegalovirus*. *C. difficile* may be highly suspected by seeing “psuedomembranes” (yellowish plaques of exudate) [28,29].

Ulcerative colitis, Crohn’s disease, ischemic colitis, lymphocytic, or collagenous colitis can all be diagnosed by noting the characteristic distribution and nature of the lesions or, in the case of the microscopic colitis, by biopsies. In Crohn’s disease, colonoscopic biopsies seldom reveal the characteristic granulomas. Beyond diagnosing the cause of the diarrhea, colonoscopy can identify the extent and distribution of the process, thus helping to determine the appropriateness of topical or systemic therapy [30].

Colonoscopy is performed in ulcerative colitis and Crohn’s disease of the colon not only to establish diagnosis, but also to assess the effectiveness of therapy and to survey for dysplasia or malignancy. In established ulcerative colitis and Crohn’s colitis, colonoscopy can survey for dysplasia or cancer. In chronic (greater than 8–10 years) universal ulcerative colitis or Crohn’s colitis involving a substantial portion of the colon, colonoscopy and multiple biopsies is performed on a regular basis, usually every one or two years. If indefinite or low-grade dysplasia is found the interval between colonoscopies is shortened [31]. If the dysplasia is confined to a polyp it can be removed colonoscopically just as in noncolitic colons and if there is no dysplasia in surrounding or distant nonpolypoid mucosa, regular surveillance should continue [32]. If high-grade or multi-focal low-grade dysplasia is found in nonpolypoid mucosa the patient is generally referred for colectomy [31,33]. Surgery is also recommended for patients with ulcerative colitis with strictures that cannot be traversed with a colonoscope, since the risk of cancer in such a stricture is high [34]. In Crohn’s colitis with stricture there is debate about following with CT imaging rather than surgery [35].

In established ulcerative colitis or Crohn’s disease of the colon colonoscopy has been advocated for helping to define “remission”. Recent literature has emphasized the importance of achieving “deep remission”, a designation that encompasses not only clinical improvement but also endoscopic healing of previously noted inflammatory areas [36].

### Flexible sigmoidoscopy and colonoscopy: use in therapeutics

#### Polyps

Most colon polyps can be removed via colonoscopy. Only 5% of pedunculated or broad-based polyps removed endoscopically are found histologically to contain invasive carcinoma traversing muscularis mucosa and entering submucosa [37]. Surgical resection is not necessary in pedunculated adenomas with carcinoma if there is a margin of 1 mm to 2 mm between the carcinoma and resection margin and the carcinoma is well differentiated with no evidence of lymphatic or venous invasion [38]. The use of a permanent colonic tattoo makes it possible to localize a polypectomy site with accuracy for surgery or endoscopic follow-up [4].

Pedunculated and larger sessile polyps are removed by employing an electrically activated wire snare to lasso the stalk or base of the polyp and to guillotine and coagulate simultaneously. By constricting the tissue with the closing wire snare low electrical power is sufficient for transection and heat-sealing of blood vessels. For pedunculated polyps with thicker stalks some endoscopists inject the polypectomy site on the stalk with dilute epinephrine to vasoconstrict and minimize bleeding after resection. For larger sessile polyps endoscopic mucosal resection (EMR) can be employed, whereby the polyp is elevated by pre-injection of saline (sometimes colored with methylene blue or indigo carmine) into the polyp’s base (Figure 134.7). These injections elevate the polyp on a fluid “cushion” to minimize electro-thermal damage to adjacent colon wall. This technique is useful especially in the relatively thin walled right colon. Failure of the polyp to rise on injection suggests that it may be malignant and bound to submucosa by tumor infiltration or that the surrounding mucosa has been inflamed and become fibrotic. For polyps that cannot be encircled completely with a snare, a “piecemeal” approach of sequential snare resection can be utilized. Any residual adenoma at the base can then be destroyed by fulguration with minimally opened snare tip, insulated forceps, or argon plasma coagulator. The resected multiple adenomatous fragments can be retrieved with a special basket to permit full histologic evaluation of the polyp [39]. If a polyp

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**Colonoscopy and flexible sigmoidoscopy CHAPTER 134**

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is deemed unresectable by endoscopic means biopsies can be obtained and the site marked by injection of carbon tattoo to help guide the surgeon during subsequent operative resection.

Utilizing these techniques the therapeutic endoscopist can remove very large polyps. Another more meticulous procedure to remove large polyps in one piece is endoscopic submucosal dissection (ESD), where fluid injection is given at the edge of a polyp and using short electrically active probes, the mucosa near the polyp edge is incised circumferentially. Further fluid injections into the incision line elevate the polyp under which the probes dissect the fluid-distended submucosa resulting in a complete polypectomy. Skill is necessary to prevent deep excava-
tion through the muscularis propria resulting in a perforation [40] (see Chapter 140).

Retrieval of resected polyps for pathology analysis can be accomplished by aspirating the fragments through the suction channel into a filtered suction trap, or by re-snaring the resected polyp and removing the scope with the polyp. Alternatively, by employing a through the scope net or basket, multiple frag-
ments can be captured and the scope withdrawn together with the specimen [39].

Diminutive (2 mm to 5 mm) polyps can be removed by wire snare or biopsy forceps either with or without electrocoagula-
tion. Such “cold polypectomy” is a safe alternative, avoiding thermal injury to the base and surrounding tissue [41]. Some have advocated simple resection of smaller polyps without retrieval for pathology analysis. The argument in favor of this “resect and discard” approach is that polyps of this size rarely if ever harbor malignant cells, it avoids the additional time and effort to retrieve the resected tissue and eliminates the additional costs of pathology analysis [42].

Rectal bleeding

Since colonoscopy permits direct visualization of active or recent bleeding and can offer direct therapy, it is superior to barium studies, or CT in the evaluation of rectal bleeding. A possible exception is in patients with fulminant hemorrhage, in which case a CT angiogram or bleeding scan can be useful to identify the site and intervene therapeutically with radiological techniques to control the bleeding. The preparation can be rapid with administration of an electrolyte cathartic solution. In the case of diverticular bleeding it is possible occasionally to see active bleeding emanating from a specific diverticular orifice which can be treated by injection and/or electro-cautery, or application of clips for hemostasis. However, more often, multiple diverticula are seen with blood but no active bleeding. For bleeding vascular lesions (e.g. telangiectasias, angiodyplasias, hemangiomas, and postradiation changes), electrocoagulation, argon plasma coagulation, or injection with dilute epinephrine can be effective therapy [43].

Colon polyps seldom present with significant rectal bleeding unless they are in the distal colon. However, the site of a recent colonoscopic polypectomy may bleed copiously. Rectal bleeding following polypectomy may occur within hours or days of the procedure or up to 3 weeks afterwards with premature sloughing of the clot or eschar before re-epithelialization of the colonic mucosa is complete. Sometimes the patient has resumed aspirin, nonsteroidal anti-inflammatory medication, or anti-coagulants, interfering with intrinsic hemostasis. Usually, this postpolypec-
tomy bleeding is transient. But with continued bleeding or hemodynamic instability a repeat colonoscopy can identify the polypectomy site and the bleeding stopped by injection, coagulation, clips or use of combined modalities to stop the bleeding [44].

Vascular ectasias that are bleeding can be treated with colon-
oscopy injection, or cautery. Similarly radiation proctopathy with angiectasias in patients who have received prostate or pelvic radiation therapy can be managed effectively with argon plasma coagu-
ation or dilute topicaly applied formalin [45].

Colonic obstruction

Large bowel obstruction may be due to fecal impaction, obstructing tumor, stricture, volvulus, ileus, or pseudo-
obstruction (Ogilvie syndrome). Colonoscopy can be used diagnostically and therapeutically for all but fecal impaction though added caution is often necessary to avoid perforation, possibly through creating closed loop obstructions and insufflation. Stents can be deployed via guide wires delivered through a stenosis to bridge obstructing tumors and strictures [46]. Strictures can be dilated with balloons passed through the scope and inserted through the stricture under direct vision. This technique is most useful for short strictures such as at surgical anastomoses, as opposed to the longer strictures of Crohn’s disease [47]. Volvulus can be reduced by passing the tip of the colonoscope through the twist (providing there is not advanced ischemic damage), and using suction to decompress above the
narrowing [46]. Sometimes a tube is placed and left in to prevent repeat volvulus.

**Foreign body removal**

Gallstones that have migrated to the ileo-cecal valve ("gallstone ileus"), ingested bones of fish or chicken, toothpicks, needles, dental bridges, and contraband can be removed from the colon utilizing baskets, snares, or biopsy forceps [48].

**Delivery of “therapeutic microbiome”**

*C. difficile* has become increasingly resistant to antibiotic eradication but responds to intra-colonic infusions of homogenates of “healthy” donor stool. Flexible sigmoidoscopes and colonoscopes are utilized to deliver this therapy [49].

**Colonoscopic findings**

**Polyps and cancer**

Polyps appear as protuberances from the otherwise flat, glistening background of colonic mucosa. Polyps are described as “pedunculated” or “sessile” depending on the presence or absence, respectively, of a stalk between the polyp and mucosal surface. Pedunculated polyps generally are easier to remove because the stalk separates the polyp head from the mucosal surface. Sessile polyps present the challenge of shaving the resection too close and violating the integrity of the colonic wall with electric burn or perforation or, alternatively, leaving adenomatous cells behind that can regrow into a recurrent polyp. Larger sessile polyps may need to be removed piecemeal by multiple snare applications, perhaps with preliminary injection of saline with or without epinephrine (sometimes colored with a dye) into the submucosa aimed at raising the polyp above its surrounding mucosa and using the fluid as a protective buffer beneath the polyp for the snaring and electro-cautery [39].

Histopathologically most polyps are classified as “hyperplastic” or “adenomatous”. Hyperplastic polyps are composed of relatively normal cells heaped into a protuberance; adenomatous polyps contain cells that are “dysplastic”. It is the adenomatous polyps that are considered potentially premalignant. The adenomatous polyps are sub-classified as tubular, tubulo-villous or villous, and the degree of dysplasia as low- or high-grade [50]. Macroscopic close inspection of a polyp may reveal a granular “cerebriform” pattern typical of an adenomatous polyp or the smooth texture of a hyperplastic polyp (Figure 134.7) [51]. Unfortunately, even with all the technical advances of instrumentation our ability to differentiate between these two types of polyps remains imperfect and most endoscopists try to resect all observed polyps.

In recent years, as the optical resolution of colonoscopies has improved, attention has focused on the presence of flat “serrated” polyps. These are more common in the right colon and may appear as a subtle change in texture compared to the surrounding mucosa [52]. There is some debate about the prognosis for these polyps but most endoscopists regard them as they would an adenomatous polyp with removal and follow-up within three to five years (Box 134.2) [23].

To complicate polyp identification in chronic colitis there may be “pseudopolyps” which typically have smooth surfaces and a whitish exudative cap. These polyps are primarily inflammatory and have no malignant potential and need not be biopsied or removed. A challenge for endoscopists in colonoscoping patients with long-standing colitis is to differentiate between pseudopolyps and dysplastic polyps that need to be resected.

Carcinomas tend to have a broad base and may be firm, friable, and sometimes ulcerated. When attempts to resect these broad-based lesions by injecting fluid to raise them from the surrounding mucosa are not successful, this indicates that the lesion is bound to and infiltrates the submucosa [39]. Multiple biopsies, obtained from several aspects of the lesion may be necessary to make the diagnosis definitively because many cancers have nonmalignant adenomatous or necrotic regions.

**Colitis**

Mucosal changes of colitis have a broad spectrum of abnormalities, ranging from highly friable, purulent “raw meat” appearance in severe ulcerative colitis or ischemia to a normal pattern in microscopic colitis. Ulcerative colitis, by definition, is a mucosal disease that involves the rectum and may extend upward continuously and may present as proctitis, proctosigmoiditis, left-sided colitis, or pan-colitis. In its most mild appearance there is edema, appearing as a loss of the glistening, transparent mucosa and visible submucosal vessels. More advanced colitis includes erythema, friability, exudate and ulcerations. Biopsies of involved colon will reveal inflammation. Intubation of the ileo-cecal valve in ulcerative colitis reveals a normal terminal ileum [53].

Crohn’s disease, unlike ulcerative colitis, involves all layers of the colonic wall. Therefore, the mucosal inspection afforded by colonoscopy may be less definitive than in ulcerative colitis. The earliest mucosal lesion of Crohn’s is that of small “aphthoid” ulcerations with surrounding normal appearing mucosa. In more advanced cases the ulcerations may coalesce to form an interlacing “cobblestone” appearance of edematous mucosa encircled by ulcerations. Unlike ulcerative colitis Crohn’s may spare the rectum and be discontinuous, or “skip” from one involved area to another with intervening normal mucosa. Crohn’s is more likely to stricture than ulcerative colitis and often involves the terminal ileum or may cause stenosis of the ileo-cecal valve prohibiting intubation. Biopsies of affected areas are usually nondiagnostic but will reveal nonspecific inflammation and uncommonly granulomas [53].

Surveillance for dysplasia or cancer in chronic ulcerative or Crohn’s colitis involves collecting four-quadrant biopsies from every 10 cm segment throughout the colon as well as any suspicious areas. Discrete dysplastic polyps are resected as in the noncolitic colon [31]. With the advent of chromoendoscopy some authorities have advocated spraying the entire mucosa
with dilute methylene blue or indigo carmine dye to delineate abnormalities that might be overlooked with white-light inspection. The dye can be applied through a spray catheter or by adding the coloration to the foot-controlled jet sprayer used to clean the field with water. Some society guidelines recommend obtaining biopsies only from lesions visible by chromoendoscopy (“targeting”) rather than performing multiple nontargeted biopsies throughout the colon (“random” biopsies) [54].

Ischemia produces a segmentally abnormal colonoscopic appearance, ranging from edema to erythema to frank ulceration and purplish or black blebs (“thumb-prints”) of cyanotic mucosa. The segmental distribution typical of ischemia characteristically is in the vicinity of the splenic flexure or proximal descending colon due to the lack of redundant vascularization of this colonic segment [55].

Microscopic colitis presents with nonbloody diarrhea and can only be diagnosed by colonoscopic biopsy. The macroscopic appearance of the mucosa is normal or slightly edematous. Biopsies reveal infiltration of lymphocytes or thickening of the sub-epithelial layer with collagen [56].

**Contraindications, alternatives and limitations of colonoscopy**

**Low-yield indications**

Colonoscopy has a relatively low yield in patients with established irritable bowel syndrome or chronic abdominal pain who have had previous negative colonoscopic examinations [57]. For polyp surveillance, if adequate and a careful examination was performed and the cleansing was sufficient, colonoscopy does not need to be repeated at short intervals. The polyp to cancer sequence is not rapid and the likelihood of developing an interval cancer of the colon within 10 years after careful colonoscopy is low [23].

**Contraindications**

Colonoscopy is usually well tolerated and in most cases can be performed in an office or ambulatory surgical center. But since the preparation and sedation inevitably involve some shifts of fluids and electrolytes and vagally-mediated influences from air insufflation or mesenteric stretching may all predispose to hypotension and cardiac arrhythmias, it is best to perform ambulatory colonoscopy on patients with well-controlled comorbid conditions. Recent myocardial infarction and coronary artery stenting, unstable angina, as well as poorly controlled diabetes, hypertension, pulmonary, or renal conditions are relative contraindications for elective colonoscopy [58].

Acute diverticulitis, involving as it does at least a microperforation of a diverticulum, is a contraindication for colonoscopy. Similarly, severely active ulcerative, Crohn’s, infectious, or ischemic colitis encountered on introducing the scope should discourage the endoscopist from attempting complete colonoscopy lest this result in perforation of the already inflamed colon wall. Toxic megacolon is an absolute contraindication because the diseased colon is already highly compromised [2].

**Limitations**

Colonoscopy remains the best screening and treatment modality for the colon but it is not perfect. Polyps and cancers can be missed due to sub-optimal preparation, endoscopist haste, subtle camouflaged lesions, the obscuring of abnormalities by haustral folds, or “blind spots” at the flexures, tortuous areas, caput of the cecum, and rectal ampulla. Several passes of the colonoscope may be necessary before clearing an area properly. No matter how much diligence and expertise is expended by the endoscopist there will be a small percentage of colon not scrutinized. This has been demonstrated in studies of repeat (“tandem”) colonoscopies. It has been estimated that even for “quality” colonoscopy the miss rate exceeds 25% for adenomas between 1 mm and 5 mm, 10% for adenomas between 6 mm and 9 mm, and 2% for adenomas larger than 10 mm [59]. Cancers may be missed as they can be intramucosal, hidden within strictures, or even extrinsic to the colonic lumen [60].

Finally, it must be acknowledged that complete colonoscopy is not possible in all patients, even in the most expert hands. It is crucial to admit this and seek alternative, even if less ideal, means of viewing the entire colon. As the latest guidelines encourage longer intervals between colonoscopy examinations there is more pressure on endoscopists to assure that each examination is as complete and thorough as possible.

**Alternatives**

Abdominal rapid sequence spiral CT or MR colonography can provide a reconstructed tubular view of the colonic lumen (“virtual colonoscopy”). These studies have replaced barium enema as an alternative to colonoscopy. Haustral folds, diverticula, polyps greater than 10 mm and tumors can be readily identified. In addition, the status of extra-colonic organs can be assessed. This is a reasonable alternative when patients refuse colonoscopy and is the study of choice when a colonoscopy cannot be completed to the cecum. However, its disadvantages include radiation exposure, lack of biopsy and therapeutic capability, false positives from retained stool and failure to see bleeding sites, or small, or flat lesions. As of this writing, the sensitivity of optical colonoscopy for the detection of small and flat polyps remains superior to virtual colonoscopy [19].

**Complications of colonoscopy**

**Bleeding**

Significant bleeding after diagnostic colonoscopy and conventional punch biopsies is rare. Some have suggested that these small biopsies can be taken while the patient is still therapeutically anticoagulated or remains on antiplatelet therapy [7].

Polypectomy carries a small risk of immediate or delayed hemorrhage, particularly in patients taking anticoagulants or
agents such as fentanyl and midazolam are usually uneventful. Sedation-related parenteral antibiotics.

If only a small amount of free air is present and the patient perforation requires hospitalization but not necessarily surgery be treated with liquid, or soft diet and perhaps antibiotics. Frank than a perforation. This “postpolypectomy burn syndrome” can only a transmural burn that is localized and self-sealing rather delayed for several days. Sometimes the fever and pain represent torsion and, with through and through perforation, even subcutaneous emphysema. Perforation may occur immediately or be delayed for several days. Sometimes the fever and pain represent only a transmural burn that is localized and self-sealing rather than a perforation. This “postpolypectomy burn syndrome” can be treated with liquid, or soft diet and perhaps antibiotics. Frank perforation requires hospitalization but not necessarily surgery [61]. If only a small amount of free air is present and the patient is comfortable and stable it may be safe to treat the patient with therapeutic oral anticoagulation [7].

Bleeding after polypectomy may be immediate or be delayed as long as three weeks after the procedure. It is more likely to occur in patients who have resumed antithrombotic medications. In most instances it is self-limited [61]. Patients are advised to stay on a low roughage diet and discontinue any medication that could be perpetuating the bleeding. If the bleeding does not cease or there is hemodynamic instability a repeat colonoscopy may be necessary to treat the polypectomy site. This may entail further cautery, argon coagulation, or placement of clips [62].

Perforation
The average transmural wall thickness of the distended colon is only about 2.2 mm, thicker in the left and thinner in the right colon. Despite this seemingly narrow margin for error, the perforation rate with colonoscopy is very low and has been estimated between 1 per 10 000 (0.01%) and 3 per 1000 (0.3%) colonoscopies. The reported mortality rate directly attributable to colonoscopy is approximately 0.007% [61].

Diagnostic colonoscopy rarely leads to perforation. When perforation occurs it is likely due to a linear tear of the wall caused by tangential radial force of the looped instrument. Because the tear is not in the field of vision it may not be suspected or appreciated immediately [63]. Unstable vital signs, abdominal distension, crepitus, and persistent pain after the procedure should alert the endoscopist to the possibility of perforation. Abdominal x-rays, or CT scan will be diagnostic, demonstrating free air (pneumoperitoneum) in the abdominal cavity.

When therapeutic colonoscopy is performed the thermal energy utilized to remove a polyp occasionally can burn through the full thickness of the colonic wall, resulting in perforation. Full-thickness thermal injury may lead to pain, fever, leukocytosis and, with through and through perforation, even subcutaneous emphysema. Perforation may occur immediately or be delayed for several days. Sometimes the fever and pain represent only a transmural burn that is localized and self-sealing rather than a perforation. This “postpolypectomy burn syndrome” can be treated with liquid, or soft diet and perhaps antibiotics. Frank perforation requires hospitalization but not necessarily surgery [61]. If only a small amount of free air is present and the patient is comfortable and stable it may be safe to treat the patient with parenteral antibiotics.

Sedation-related
Colonoscopies performed under intravenous sedation with agents such as fentanyl and midazolam are usually uneventful. The medications are given by the endoscopist with the assistant continually monitoring the patient’s consciousness, comfort, and vital signs. Medications to reverse the sedation are seldom necessary but should be available. Propofol is usually administered by an anesthesiologist because it produces a deeper level of sedation and requires constant vigilance. Transient hypoxia and hypotension may be noted and managed with nasal supplemental oxygen and intravenous fluids. A full armamentarium of resuscitation equipment should be fully stocked, up to date, and readily available. Patients are advised to have someone escort them home, since they may be groggy, have amnesia for the discharge instructions and may not be fully capable to make correct decisions [64].

Sepsis
It is rare for any infectious sequelae to occur after colonoscopy. Despite the reported transient bacteremia following the procedure fever, septicemia, and endocarditis are decidedly rare events. There may be occasional phlebitis at the IV site used to administer sedation. Prophylactic antibiotics may be administered in the presence of artificial heart valves or with recent joint replacement or vascular surgery but there is little evidence to support this practice [13].

Costs
Price may vary depending upon location and local markets. The cost may include endoscopist, surgical or hospital unit facility fee, anesthesiologist, pathologist, and medications. Other factors that need to be considered in the overall cost of colonoscopy are the endoscopy equipment purchase and maintenance, staffing, endoscopic accessories, and supplies. Nevertheless colonoscopy is a cost-effective tool for colon cancer screening when compared to the cost of radiographic CT equipment or treatment of colon cancer [65].

Emerging and future developments in colonoscopy
The last decade has witnessed the emergence of numerous advances and it can be anticipated that colonoscopy will continue to improve. New technologies aim to enhance the efficacy of mucosal inspection and allow for more accurate characterization of colonic lesions. While some are widely available, others are limited to specialized centers due to their expense and requisite expertise.

Toward better inspection of the colonic surface
Cap-assisted colonoscopy uses a transparent cap attached to the tip of the colonoscope to flatten haustral folds thereby increasing the visualized mucosal surface area. Alternatively, a cuff with short flexible finger-like protrusions attaches to the end of
a colonoscope with the aim of holding colonic folds open as the colonoscope is withdrawn, improving the view of the mucosa. In clinical trials, both of these devices have been shown to improve adenoma-detection rates as compared with standard colonoscopy [66,67].

A more high-tech approach to improving detection is the use of supplementary cameras to allow a wider field of view for the endoscopist. A retro-viewing camera with its own light source (Third Eye Retroscope) can be inserted through the working channel of a colonoscope to provide a continuous retrograde view of the colon during withdrawal. Images are displayed side-by-side with the standard forward view of the colonoscope. In one randomized, multi-center trial a significant improvement in adenoma detection rate was noted using such an approach as compared with standard, forward-viewing colonoscopy [68]. Another new technology uses three video chips (on the front as well as both sides of the scope tip) to provide a 330° angle view of the colon displayed on three screens. A recent randomized multi-center trial found that examinations using this device had a significantly lower adenoma miss rate than conventional colonoscopy [69]. These emerging technologies may lead to more accurate colonoscopy, fewer missed pre-malignant polyps and early malignancies, and make longer intervals between exams feasible.

**Toward closer study of observed lesions**

Chromoendoscopy, the application of dye to the colonic surface to highlight subtle abnormalities not appreciated by white light illumination, has failed to improve adenoma detection but has been reported to be effective in lesion characterization and dysplasia detection in inflammatory bowel disease (IBD) [70]. The limitations of conventional chromoendoscopy have led investigators to develop “virtual chromoendoscopy” systems. These technologies utilize light filters or postprocessing image enhancement to improve visualization of the colonic vasculature and pit pattern. Various platforms are commercially available including narrow-band imaging and autofluorescence imaging. Studies assessing adenoma detection rates using these systems have yielded inconsistent results suggesting little or no incremental benefit over white-light colonoscopy thus far [71]. Like dye-based chromoendoscopy, these modalities may serve as adjuncts to white-light colonoscopy by helping identify and characterize lesions.

Imaging technologies have evolved to allow colonoscopy to move beyond inspection of the colonic surface. Confocal laser endomicroscopy (CLE) utilizes specialized probes to generate real-time, *in vivo* histologic images that allow the endoscopist to perform a “virtual biopsy” and carry out ultra-high magnification pathologic evaluation during the procedure. CLE has the potential to be a powerful tool in accurately differentiating benign, inflammatory and neoplastic lesions in the colon [72].

EUS permits the evaluation of structures beyond the colonic wall. Colorectal EUS has proven valuable in staging neoplastic lesions. This is crucial since early cancers which have not invaded the submucosa may be amenable to endoscopic resection while more advanced lesions require surgery [73].

**Toward making colonoscopy more therapeutic**

Clips deployed through the colonoscope have been successful in sealing perforations and fistulas [74]. The use of colonic stents for obstructing lesions is becoming a more utilized treatment for obstructing colorectal malignancies [75]. With the further development of suturing or stapling accessories it can be anticipated that segmental or total colon resection may be possible through a colonoscope.

**Toward making colonoscopy easier for the patient**

Precolonoscopic preparations can be expected to become more palatable, quick, and effective. Anticoagulants will become even shorter acting and easier to stop, and subsequently resume. Sedation will be less necessary and safer. Tissue sampling will become less arduous thereby shortening the procedure of colonoscopy. Accessories can be expected to continue to improve, with safely re-usable equipment and increasing cost-effectiveness of this modality.

**Toward making colonoscopy easier for the endoscopist**

Several devices are being developed to aid in the advancement of the colonoscopy by decreasing looping of the scope thus making the procedure simpler for the endoscopist and less uncomfortable for the patient. Variable stiffness scopes, special over-tubes, “self-navigating” scopes, and “self-propelling” scopes are in development [76]. Another approach is the use of a “scope-positioning” system which employs a magnetic field locator to read the force emitted by miniaturized electromagnets embedded in the endoscope. A computer program produces a replica of scope shape as well as tip position which aids the endoscopist during insertion [77].

Tubeless endoscopy is already a reality for studying the small bowel with capsule technology and is being aggressively developed for colonoscopy. Robotic endoscopy systems are under development for both diagnostic and therapeutic purposes [76].

Colonoscopy has evolved from a primarily diagnostic to an important therapeutic procedure and is becoming more useful for treatment and cure. Just as laparoscopy revolutionized surgery so is colonoscopy likely to become an even more “minimally invasive” therapeutic modality. While many of the aforementioned devices are currently limited to tertiary-care and research centers because of their costs and unproven usefulness, it is possible that they will become more widely available in the future. It can be hoped that adopting these technologies will allow endoscopists to perform procedures with even more diagnostic accuracy and therapeutic capability.

References are available at www.yamadagastro.com/textbook
Further reading

Key references: 1, 2, 6, 21, 22, 23, 24, 39, 52, 76.

CHAPTER 135

Endoscopic retrograde cholangiopancreatography

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a specialized endoscopic procedure for the management of pancreatic and biliary diseases, in which the common bile duct and/or the pancreatic duct are accessed via papillary orifices or surgical anastomoses. Cannulation is achieved using a variety of catheter devices, typically via the accessory channel of a specialized side-viewing endoscope (also known as a duodenoscope), in order to access the biliary or pancreatic ducts. Contrast injection allows radiographic opacification of the ducts followed by therapeutic and diagnostic interventions.

Diagnostic ERCP using a specialized fiberoptic duodenoscope was first described in 1968, and biliary sphincterotomy to facilitate bile duct stone removal in 1973 [1,2]. ERCP offered a less invasive means of evaluation and management of pancreaticobiliary disorders than open surgery. Over the ensuing four decades, improvement in techniques and accessories has made ERCP the preferred modality for management of these conditions. However, ERCP is an invasive procedure that may result in localized or systemic complications with potentially significant risk of morbidity and even mortality. There has been a concerted effort to identify and understand risk factors associated with complications, and implementation of measures to minimize these complications. Simultaneously, there have been advances in noninvasive imaging modalities, including magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), and contrast-enhanced computed tomography (CT) and endoscopic ultrasonography (EUS), allowing detailed and high-resolution evaluation of the biliary tree and its surrounding structures, as well as the pancreatic duct and pancreatic parenchyma. In the current era, ERCP is primarily a therapeutic procedure used in conditions requiring drainage of the biliary and pancreatic ducts (e.g., stone or strictures, or leaks). In addition, ERCP plays a therapeutic role in the excisional or ablative management of tumors of the major or minor papilla and selected intraductal tumors. Diagnostic ERCP is now reserved for diseases in which a diagnosis remains unclear despite noninvasive imaging modalities, such as in the evaluation of indeterminate strictures of the bile duct.

Indications for endoscopic retrograde cholangiopancreatography

ERCP is now primarily a therapeutic modality for biliary and pancreatic disorders [3,4]. While there are several specific disorders that lead to the need for ERCP, the primary goal of therapeutic ERCP is to reestablish drainage of the biliary and
pancreatic ducts into the duodenum or surgically anastomosed lumen. Conditions requiring therapeutic ERCP can broadly be divided into those in which there is impairment of flow (biliary or pancreatic stones; malignant or benign strictures) and ductal leaks. Leaks may occur as a result of surgery (e.g., cholecystectomy, pancreatic resection, liver transplantation, etc.), trauma, or as a de novo complication of diseases such as necrotizing pancreatitis. Urgent or emergent therapeutic ERCP is indicated when establishing drainage is essential, with or without proven cause of obstruction, such as in the setting of ascending cholangitis. In the past, ERCP was the first-line modality in the management of patients with suspected biliary obstruction. However, the role of ERCP has evolved significantly over the last two decades [5,6].

In some situations the findings from imaging modalities are not conclusive or the exact etiology of an underlying condition may not be clear (e.g., indeterminate nature of a biliary stricture), in which case ERCP with intraductal imaging and biopsy can play an important role in diagnosis. The role of ERCP in pancreatic indications such as idiopathic recurrent acute pancreatitis and chronic pancreatitis is controversial, as the quality of evidence supporting efficacy in these settings is highly variable [7]. The role of ERCP is even more controversial in sphincter of Oddi dysfunction (SOD), a syndrome in which patients, typically young women with upper abdominal pain, with or without pancreatic and liver enzyme abnormalities and/or ductal dilation, may undergo manometry, and/or biliary and pancreatic sphincterotomy. Because SOD is associated with a high risk of ERCP-related complications, and efficacy of interventions such as biliary and/or pancreatic sphincterotomy is under some doubt, the procedure should only be considered after extensive evaluation for other etiologies of pain have been excluded.

Finally, continuing improvements in endoscopic technology and development of specialized accessories has led to the application of access and drainage outside pancreatic and biliary ductal structures. EUS may be used to obtain antegrade access to the bile duct or pancreatic duct and a wire passed through the papillary or anastomotic orifice in order to allow completion of ERCP (rendezvous procedure) when, for example, ERCP access is not possible due to duodenal or ampullary distortion by tumor, intradiverticular papilla, or postsurgical ductal anastomoses. Currently, drainage and debridement of intraabdominal and retroperitoneal collections such as pseudocysts, walled off pancreatic and peripancreatic necroses, and postoperative abscesses are now routinely performed through ERCP, but usually after access is obtained using EUS guidance. Thus, in the modern era, advanced endoscopists are increasingly using therapeutic EUS in combination with ERCP during the same or tandem procedures in the endoscopic management of pancreaticobiliary diseases.

### Complications of endoscopic retrograde cholangiopancreatography

Diagnostic and therapeutic ERCP can be associated with a variety of complications, including pancreatitis, hemorrhage, perforation, infection, and cardiopulmonary complications. In prospective series the overall short-term complication rate of ERCP is typically 5%–10% [8–13]. The severity of complications varies from mild (resulting in minimal morbidity) to severe (requiring prolonged hospitalization or additional interventions, or even long-term disability or death). Consensus definitions are widely used to report complications and to standardize outcome assessment across centers and studies (Table 135.1).

#### Table 135.1 Consensus definitions for the major complications of endoscopic retrograde cholangiopancreatography.

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Pancreatitis</td>
<td>Clinical pancreatitis, amylase at least 3 times normal at more than 24h after the procedure, requiring admission or prolongation of planned admission to 2–3 days</td>
<td>Pancreatitis requiring hospitalization of 4–10 days</td>
<td>Hospitalization for more than 10 days, pseudocyst, or intervention (percutaneous drainage or surgery)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Clinical (i.e., not just endoscopic) evidence of bleeding, hemoglobin drop &lt;3g, no transfusion</td>
<td>Transfusion (4 units or less), no angiographic intervention or surgery</td>
<td>Transfusion 5 units or more, or intervention (angiographic or surgical)</td>
</tr>
<tr>
<td>Perforation</td>
<td>Possible or only very slight leak of fluid or contrast, treatable by fluids and suction for ≤3 days</td>
<td>Any definite perforation treated medically 4–10 days</td>
<td>Medical treatment for more than 10 days, or intervention (percutaneous or surgical)</td>
</tr>
<tr>
<td>Infection (cholangitis)</td>
<td>&gt;38°C for 24–48h</td>
<td>Febrile or septic illness requiring more than 3 days of hospital treatment or percutaneous intervention</td>
<td>Septic shock or surgery</td>
</tr>
</tbody>
</table>

*Any intensive care unit admission after a procedure grades the complication as severe. Other rarer complications can be graded by length of needed hospitalization.*
Acute pancreatitis is the most common complication of ERCP, and likely results from multiple factors including injection and manipulation of the pancreatic orifice and pancreatic duct [8–23]. The risk of ERCP-related pancreatitis ranges from 2% to 20%, depending largely on patient and procedural variables, as well as on definitions used. Pancreatitis can range from mild, with pain requiring 1 or 2 days extra hospitalization, to necrotizing (Figure 135.1). Risk is highest in patients with suspected sphincter of Oddi dysfunction, reaching up to 20%, especially when combined with other risk factors, and is much lower in other conditions, for example <5% for bile duct stones. Some of the procedural and operator-related factors that increase the risk of pancreatitis are listed in Table 135.2.

There are many strategies to reduce the risk of post-ERCP pancreatitis (Box 135.1). To summarize, they consist of: (1) recognition of patient-related risk factors, with avoidance of ERCP or modification of other strategies in high-risk patients; (2) recognition and modification of procedure-related risk factors, especially in high-risk patients; (3) placement of prophylactic pancreatic stents in appropriate high-risk patients; and (4) pharmacological prevention.

Technique-related advances include use of guidewire cannulation, which has been shown in metaanalyses to reduce pancreatitis rates and improve cannulation success, presumably by minimizing contrast injection and instrumentation of the pancreas using conventional techniques [15]. The most extensively studied technique for reduction of post-ERCP pancreatitis is placement of protective small-caliber pancreatic stents (Figures 135.2 and 135.3). Pancreatic stent placement has been shown to decrease the risk of post-ERCP pancreatitis of all severities by approximately two-thirds in more than 10 prospective randomized controlled trials and at least five metaanalyses primarily involving high or very high-risk patient groups [16–22].

### Table 135.2 Risk factors for post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in multivariate analyses.

<table>
<thead>
<tr>
<th>Definite</th>
<th>Maybe</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected SOD</td>
<td>Acinarization</td>
<td>Small CBD diameter</td>
</tr>
<tr>
<td>Young age</td>
<td>Female gender</td>
<td>SO manometry</td>
</tr>
<tr>
<td>Normal bilirubin</td>
<td>Absence of CBD stone</td>
<td>Biliary sphincterotomy</td>
</tr>
<tr>
<td>History of post-ERCP pancreatitis</td>
<td>Lower ERCP case volume</td>
<td></td>
</tr>
<tr>
<td>Difficult or failed cannulation</td>
<td>Trainee involvement</td>
<td></td>
</tr>
<tr>
<td>Pancreatic duct injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic guidewire placement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic tissue sampling by any method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic sphincterotomy (major or minor papilla)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon dilation of intact biliary sphincter</td>
<td></td>
<td></td>
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<tr>
<td>Precut sphincterotomy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant by multivariate analysis in most studies.

*Significant by univariate analysis only in most studies.

*Not significant by multivariate analysis in any study.

CBD, common bile duct; SOD, sphincter of Oddi dysfunction; SO, sphincter of Oddi.

### Box 135.1 Strategies for prevention of post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis: the four Ps.

**Patient selection:**
Avoidance of unnecessary or marginally indicated ERCP, especially in higher-risk patients, by using alternative imaging techniques (magnetic resonance cholangiopancreatography, endoscopic ultrasonography, intraoperative cholangiography)

**Procedural modification:**
Efficient cannulation, minimizing pancreatic injection and instrumentation

**Pancreatic stents:**
Placement of pancreatic stents in high-risk cases

**Pharmacology:**
Administration of a prophylactic drug before or after high-risk cases
Pancreatic stent placement is increasingly used as a primary method to reduce risk of post-ERCP pancreatitis in routine practice, and is increasingly considered standard of care in high-risk circumstances [23]. However, pancreatic stent placement itself may be complicated by failed attempts, or may cause complications including migration into the duct, stent-related ductal or parenchymal injury, or duct perforation [24–27]. The optimal techniques and stents for prevention of post-ERCP pancreatitis are undergoing continuing investigation.

Pharmacological prevention of post-ERCP pancreatitis has been a long sought goal, and many agents have been investigated. Most have turned out to be disappointing or unfeasible due to prolonged administration and expense. Nonsteroidal antiinflammatory drugs (NSAIDs) administered by a rectal, but not oral route, have been demonstrated in randomized controlled trials and metaanalyses to reduce risk of post-ERCP pancreatitis by about one-half [28–30]. Excess adverse renal and bleeding events have not been seen in carefully selected patient groups. Because most studies were performed in patients at low or mixed risk of post-ERCP pancreatitis, the relative role of NSAIDs compared to or in addition to pancreatic stents is unclear and is undergoing investigation.

The risk of hemorrhage from ERCP is primarily related to sphincterotomy, and is most significantly increased in patients with ascending cholangitis, presence of coagulopathy, or treatment with an anticoagulant within 3 days of sphincterotomy [8]. Intraprocedural bleeding also elevates risk of delayed hemorrhage, but can almost always be controlled during the procedure or at a delayed presentation by the injection of dilute epinephrine, balloon tamponade, placement of clips (Figure 135.4), or placement of a fully covered self-expanding metal biliary stent (FCSEMS) for mechanical tamponade [31].

Perforation is a rare but serious complication of ERCP can occur by several mechanisms: (1) guidewire puncture may happen at any site but is rarely consequential as long as ductal drainage is achieved; (2) at the periamplillary region in the setting of sphincterotomy, which is generally more significant; or (3) at the bowel wall, especially in patients with difficult access or altered anatomy, and almost always mandates intervention of some kind. Early recognition is critical (Figures 135.5 and 135.6), and can make it possible to manage the perforation by endoscopic techniques, either closure of sphincterotomy leaks by FCSEMS, clips, or closure of sphincterotomy or bowel perforations using standard or over-the-scope clips [32,33]. Surgery is usually required for large perforations, those that
cannot be controlled by endoscopic or other minimally invasive routes, and those with delayed recognition resulting in large retroperitoneal or intraperitoneal collections.

Overall complications include pancreatitis, hemorrhage, infection, especially from occluded stents (Figure 135.7), perforation, cardiopulmonary, and others. Risk factors for overall complications are shown in Table 135.3. In the past, sedation and analgesia for ERCP was primarily administered by endoscopists or their nurses and assistants. There has been a trend towards the use of monitored anesthesia care or general anesthe-sia provided by an anesthetist. Anesthesia-related complications are now very rare (less than 0.5%). Death from ERCP complications is rare (<0.5%) and is usually a consequence of cardiopulmonary compromise, either directly from the procedure or indirectly as a result of stress from complications. Acute and chronic comorbid illnesses likely play an important role [8].

The importance of expertise in determining complications and outcomes of ERCP is intuitive and well recognized but has been difficult to demonstrate clearly in the literature. Large regional studies, mostly from European countries with centralized healthcare systems, have shown that higher case volumes are associated with improved technical success and lower complications, while some other studies do not bear out this difference, perhaps because of a different mix of cases and higher success rates at high-volume compared to low-volume centers.

Figure 135.4 Delayed hemorrhage 3 days after biliary sphincterotomy that included a protective pancreatic stent (white): (a) fresh bleeding from the cut edge of the sphincterotomy just above the pancreatic stent; (b) injection of epinephrine to control the bleeding; (c) careful placement of a single endoscopic clip on the bleeding vessel, taking care to avoid the pancreatic orifice as defined by the pancreatic stent.

Figure 135.5 Large retroperitoneal perforation recognized during a biliary sphincterotomy. Extensive air can be seen outlining the right kidney, representing a large retroperitoneal leak at the sphincterotomy site. A nasobiliary drain has been placed and contrast fills the bile duct and duodenal sweep.

Figure 135.6 Computed tomography scan showing small amount of retroperitoneal air (arrows) immediately after endoscopic ampullectomy, recognized during the procedure and treated by endoscopic clipping, with uneventful recovery.
The duodenoscope is advanced to the second portion of the duodenum and aligned with the major papilla (or minor papilla for dorsal pancreatic duct cannulation) in order to achieve access to the biliary and/or pancreatic ducts. Deep cannulation and wire placement are essential for successful completion of diagnostic and therapeutic ERCP. Access can be achieved using several devices, including papillotomes, guidewires, cannulas, and precut papillotomes. Once deep cannulation has been achieved, radiopaque contrast is injected under fluoroscopic visualization to confirm cannulation and to delineate ductal anatomy and abnormalities. Although obtaining biliary or pancreatic access may be straightforward, it can occasionally be challenging for novice and advanced endoscopists alike. Many techniques and devices can facilitate biliary or pancreatic cannulation when standard cannulation technique is unsuccessful (Figures 135.8–135.13). Increasingly, pancreatic ductal access with guidewires and protection with pancreatic stents is used to facilitate biliary access. Precut sphincterotomy refers to an incision made with a papillotome to gain entry into the desired duct, and is generally associated with increased complications, whether due to prior access attempts or the precut itself. No approach is universally superior to another in achieving biliary access and the ideal approach is determined by operator expertise and the clinical situation. When ERCP cannulation fails, in appropriate circumstances, alternative approaches include EUS-guided rendezvous to deliver a transpapillary wire that can be used for retrograde ERCP cannulation [38–41].

### Table 135.3 Risk factors for overall complications of endoscopic retrograde cholangiopancreatography (ERCP) in multivariate analyses.

<table>
<thead>
<tr>
<th>Definite</th>
<th>Maybe</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Young age</td>
<td>Comorbid illness</td>
</tr>
<tr>
<td>Suspected SOD</td>
<td>Pancreatic contrast injection</td>
<td>Small CBD diameter</td>
</tr>
<tr>
<td>Difficult cannulation</td>
<td>Failed biliary drainage</td>
<td>Female sex</td>
</tr>
<tr>
<td>Precut sphincterotomy</td>
<td>Trainee involvement</td>
<td>Billroth II gastrectomy</td>
</tr>
<tr>
<td>Lower ERCP case volume</td>
<td>Periampullary diverticulum</td>
<td></td>
</tr>
<tr>
<td>Percutaneous biliary access</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Significant by multivariate analysis in most studies
b Significant by univariate analysis only in most studies
c Not significant by multivariate analysis in any study

CBD, common bile duct; SOD, Sphincter of Oddi dysfunction.

[11,34–36]. Complications of sphincterotomy have been shown to correlate with case volume [8]. It is therefore recommended that ERCP be carried out at centers with demonstrated satisfactory outcomes, and that high-risk patients or complex procedures should be performed by expert endoscopists at specialized, high-volume centers [31,37].

### Therapeutic and diagnostic techniques

ERCP is usually performed using a dedicated side-viewing endoscope with the patient positioned prone on a fluoroscopic table. The duodenoscope is advanced to the second portion of the duodenum and aligned with the major papilla (or minor papilla for dorsal pancreatic duct cannulation) in order to achieve access to the biliary and/or pancreatic ducts. Deep cannulation and wire placement are essential for successful completion of diagnostic and therapeutic ERCP. Access can be achieved using several devices, including papillotomes, guidewires, cannulas, and precut papillotomes. Once deep cannulation has been achieved, radiopaque contrast is injected under fluoroscopic visualization to confirm cannulation and to delineate ductal anatomy and abnormalities. Although obtaining biliary or pancreatic access may be straightforward, it can occasionally be challenging for novice and advanced endoscopists alike. Many techniques and devices can facilitate biliary or pancreatic cannulation when standard cannulation technique is unsuccessful (Figures 135.8–135.13). Increasingly, pancreatic ductal access with guidewires and protection with pancreatic stents is used to facilitate biliary access. Precut sphincterotomy refers to an incision made with a papillotome to gain entry into the desired duct, and is generally associated with increased complications, whether due to prior access attempts or the precut itself. No approach is universally superior to another in achieving biliary access and the ideal approach is determined by operator expertise and the clinical situation. When ERCP cannulation fails, in appropriate circumstances, alternative approaches include EUS-guided rendezvous to deliver a transpapillary wire that can be used for retrograde ERCP cannulation [38–41].
Figure 135.9 Schematic showing “double wire” or “pancreatic guidewire” assisted biliary cannulation, in which a pancreatic guidewire is used to facilitate biliary cannulation. Pancreatic stent placement is recommended when access is achieved.

Figure 135.10 Schematic showing needle knife precut for biliary access using a freehand technique starting at the papillary orifice and cutting cephalad, with no protective pancreatic stent.

Figure 135.11 Schematic showing needle knife fistulotomy for biliary access in which the roof of the papilla is punctured directly, avoiding the papillary orifice, a technique suitable primarily for patients with prominent papilla and dilated bile duct.

Figure 135.12 Schematic showing needle knife precut for biliary access using a freehand technique starting at the papillary orifice and cutting cephalad, with prior placement of a protective pancreatic stent.
Sphincterotomy with regards to other complications, especially pancreatitis. Balloon dilation of intact biliary sphincter has been associated with a markedly increased risk of pancreatitis in one study from the United States, and a metaanalysis of pooled studies [45,46]. In contrast, studies from Asia report no significant increase in the risk of pancreatitis, especially if balloon dilation is performed for 5 min or longer rather than 1 min, as is widely done elsewhere [47–49].

Prosthetic stent placement

Prosthetic stent placement is an integral part of diagnostic and therapeutic ERCP. Stent placement is intended to optimize drainage of the biliary or pancreatic ducts. Primary indications for biliary stent placement are palliation of malignant and treatment of benign strictures, bile leaks, and to temporize or facilitate bile duct stone removal. Pancreatic stents are also placed for the treatment of recurrent pancreatitis, strictures, duct leaks, to facilitate pancreatic stone removal, and to reduce risk of post-ERCP pancreatitis.

Stents are hollow tubular devices that may broadly be divided into two categories, plastic and metal (Box 135.2). Plastic biliary stents are typically available in diameters ranging from 7 Fr to 11.5 Fr, lengths ranging from 5 to 22 cm, either straight or curved configurations, and with or without flanges or pigtails anchoring options at either end, and without or without side holes. They may be composed of hard (polyethylene) or soft (polyurethane or derivative) materials (Figure 135.14). There is no clearly demonstrated significant difference in the patency and drainage characteristics of various configurations of plastic biliary stents. However, rigid stents can be more difficult to remove in case they migrate above a stricture or inside the duct, and can result in significant bowel injury if they migrate outwards [50]. Metal biliary stents have a wire mesh design, which is either interwoven or laser cut into metal framework, resulting...

**Figure 135.13** Schematic showing transpancreatic precut sphincterotomy for biliary access, in which the papillotome is intentionally lodged in the pancreatic duct and the septum incised in order to gain biliary access.

**Box 135.2 Limitations of plastic and metal biliary stents.**

**Plastic stents**
- Excessive length to diameter
- Lack of conformability
- Early occlusion
- Risk of migration
- Bacterial colonization
- Cholangitis from stent occlusion or nondrained segments
- Difficulty in placement of multiple stents

**Metal stents**
- Placement in patients with benign disease
- Placement in wrong segmental ducts
- Preclude resection
- Tumor ingrowth
- Stone formation
- Reactive hyperplasia
- Cholangitis – early or late
- Erosion into vessels (bleeding)
biliary stents are significantly more expensive than plastic biliary stents (approximately $1000–$2600 compared to $35–$150 US Dollars). However, the cost of the stent may be offset by the need for fewer procedures and reduced procedure-related morbidity in patients who require long-term stenting. The choice of appropriate stent varies by clinical scenario, stent availability, and operator expertise.

Similar to biliary plastic stents, pancreatic stents are made of hard (polyethylene) or more recently of soft (polyurethane or derivatives) plastic and come in a variety of sizes (3 Fr–10 Fr), lengths (2–22 cm), anchoring options (with or without internal and external flanges), and external configuration (straight with dual flanges, or single pigtail) [38]. Longer stents have multiple side holes in order to optimize drainage of pancreatic duct side branches. Techniques and equipment for accessing pancreatic ducts and deep placement of guidewires and stents in pancreatic ducts are quite different from those used for biliary access. The role of pancreatic stents in specific diseases is discussed below.

Cholangioscopy

Cholangioscopes allow direct visualization of the bile duct and directed tissue acquisition as well as directed therapy, for example difficult bile duct stones. There are currently three options for cholangioscopy: (1) mother–daughter scope (Olympus America, Center Valley, PA; Pentax, Orangeburg, NT); (2) Spyglass (Boston Scientific, Natick, MA); or (3) slim or ultraslim upper endoscopes (a variety of manufacturers) [52]. In the mother–daughter system, a small choledochoscope is advanced through the working channel of the duodenoscope. This system is fragile and generally requires two operators. The Spyglass system, also referred to as a single-operator cholangioscope (SOC) system, uses a 10 Fr disposable sheath through which a fiberoptic bundle is advanced into the bile duct. There is a four-way control, as for an endoscope, in order to steer the sheath inside the bile duct. Water irrigation maintains visualization of the duct. There is an additional channel that allows tissue acquisition or advancement of therapeutic devices such as stone lithotripsy probes. Limitations of the Spyglass system are that with each subsequent use, the image quality deteriorates due to breakage of individual fibers of the fiberoptic bundle, the cost of a replacement fiber is high (> $2000) and there is a 7%–10% risk of cholangitis due to prolonged water irrigation in the bile duct [53–55]. Despite these limitations, Spyglass is increasingly popular because it requires only a single operator and allows intraductal evaluation and therapy with relative ease. The third option for cholangioscopy is the placement of an ultraslim upper endoscope directly into the bile duct. This has the advantage of providing high-quality digital video images and a large endoscope channel for devices. However, the duct may be too small to accommodate the endoscope or the scope may fall out of the ampullary opening as it is advanced due the formation of a loop in the duodenum [56–58]. The role of cholangioscopy in the management of biliary diseases is discussed later in this chapter.
Biliary diseases

Bile duct stones
The most common indication for ERCP is the removal of bile duct stones. In the past, ERCP was performed in a high proportion of patients suspected of having bile duct stones. Because such patients can now be evaluated with great accuracy using alternative less-invasive modalities, ERCP should only be considered for patients with a high suspicion of, or confirmed, bile duct stones, or in fragile patients in whom sphincterotomy is planned in lieu of cholecystectomy.

Patients with suspected bile duct stones typically present with abdominal pain, elevation of liver enzyme tests, and evidence of gallstones on imaging, for which the first-line modality is typically transabdominal ultrasound of the gallbladder. Intra ductal stones cannot be diagnosed in the majority of patients using transabdominal ultrasound as it has a low sensitivity for bile duct stones due to poor visualization of the distal bile duct. Ultrasound is sensitive for detection of dilation of the bile duct due to an obstructing stone in the duct but is a non-specific predictor of bile duct stones [59]. In the past, most such patients would undergo ERCP for diagnostic and therapeutic purposes. However, a significant proportion of patients pass their bile duct stone prior to ERCP and therefore do not need to be exposed to the risks of ERCP for diagnostic purposes alone. MRCP, EUS, and intraoperative cholangiography or ultrasonography offer alternative imaging modalities to evaluate the bile duct without exposing patients to an unnecessary ERCP [60–64]. A risk stratification system based on factors predictive of bile duct stones and an algorithm to categorize patients according to the most appropriate imaging or therapeutic modality has been developed [5].

Biliary stone removal
After biliary access is obtained, in most cases a biliary sphincterotomy is performed over a guidewire to widen the biliary orifice (Box 135.3; Figure 135.16). If sphincterotomy is contraindicated (e.g., in the setting of coagulopathy), or when preferred, the biliary orifice can be widened by stretching the biliary orifice using a balloon catheter, a process referred to as endoscopic papillary balloon dilation (EPBD). Once the papillary orifice is enlarged, most small stones can be removed using a stone extraction balloon or a wire basket. A stone extraction balloon has an inflatable balloon that is advanced into the bile duct over a guidewire. The balloon is advanced above the distal most stone and inflated to the size of the bile duct upstream from the stone. Downward traction of the catheter along the plane of the duct is then used to deliver the stone from the biliary orifice. Contrast injection through the inflated balloon (occlusion cholangiogram) can be performed to confirm that all stones have been removed. In the setting of multiple stones, stone removal is initiated in the distal duct with sequential removal of more proximal stones in order to minimize the risk of stone impaction at the biliary orifice. Stone balloon catheters come in a variety of sizes (5–20 mm) and have the advantage that they are easy to use [65]. Disadvantages are that the inflated balloon can slip past a stone in the duct and the balloon can rupture, especially in the setting of large, hard stones.

Stone retrieval baskets have four or more circumferentially arranged wires and an outer sheath. In the closed position, the basket wires are covered by the sheath. The closed basket device...
Approximately 10%–15% of patients have “difficult bile stones.” These include single or multiple large bile duct stones (usually >1 cm), stones occurring in the setting of unfavorable ductal anatomy such as a stricture below the stone, or a large stone in a small duct, and stones in patients with altered surgical anatomy. In such situations more advanced techniques are required to remove bile duct stones. Three main approaches may be used in patients with normal anatomy: (1) placement of stent in the bile duct to facilitate stone removal at a later time; (2) lithotripsy to break up stones; and (3) large balloon dilation of the biliary orifice after biliary sphincterotomy to facilitate stone removal (Figures 135.17–135.19). Each of these approaches is discussed further below and although a single technique may be preferable or sufficient to remove stones in some patients, often a combination of techniques is used for very large, multiple, or otherwise difficult stones (Figures 135.20–135.24).

Figure 135.17 Endoscopic papillary large balloon dilation to extract a very large bile duct stone after sphincterotomy but without requiring mechanical lithotripsy: very large stone (arrows), followed by balloon dilation to 15 mm (left to right).

Figure 135.18 Endoscopic papillary large balloon dilation to extract a very large bile duct stone after sphincterotomy, same patient as Figure 135.17, showing postsphincterotomy (a), 15-mm balloon dilation (b), and dramatically enlarged papillary orifice (c) allowing sight up the common bile duct and cystic duct from the duodenum.

Figure 135.20–135.24
setting to prevent distal migration of the stents into the duodenum and to facilitate stone breakdown. This approach is especially useful in patients considered to be poor candidates for prolonged endoscopic procedures, if additional equipment needed for stone removal is not available, or complete stone removal is not accomplished in a single setting. Depending on the number of stents placed, ERCP can be repeated after a period of weeks to months to remove the remaining stones. The stents may be left indefinitely in elderly patients with a plan to repeat ERCP only if signs of biliary obstruction develop [66–68].

Large balloon dilation of biliary orifice
In endoscopic papillary large balloon dilation (EPLBD) the biliary sphincter is dilated with a large-diameter (12–20 mm) dilation balloon after endoscopic biliary sphincterotomy, resulting in a very large orifice to facilitate removal of large or multiple stones with less chance of impaction in the distal bile duct or papillotomy [43,69] (Figures 135.17–135.19 and 135.23). Controlled radial expansion balloons that deliver stepwise inflation are typically used. The length of the sphincterotomy prior to dilation, size of dilation balloon, and rate and duration of inflation vary by center. It is generally recommended that the dilation should be performed slowly with gradual dilation of the balloon to a maximum and that the balloon size be limited to that of the native distal duct. In a randomized controlled trial, EPLBD with limited sphincterotomy compared to sphincterotomy alone resulted in similar success and complication rates, but significantly less need for mechanical lithotripsy and lower costs [70–74].

Overall, adverse events have been reported to occur in 7.9% of patients (156 of 1984) and included bleeding (which may be delayed) in 3.4%, pancreatitis (mild to moderate with no severe cases) in 2.6%, and perforation in 0.6% of patients in one large

Figure 135.19 Basket extraction of a very large stone using endoscopic papillary large balloon dilation after sphincterotomy, same patient as Figures 135.17 and 135.18. Basket capture (a) followed by delivery of a 2-cm stone intact into duodenum (b).

Figure 135.20 Extremely large bile duct stone (3 × 4 cm).

Stent placement
The placement of multiple stents adjacent to large bile duct stones serves three purposes. Firstly, it allows drainage of bile around large stones, thus minimizing the risk of obstruction and cholangitis. Secondly, friction from the stents rubbing against stones facilitates stone breakage and, finally, the presence of multiple stents across the biliary orifice allows dilation of the distal bile duct and orifice to facilitate stone removal in the future (Figure 135.21c). Hard polythene stents with complete internal and external pigtails are recommended in this
Figure 135.21 Extremely large bile duct stone ($3 \times 4$ cm) (a), failure of mechanical lithotripsy basket to capture stone (b), followed by placement of multiple biliary stents (c). Source: Courtesy of Rajeev Attam, MD.

Figure 135.22 Direct cholangioscopy for intraductal lithotripsy of stone in Figures 135.20 and 135.21: using pediatric forward viewing endoscope (a), single operator cholangioscopy through the duodenoscope (c), and holmium laser lithotripsy (b) performed through direct peroral cholangioscopy. Source: Courtesy of Rajeev Attam, MD.

Figure 135.23 Large balloon dilation (12 mm) to facilitate extraction of stone fragments (Figures 135.20–135.22), after placement of a protective pancreatic stent (b).
review [75]. The presence of cirrhosis, a complete sphincterotomy at the time of the large balloon dilation, and presence of a biliary stricture were associated with an increased risk of complications. Careful patient selection, a less than complete sphincterotomy, and minimal balloon dilation in patients with a biliary stricture were recommended [75].

**Lithotripsy techniques**

Fragmentation of large or difficult stones may be achieved using various approaches including mechanical lithotripsy, intraductal electrohydraulic or laser lithotripsy, and extracorporeal shock wave lithotripsy (ESWL). The specific approach is determined by the nature of the stones and the availability of equipment and expertise.

Mechanical lithotripsy is commonly used due to its relative ease and availability. Mechanical lithotripsy may be performed using standard stone removal baskets that are lithotripsy compatible or dedicated baskets designed for lithotripsy. The procedure involves capturing of a stone in the basket and application of external pressure using a dedicated lithotripsy handle. The stone is thus crushed between the basket wires and outer sheath of the basket. A wide selection of mechanical lithotripsy baskets is available [65]. The basket and stone may occasionally become lodged in the distal bile duct or biliary orifice. Many baskets therefore have a mechanism for the wires to break free if continued pressure is applied using the lithotripsy handle. In rare cases, the basket and stone may still not be removable, in which case the outer sheath of the basket and the duodenoscope are removed from the patient exposing the basket wires through the patient’s mouth. A specially designed metallic sheath can then be placed over the wire and the proximal end of the wire connected to a salvage lithotripsy handle. Cranking the handle with the locked wire in place advances the metal sheath against the trapped stone allowing the stone or the wires around it to break. Mechanical lithotripsy is widely used and stone removal can successfully be achieved in about 90% of patients with difficult stones [76–79]. When mechanical lithotripsy fails this is usually because the stone is wedged, without space in the duct for the basket to expand around the stone (Figure 135.21).

**Intraductal electrohydraulic and laser lithotripsy**

Intraductal lithotripsy techniques using electrohydraulic or laser have been gained considerable popularity over the last few years, in part due to more widespread availability of intraductal cholangioscopy. In both techniques a small probe is advanced into the bile duct and onto the stone under direct vision, and a dedicated generator provides high-frequency shock waves in a water medium using either electrical or pulsed laser energy (Figure 135.22). Stone fragmentation occurs by transmission of the shock waves from the probe to the stones through the water medium. The water medium also helps absorb the shock waves, thus minimizing the risk of ductal injury. Intraductal lithotripsy techniques are indicated in patients with large stones that are “boxed in” in a small duct, occur above a stricture, or are not amenable to removal by mechanical lithotripsy. The efficacy of both techniques has been demonstrated in several reports [54,80–83]. These technologies have the advantage that stone removal can be accomplished in the same setting as the initial ERCP, using either direct per oral cholangioscopy via a forward-viewing endoscope, or dedicated cholangioscope through the ERCP duodenoscope (Figure 135.22). The main risk with both is that of ductal injury or cholangitis from the infusion of fluid required during cholangioscopy.

**Extracorporeal shock wave lithotripsy**

In extracorporeal shock wave lithotripsy (ESWL) shock waves are generated outside the body using electrohydraulic or piezoelectric energy generators and are transmitted via a liquid medium, usually in the form of a fluid-filled cushion bath, to the area of interest including kidney, pancreatic, and biliary...
stones. The procedure typically requires general anesthesia. Because most bile duct stones are radiolucent, fluoroscopic visualization of bile duct stones may not be possible and alternative methods, such as transabdominal ultrasound imaging or ERCP-guided nasocystic drain placement to inject contrast into the bile duct or stent placement, are needed to target treatment. Although ESWL is used for pancreatic stones commonly, at least in the United States, it is rarely used for bile duct stones, due to the availability of other effective techniques to facilitate bile duct stone removal and the fact that ERCP is still required after ESWL to remove stone fragments from the bile duct.

**Role of endoscopic retrograde cholangiopancreatography in disease associated with gallstone disease**

Biliary stone disease may be asymptomatic or manifest clinically with pain, ascending cholangitis, acute pancreatitis, acute cholecystitis, or rarer complications such as cholecystoenteric fistula or impacted stone in the terminal ileum.

In general, removal of bile duct stones is recommended whether or not patients are symptomatic, due to the risk of cholangitis, pancreatitis, and other complications. In contrast, gallbladder stones generally only mandate intervention when symptomatic. While cholecystectomy is the preferred approach, patients with acute cholecystitis who are considered to be poor surgical candidates (e.g., terminal disease, in the setting of another severe acute illness, coagulopathy including advanced liver disease, etc.) have traditionally been treated with percutaneous drainage of the gallbladder (cholecystostomy). An alternative approach is to perform ERCP and place a stent through the papillary orifice and cystic duct into the gallbladder thus achieving internal drainage and avoiding the morbidity associated with percutaneous drainage catheters [84,85] (Figure 135.25).

**Biliary leaks**

Bile duct leaks most commonly result from iatrogenic injury, especially choledochojejunostomy. Although the incidence of bile duct complications after laparoscopic cholecystectomy has decreased compared to the 1990s when laparoscopic cholecystectomy was first introduced, having plateaued in the 0.2%–0.4% range, similar to that of open cholecystectomy [86–89]. Patients with aberrant intrahepatic anatomy are particularly prone to leaks and injury (Figure 135.26). Any surgical procedure involving the liver or extrahepatic biliary system may result in bile duct leaks. Bile leaks occur in up to 25% of patients after liver transplantation, with the highest incidence after living donor liver transplantation [90].

In the setting of cholecystectomy, the leak may be recognized at the time of surgery, especially if an intraoperative cholangiogram is performed or in the postoperative period, either by the presence of bile in a surgical drain or later based on symptoms and imaging. With nondrained leaks, abdominal pain, fever, and leukocytosis are typical, and some patients progress to frank peritonitis. Although a transabdominal ultrasound or abdominal CT scan may show a fluid collection suggestive of a leak, the diagnosis is most commonly made with a hepatobiliary radionuclide scan.

Optimal management of biliary leaks is determined by the degree of bile duct injury. Simple leaks from the cyst duct or a small aberrant branch of the liver to the gallbladder fossa (duct of Luschka) can be treated endoscopically. The goal of ERCP is to decrease the transpapillary pressure in the biliary system to allow preferential biliary drainage into the duodenum, permitting the leak to heal. This is most commonly achieved by placement of a transpapillary stent (typically up to 10 Fr stent) in the bile duct, with or without sphincterotomy [91]. The most commonly practiced approach, at least in the USA (including the authors), is to perform both. As a general rule, the stent does...
Endoscopic retrograde cholangiopancreatography

CHAPTER 135

or ligated duct can be crossed using an ERCP, PTC, or even EUS-guided approach, following which it may be possible to treat the ductal injury using a transpapillary approach at ERCP [95].

Biliary strictures

Biliary strictures may be benign, malignant, or indeterminate, implying that a definitive etiology cannot be determined based on initial presentation and evaluation (usually cross-sectional imaging) (Box 135.4 and Table 135.4). The role of ERCP in the management of benign strictures is to establish biliary drainage and to treat the stricture with the aim of achieving complete stricture resolution, whereas in malignant strictures the primary aim is to establish biliary drainage either prior to surgery or for palliative purposes. Evaluation of indeterminate biliary strictures represents one of the few indications for which ERCP is performed for both diagnostic and therapeutic purposes. Several ERCP-guided tissue sampling techniques, as well as intraductal cholangioscopic evaluation, may be indicated.

Benign strictures

Benign strictures of the biliary tree primarily occur in the setting of surgery, typically cholecystectomy, after surgical biliary anastomosis such as after liver transplantation (Figures 135.27 and 135.28), or in the setting of chronic pancreatitis. Other less common etiologies are shown in Box 135.4. Primary sclerosing cholangitis and IgG4 cholangiopathy are

![Figure 135.26 Cholangiograms showing a postcholecystectomy leak from an aberrant, low-insertion, right posterior sectoral duct, into which the cyst duct drained and was inadvertently injured during cholecystectomy. Leak shown by arrows (a) and 10 Fr stent placed transpapillary into right posterior sectoral duct bridging the leak (b) (arrows).](image-url)
also important causes of benign strictures but require an approach somewhat different from other, more focal benign strictures.

Biliary injury with subsequent development of strictures occurs in up to 0.5% of operations involving the biliary tree, most commonly cholecystectomy, and may occur secondary to direct injury with clips, cautery, or transection, or through indirect injury from interruption of the vascular supply to a segment of the biliary tree. Benign anastomotic strictures are discussed below. Distal biliary strictures occur in up to 30% of patients with chronic pancreatitis and may be difficult to treat because of the fibrotic and often calcified pancreatic tissue surrounding the distal bile duct. Symptoms attributable to benign biliary strictures can range from relatively mild abdominal discomfort to symptoms of obstruction with jaundice, pruritus, and even cholangitis. Left untreated, chronic biliary obstruction can ultimately lead to secondary biliary cirrhosis and eventually end-stage liver disease. Stones forming above strictures can be particularly difficult to manage because of the relatively small portal for stone extraction [96].

Prior to endoscopic or surgical therapy, great care must be taken to ensure that the stricture is indeed benign. Comparison of various sampling techniques is shown in Table 135.4. Often, as with cholecystectomy-related injury, the clinical history is sufficient to make a presumptive diagnosis. In ambiguous clinical settings such as chronic pancreatitis where there is a risk of a superimposed malignant stricture, further evaluation with

### Table 135.4

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangiography</td>
<td>74–85</td>
<td>70–75</td>
<td>74–79</td>
<td>70–82</td>
<td>72–80</td>
</tr>
<tr>
<td>Brush cytology</td>
<td>30–57</td>
<td>90–100</td>
<td>94–100</td>
<td>8–62</td>
<td>–</td>
</tr>
<tr>
<td>Endobiliary forceps biopsy</td>
<td>43–81</td>
<td>90–100</td>
<td>94–100</td>
<td>31–75</td>
<td>–</td>
</tr>
<tr>
<td>FISH</td>
<td>34–48</td>
<td>91–100</td>
<td>100</td>
<td>60–88</td>
<td>70</td>
</tr>
<tr>
<td>DIA</td>
<td>38–49</td>
<td>77–98</td>
<td>69–97</td>
<td>50–87</td>
<td>56–64</td>
</tr>
<tr>
<td>EUS without FNA</td>
<td>78</td>
<td>84</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>EUS-guided FNA</td>
<td>43–89</td>
<td>100</td>
<td>100</td>
<td>29–67</td>
<td>80–91</td>
</tr>
<tr>
<td>IDUS</td>
<td>83–91</td>
<td>50–92</td>
<td>92–96</td>
<td>67–100</td>
<td>76–90</td>
</tr>
<tr>
<td>Cholangioscopy with or without biopsy</td>
<td>89–96</td>
<td>96–100</td>
<td>89–100</td>
<td>91–96</td>
<td>–</td>
</tr>
<tr>
<td>SOC impression</td>
<td>78–100</td>
<td>77–82</td>
<td>80–88</td>
<td>80–92</td>
<td>80–89</td>
</tr>
<tr>
<td>SOC-guided biopsy</td>
<td>49–82</td>
<td>82–100</td>
<td>100</td>
<td>72–100</td>
<td>75–82</td>
</tr>
<tr>
<td>OCT</td>
<td>79</td>
<td>69</td>
<td>75</td>
<td>73</td>
<td>74</td>
</tr>
</tbody>
</table>

DIA, digital image analysis; EUS, endoscopic ultrasound; FISH, fluorescent in situ hybridization; FNA, fine-needle aspiration; IDUS, intraductal ultrasound; NPV, negative predictive value; OCT, optical coherence tomography; pCLE, probe-based confocal laser endomicroscopy; PPV, positive predictive value; SOC, single operator cholangioscopy.
endoscopic ultrasound and fine-needle aspiration may be necessary to exclude malignancy. Proximal strictures should (ideally) be evaluated by MRCP prior to ERCP. MRCP is particularly useful as it is noninvasive, does not require contrast, and allows evaluation of the bile ducts both above and below the level of the stricture. By allowing imaging of the entire biliary tree, MRCP provides a “roadmap” that can be used to plan therapy and target specific ducts at the time of ERCP.

Endoscopic management of benign biliary strictures involves balloon dilation followed by placement of one or more plastic stents to dilate the stricture and “remold” the stenotic part of the duct. This approach has been shown to be effective in multiple studies, with results depending on the location of the stricture. Common bile duct strictures respond better than strictures involving the hilum. The general approach is to place the maximal number of stents that can be accommodated in the duct(s). Stent exchange and addition of more stents if possible is performed at 3-monthly intervals for up to 1 year; this results in stricture resolution in 74%–90% of patients, with recurrence in 20%–30% of patients in both short and long-term follow-up [97–99]. Benign strictures related to chronic pancreatitis typically occur in the distal bile duct and are usually treated using the same approach involving placement of multiple plastic stents over a prolonged period of time. However, these strictures have a higher relapse rate due to the occurrence of the stricture in the setting of fibrosis and often a calcified and permanently scarred pancreas [98,100,101].

While uncovered metal biliary stents are contraindicated, FCSEMS are increasingly being used for the management of benign biliary strictures. Early results have been promising, with clinical success in up to 90% of patients. However, long-term efficacy of these stents has not yet been proven. FCSEMs...
offer the advantage of a larger lumen and more radial force than plastic stents, although the cumulative diameter of plastic stents can be greater than that of a single 10-mm FCSEMS and provide the additional benefit of biliary drainage in the space between the stents [102–104]. Placement of FCSEMS may lead to the need for fewer ERCPs due to the larger lumen of the stents. Because sludge occlusion occurs fairly frequently, ERCP is typically repeated at 3 to 4-month intervals to minimize the risk of cholangitis due to stent occlusion. Other disadvantages of fully covered stents are considerably higher cost and, depending on the type FCSEM stent used, the risk of stent migration, both into the proximal duct or out into the small intestine with some stents. Stents with antimigratory flanges can minimize the risk of migration. Some benign strictures are refractory to endoscopic therapy regardless of the type and number of plastic stents used to treat them. A multidisciplinary approach, including consultation with an experienced hepatobiliary surgeon, rather than repeated ERCPs is strongly recommended in such patients. A detailed discussion regarding the types of surgery is beyond the scope of this chapter. However, proximal strictures such as those involving the hilum or the extrapancreatic bile duct are usually treated with a bilioenteric bypass (Roux-en-Y hepaticojejunostomy).

Primary sclerosing cholangitis (PSC) is an inflammatory disease associated with scarring of the intra- and extrahepatic biliary system resulting in biliary strictures, secondary biliary stones, and, in some patients, progression to cholangiocarcinoma. The diagnosis of PSC can be made using noninvasive imaging modalities and confirmed by liver biopsy. The primary role of ERCP in patients with PSC is for the removal of stones and treatment of extrahepatic or hilar strictures (also known as dominant strictures) felt to be causing symptoms (e.g., recurrent cholangitis or stone disease) or laboratory abnormalities (e.g., elevation of alkaline phosphatase and bilirubin). Stent placement is associated with an increased risk of recurrent cholangitis in the setting of PSC, so that when possible it is recommended that strictures be treated primarily with balloon dilation [105,106]. Short-term stent placement is reserved for high-grade or recurrent strictures with the goal of removing stents at the earliest opportunity. Cholangiocarcinoma develops in approximately 10%–15% of patients with PSC. ERCP is not recommended for screening purposes due to the poor yield of tissue acquisition techniques (sensitivity of 18%–40%) and the risk of complications, especially cholangitis [107]. However, it has been recommended that brushings and biopsies (for cytological and histological analysis, respectively) be obtained from dominant strictures at the time of the initial ERCP. ERCP-guided tissue acquisition is also recommended in patients who develop a new stricture with concern for malignancy or have a deterioration in their clinical condition, for example development of jaundice, worsening liver function, or weight loss [107]. In addition to routine bile duct brushing and biopsies, cells may be collected for molecular analysis techniques, such as fluorescence in situ hybridization (FISH) to evaluate for changes in DNA, which may be suggestive of malignancy. In the setting of PSC, the addition of FISH analysis has been shown to increase the detection of malignancy but at the expense of specificity [108,109].

Malignant biliary strictures
Malignant strictures of the biliary tree may be divided into two categories: those occurring in the extrahepatic bile duct, such as in the setting of pancreatic cancer, and those occurring more proximally, also referred to as hilar strictures. Either can be due to primary tumors, local extension, or metastases. Patients with malignant biliary obstruction typically present with painless jaundice, pruritus, fatigue, anorexia, and/or weight loss. Pain usually occurs in more advanced disease, and the presentation of pancreatic cancer may be preceded by the onset of diabetes. The presence of a mass lesion in the head or neck of the pancreas resulting in a stricture of the common bile duct and the pancreatic duct, known as the double-duct sign, on cross-sectional imaging such as CT and MRI/MRC, is highly suspicious for pancreatic cancer, although chronic pancreatitis and autoimmune pancreatitis may occasionally present similarly.

Noninvasive imaging, including contrast-enhanced CT scan and in the case of hilar strictures an MRCP, should be performed prior to invasive imaging and procedures. For tissue diagnosis, endoscopic ultrasound with fine-needle aspiration of a mass lesion is the diagnostic study of choice for pancreatic cancers and, to a lesser extent, hilar tumors associated with masses. Local and regional evaluation, including tissue sampling of liver metastases, lymph nodes, and the left adrenal gland, can be done at the same time. EUS-guided sampling of the liver or the bile duct is generally avoided in patients with suspected cholangiocarcinoma who may be potential candidates for resection, or in a few centers liver transplantation, in order to minimize the risk of seeding the needle tract with malignant cells.

Distal malignant obstruction
The primary role of ERCP in the management of patients with pancreatic cancer and other causes of distal malignant obstruction is to relieve jaundice and associated symptoms. There are three main contexts for biliary stenting: prior to surgery in patients considered to have resectable disease, prior to neoadjuvant chemotherapy in patients deemed to have advanced but potentially resectable disease if the tumor is responsive to treatment, and for palliative purposes in patients with advanced disease. There is general consensus that ERCP with biliary stent placement is indicated in the latter two groups to alleviate symptoms associated with biliary obstruction (jaundice, pruritus, malabsorption, and secondary cholangitis) and to allow normalization of liver function prior to chemotherapy (neoadjuvant or palliative) [110–113]. The role of ERCP for stent placement in patients considered to have resectable disease is under scrutiny, with at least one randomized trial suggesting worse outcomes with preoperative stenting than no ERCP at all.
(1) more than 50% drainage of liver volume based on hepatic sectors was a strong predictor of drainage effectiveness, especially in Bismuth type three or IV patients; (2) intubating an atrophied sector was ineffective and was associated with increased risk of cholangitis and should thus be avoided; and (3) more than 50% volume drainage is associated with a longer survival. Achieving drainage of more than 50% of liver volume often requires more than one of three sectors to be stented – sometimes on the same lobe, sometimes opposite lobes.

Limitations of the randomized trial [104] included low technical success rates (69%–83%) and use of plastic stents rather than metallic stents, which are currently preferred for neoadjuvant therapy, a strategy not offered in that study (Figure 135.29).

**Hilar malignant obstruction**

Hilar tumors can be characterized by level of ductal obstruction, commonly referred to as Bismuth–Corlette classification I–IV, depending on the number and extent of foci of obstruction. The Bismuth–Corlette classification has a role in determining the extent of drainage, but its importance may have been overemphasized. Understanding hepatic segmental anatomy and sectoral ductal anatomy with its many variations is a prerequisite for optimal endoscopic drainage. Both CT scan and three-dimensional MRCP greatly facilitate understanding of hepatic segmental and ductal anatomy, and should be performed prior to considering ERCP, as complete injection of all sectors above the hilum poses a very high risk of cholangitis (Figures 135.30–135.33). The segmental ducts typically coalesce to form three main sectoral ducts – the right anterior sectoral duct (draining segments V and VIII), the right posterior sectoral duct (draining segments VI and VII), and the left main hepatic duct (draining segments II–IV). Variations in confluence of these sectors and differing extent of tumors, as well as replacement of sectors by tumor or atrophy, have major implications for the approach to effective and safe drainage. Whether palliative endoscopic stenting should be unilateral (perhaps best referred to as single) or bilateral (perhaps best referred to as multiple) has been debated for many years, with varying opinions based on anecdotal evidence and conflicting data [119–121]. The principle governing drainage had been that approximately 50% or greater of the liver needs to be drained for effective palliation and is associated with improved survival [122]. One study suggested that:

![Figure 135.29](image1)

- Distal malignant biliary stricture caused by pancreatic mass effect from pancreatic ductal adenocarcinoma. Cholangiogram showing stricture (a), placement of metallic stent (b), and complete drainage after deployment of stent (c).

![Figure 135.30](image2)

- Cholangiogram showing intraductal forceps biopsy of hilar malignant biliary stricture (arrow), a technique recommended in addition to brush cytology.
Increasingly, the concept of “unilateral” and “bilateral” drainage is becoming outdated.

Cumulative data, including a randomized comparative trial, support the conclusion that metallic stents are superior to plastic stents for palliation of distal tumors and hilar tumors alike, with respect to early and late complications, stent patencies, need for repeat interventions, and perhaps mortality [123–126]. Placement of a single metal stent is relatively straightforward (Figure 135.32). In contrast, placement of two metal stents can be challenging. The stents may be placed side-by-side or stent-through-stent (Y configuration) (Figure 135.33). While achievable in most cases, placement of multiple metal stents can be challenging even when performed by expert endoscopists in high-volume centers. It is essential that a diagnosis of unresectable malignancy has been firmly established and that the correct sectors and segmental ducts be accessed before placement of a metallic stent. When in doubt, plastic stenting is a reasonable substitute [127].

Localized treatment of malignant hilar strictures, typically for palliative purposes in the setting of unresectable disease, can be performed during ERCP using photodynamic therapy (PDT) or radiofrequency ablation (RFA). PDT involves the systemic administration of a photosensitizing agent, which is activated locally in the region of the tumor using a light emitting probe introduced via ERCP. The main risks associated with PDT are cholangitis (up to 25% of patients) and phototoxicity (in about 10.2% of patients), the latter from exposure of the skin to natural light. PDT has been shown to add survival advantage compared with plastic stents alone in a number of studies [128,129]. Problems with these data are that the control groups received conventional plastic stents, which are known to perform poorly in hilar malignancy.

A more recent development has been the introduction of a bipolar catheter, which uses radio waves to generate heat to destroy tumor cells locally. The Habib EndoHPB (EMcision UK, London, United Kingdom) has been used for both malignant hilar and pancreatic cancer-related strictures [130,131]. Ablation in the region of the cyst duct may lead to cholecystitis due to obstruction of the cystic duct and thermal injury in the hilum predisposes patients to the development of cholangitis as well as localized infections, including abscess formation. Although, preliminary reports using this device described encouraging short-term results with minimal complications, long-term follow-up and large studies demonstrating the efficacy of this device are needed [130,132].
**Indeterminate biliary strictures**

Determining the etiology of a biliary stricture based on clinical presentation and initial imaging modalities may be challenging. Diagnosis requires a multimodality approach including blood tests and cross sectional radiological studies (CT and MRI/MRCP, and EUS). ERCP should generally be reserved as the last step for tissue acquisition as well as therapy. Several techniques for biliary evaluation and tissue acquisition have been described (Table 135.4) [73]. Tissue sampling at ERCP should almost always include both brush cytology and forceps biopsy (Figure 135.30), due to substantially higher yield than either alone. Tissue obtained from ERCP may be sent for routine cytology, histology, and advanced cytological techniques such as FISH or digital image analysis (DIA) to evaluate for molecular changes in the DNA of biliary epithelial cells that may be suggestive of malignancy. Intraductal assessment may include intraductal ultrasound to assess for duct wall abnormalities and direct visualization by cholangioscopy with or without directed biopsies. The biliary epithelium may be evaluated for visual abnormalities using confocal laser endomicroscopy which allows for high resolution in vivo histological assessment and optical coherence tomography, which uses localized infrared light technology. Currently, the utility of the latter two techniques is limited by high cost, subjectivity, and lack of interobserver agreement [133–135].

The role of direct cholangioscopy in unexplained biliary strictures is not settled at present. While conceptually appealing, direct cholangioscopy in its most widely available form is expensive, leads to cholangitis in 7%–10% of cases due to required infusion of fluid, and allows only limited visualization and subjective diagnosis. Cholangioscopically directed biopsies are currently tiny (1 mm), providing smaller tissue samples and lower yield, and have a lower reported sensitivity of 57% and accuracy of 78% compared to fluoroscopically directed biopsies, which have a sensitivity of 76% and accuracy of 88% [136]. EUS obviates the need for cholangiography in approximately 60% of cases, and the combination of all of the above approaches leads to a tissue diagnosis in over 90% of patients [137]. Direct cholangioscopy may be reserved for a second ERCP if all of the above strategies including EUS fail to yield a diagnosis [138,139].

Cells obtained for cytology may be evaluated for DNA abnormalities using FISH and DIA. FISH is a cytogenetic technique in which fluorescently labeled DNA probes are used to detect the presence or absence of specific DNA sequences. A test of FISH positivity (that is the presence of two or more copies of specific chromosomes, usually 3, 7, 17, and 9p21) has been shown to increase the detection of malignancy [108,109]. In DIA, computer analysis of the nuclear DNA content and nuclear features is performed after digital conversion of images of cells obtained at cytology [140,141]. Both techniques are more sensitive than cytology alone, but at the expense of specificity. Thus the overall advantage of DNA probes in evaluating unexplained biliary strictures is not clear at this point.

**Endoscopic retrograde cholangiopancreatography after liver transplantation**

Complications of the biliary tract affect approximately one-third of patients after liver transplantation and result in significant patient morbidity and increased patient mortality [90]. The spectrum of biliary complications includes biliary leaks, strictures, choledocholithiasis, cast formation, papillary stenosis, and other less common conditions. An anticipatory approach and a clear understanding of the risk factors for biliary complications following liver transplantation can result in the prompt diagnosis and management of these conditions.

![Figure 135.33](image135.33.png) Cholangiograms showing placement of dual uncovered metallic stents in a "Y" configuration (stent-through-stent). The first stent has been deployed in the left hepatic duct and a second stent is passed through the lumen of that stent into right anterior sectoral duct (a), followed by deployment showing "Y" configuration (b).
Biliary strictures after liver transplantation are characterized as anastomotic strictures (Figure 135.28) or nonanastomotic strictures (Figure 135.29), which are also called ischemic strictures. Anastomotic strictures are usually short segmental areas of stenosis involving the ductal anastomosis, occur early, and are characterized by the formation of scar tissue at the anastomotic site. Nonanastomotic strictures are long, are thought to be the result of ischemic injury to the duct, and may be associated with obvious vascular compromise (hepatic artery or portal vein occlusion) or secondary causes resulting in vascular injury (cytomegalovirus, ischemia time, ABO incompatibility). Ischemic strictures are more common after donor after cardiac death (DCD) than conventional deceased donor liver transplant (DDLT). The principles of stricture management are similar to those discussed for nontransplant patients.

MRCP is the study of choice in the diagnosis of strictures. ERCP is the first-line treatment modality in the management of biliary complications and is successful in the majority of patients, with PTC reserved for situation in which ERCP is not successful (e.g., a disconnected duct or high-grade stenosis that cannot be traversed at the time of ERCP) or after Roux-en-Y hepaticojejunostomy if the biliary anastomosis cannot be reached despite enteroscopy assistance (Figure 135.34). A clear understanding of the different types of surgical reconstruction during liver transplantation is vital to the appropriate management of biliary complications and, similar to hilar strictures, a thorough understanding of the normal and variant anatomies of the liver segments and their individual and sectoral ducts is also essential. Compared to conventional DDLT, the risk of biliary complications is increased in patients who receive a liver from DCD or a living donor (LDLT).

In anastomotic strictures, multiple stents are placed in the bile duct with stent exchange and/or placement of additional stents every few months until the stricture resolves. Alternatively, FCSEMS may be used. Nonanastomotic strictures, like other hilar strictures, are more challenging due to the small size of the intrahepatic ducts and difficulty in the placement of multiple stents. In general, anastomotic strictures resolve within 3–6 months whereas nonanastomotic strictures require a long duration of therapy [99,142–145]. Anastomotic strictures after LDLT require longer stent therapy than in patients with conventional DDLT [146,147].

Biliary stone disease is common after liver transplantation and may occur independently or in the setting of strictures due to impairment in biliary flow. The formation of multiple, long, and diffuse stones, known as biliary casts, is a unique form of stone disease in the setting of liver transplantation. The exact etiology of biliary cast disease is not known but it has been associated with ischemia and strictures. Stone management is similar to that in nontransplant patients with the potential need for cholangioscopy and other advanced techniques for casts or stones occurring above strictures. Rarely, patients with a Roux-en-Y hepaticojejunostomy may require percutaneous cholangioscopy with electrohydraulic or laser lithotripsy for intrahepatic stone removal.

Biliary leaks commonly complicate liver transplantation with a higher incidence in patients with a DCD and LDLT. They usually occur in the early postoperative period. Biliary leaks are typically treated with placement of a biliary stent to bridge the leak, usually with sphincterotomy. If there is an associated biliary stricture, the stricture can be carefully dilated, and one or more stents can be placed beyond both the stricture and the leak though this is usually avoided in the first few weeks following surgery. ERCP results in resolution of >85% of leaks [142,148,149]. FCSEMS have been used in the treatment of biliary leaks considered to be refractory to conventional treatment. Despite improvements in endoscopic techniques, stents, and deep enteroscopy techniques, endoscopic therapy may not be successful or feasible in certain situations. Large anastomotic leaks (e.g., in the setting of hepatic artery compromise) may not heal with endoscopic therapy. Similarly, leaks from a perforation or compromise of a Roux-en-Y anastomosis may require surgery because of an inability to reach the anastomosis for definitive treatment.

**Ampullary tumors**

A wide variety of benign and malignant tumors involve the major or minor papillas. The most common are ampullary adenomas, which like colonic adenomas have a potential for progression to malignancy. Ampullary adenomas may occur sporadically or in the setting of familial adenomatous polyposis. ERCP allows diagnosis and often removal of ampullary tumors.
Narrow-band imaging or dye-assisted endoscopy may allow more detailed evaluation of the ampullary mucosa, and to obtain repeat biopsies of the ampullary region. EUS, MRI/MRCP, or intraductal ultrasound at ERCP can be used for staging, which is recommended for lesions greater than 2 cm in size and those with features suggestive of malignancy (ulceration, bleeding, induration) [150,151].

Candidates for endoscopic resection are ampullary tumors with: (1) size less than 4–5 cm, (2) benign histology, (3) no endoscopic evidence of malignancy, and (4) no ductal invasion [152,153]. A wide variety of techniques using various devices have been described for the resection of ampullary tumors (ampullectomy). In general, given the higher risk of complications (5%–56%, mean 19%) including retroperitoneal perforation (0%–7%, mean 0.4%), bleeding (0%–17%, mean 4%), and pancreatitis (0%–33%, mean 10%), only endoscopists with extensive expertise should perform endoscopic ampullectomy [153]. Pancreatic stent placement has been shown to decrease the risk of pancreatitis in a randomized controlled trial as well as case–control series [154,155]. Late complications such as papillary stenosis may occur. The reported clinical success of endoscopic ampullectomy varies from 29% to 100%, with an overall success rate of 79% [153]. All patients require surveillance for recurrence of adenomatous tissue even after seemingly complete resection is achieved.

**Endoscopic retrograde cholangiopancreatography in pancreatic disease**

Over the last two decades, considerable strides have been made in diagnosis and management of pancreatic diseases. Simultaneously, improvements in endoscopic technologies and techniques have enabled ERCP to play an increasingly safe and effective role in the management of pancreatic diseases. ERCP for pancreatic diseases is technically more demanding and riskier than ERCP for most biliary conditions. It should ideally be performed by dedicated endoscopists with advanced endoscopic expertise in a multidisciplinary context, including the disease processes and involvement of specialized surgeons and interventional radiologists as appropriate.

**Acute pancreatitis**

Several excellent guidelines have been published regarding management of acute pancreatitis, and specifically the role of ERCP in acute biliary pancreatitis [156–158].

ERCP may be indicated early in the course of the disease. However, even in this setting, the obstructing gallstone often passes through the ampullary orifice spontaneously, usually resulting in resolution of biliary and pancreatic obstruction and obviating the need for ERCP. Depending on the clinical picture and laboratory findings, in patients in whom there is a suspicion of a persistent stone in the bile duct an EUS, MRCP, or intraoperative cholangiography at the time of cholecystectomy should be performed for further evaluation. Pooled data from seven prospective studies, with a total of 757 patients, designed to evaluate the role of early ERCP versus conservative management of patient with acute biliary pancreatitis was reported in a metaanalysis [159]. ERCP was shown to be beneficial in two settings: (1) acute cholangitis, where it was associated with a decreased risk of mortality and local and systemic complications; and (2) persistent biliary obstruction, where it was associated with a decreased risk of complications. Importantly, routine ERCP in all patients with biliary pancreatitis was not found to improve mortality or local and systemic complications regardless of the predicted severity of pancreatitis. Thus, ERCP should be performed urgently (usually within 12 h) in patients with acute biliary pancreatitis with concomitant acute cholangitis and early in the course (usually within 24–72 h) in patients with evidence of persistent biliary obstruction.

**Complications of acute pancreatitis**

The definitions of localized complications associated with pancreatitis have been updated in order to simplify and standardize terminology and develop evidence based guidelines for their management [160]. According to the revised Atlanta criteria, there are now thought to be only four types of collections associated with pancreatitis: acute peripancreatic fluid collection occur in interstitial edematous pancreatitis; pancreatic pseudocysts are a delayed (usually >4 weeks) complication of interstitial edematous pancreatitis and are rare after acute pancreatitis; and necrosis, which may be an acute necrotic collection (in the early phase and before demarcation), or walled-off necrosis, which is surrounded by a radiologically identifiable capsule (the latter rarely develops before 4 weeks have elapsed from onset of pancreatitis). Indications for intervention include infection, biliary or gastric obstruction, and disconnected pancreatic duct [161]. Interventions for necrotizing pancreatitis have undergone a paradigm shift towards minimally invasive techniques and away from open surgical necrosectomy, with endoscopic necrosectomy emerging as a principle form of treatment. Several multicenter studies, a randomized trial, several evidence-based guidelines, and consensus statements have all endorsed the safety and efficacy of this technique [156,157,161–166]. Endoscopic transpapillary drainage and necrosectomy are generally performed using combined endoscopic ultrasound and ERCP techniques. The specific role of ERCP in these settings is to treat associated biliary obstruction, and to evaluate and treat pancreatic duct leaks or disruptions. Side leaks with an intact main pancreatic duct almost always respond to transpapillary pancreatic stenting. In contrast, pancreatic necrosis in the central portion of the pancreas may result in a completely disconnected pancreatic duct proximal and distal to the area of the necrosis. Transpapillary pancreatic stent placement may or may not help in this circumstance, and these patients may be best managed with long-term transmural stents (e.g., cystgastrostomy stents) to rechannel drainage of the disconnected portion.
of the pancreas, or by surgery to drain or remove the disconnected portion of the pancreas [161].

Recurrent acute pancreatitis
It is estimated that 20% of patients with acute pancreatitis will have one or more additional episodes of acute pancreatitis during their lifetime. Although there is no universally accepted definition, recurrent acute pancreatitis (RAP) is generally defined as the occurrence of two or more episodes of acute pancreatitis (see Chapter 82). The spectrum of conditions associated with RAP includes biliary disease (often in the form of microlithiasis not visualized by conventional cross-sectional imaging), persistent alcohol use, congenital anomalies of the pancreaticobiliary tract (pancreas divisum, annular pancreas, anomalous pancreaticobiliary junction) or duodenum (duplication cyst), genetic causes (SPINK1, PRSS1 or CFTR and other mutations), potentially sphincter of Oddi dysfunction (highly controversial), and idiopathic disease. Given the broad range of conditions associated with RAP, it is important to perform a thorough diagnostic evaluation of patients with noninvasive or minimally invasive imaging modalities such as MRCP and EUS and, in selected patients, genetic testing (typically in young patients with or without a family history of pancreatitis or cystic fibrosis).

ERCP is often performed in these patients in the hope that pancreatic sphincterotomy and/or stent placement in the major or minor papilla (Figures 135.35 and 135.36) will interrupt the cycle of recurrent pancreatitis by improving pancreatic drain-

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**Figure 135.35** Illustration showing anatomy of pancreas divisum.

**Figure 135.36** Endoscopic view of minor papilla with no visible structure or landmarks (a), and open orifice of minor papilla after spraying methylene blue and intravenous secretin administration (b).
age. Although ERCP may result in an improvement in symptoms and/or RAP episodes in some settings, the response is unpredictable, and evidence supporting efficacy of ERCP for RAP is highly variable, with very few randomized prospective trials, and substantial remaining controversy [167–169]. ERCP for RAP is technically challenging and associated with a high risk of complications, including post-ERCP pancreatitis in up to 20% of patients. Indwelling pancreatic stents may lead to ductal and parenchymal injury, strictures, and subsequent chronic pancreatitis. RAP itself often progresses to chronic pancreatitis (either obvious or subtle) and/or chronic pain irrespective of any endoscopic intervention.

Pancreas divisum is the most common congenital abnormality of the pancreatic ductal system, resulting from failed fusion of the dorsal and ventral anlage in the second month of gestation (Figure 135.35). Pancreas divisum occurs in approximately 7% of the Western population. Although usually asymptomatic, pancreas divisum may be associated with chronic pain, RAP, or chronic pancreatitis. Endoscopic minor papillotomy, intended to relieve intraductal pressure, has gained acceptance as the preferred treatment for clinical manifestations of pancreas divisum (Figure 135.36). Unfortunately, the efficacy of minor papillotomy has not been clearly established, as no randomized controlled trials have been performed. The majority of literature on this topic consists of retrospective case series with outcome measures of varying validity [170–172]. An older randomized trial of routine minor papilla stent exchange without papillotomy suggested significant improvement [167]. Most problematic in the literature regarding pancreas divisum is failure to measure quality-of-life and chronic pain burden, which are often substantially impaired in patients with pancreas divisum and recurrent pancreatitis, whether or not there is obvious morphological evidence of chronic pancreatitis. The response rate to ERCP with minor papillotomy and stent placement varies considerably by study and indication with poorest response for pain alone (25%–44%) and a slightly better response reported in the setting of chronic pancreatitis (45%–55%) [173]. An NIH-funded multicenter, pilot study evaluated the role of ERCP in patients with RAP (two or more episodes) in the setting of pancreas divisum [169]. In this study, pain and disability were measured using a validated instrument: at 6-month follow-up, only 8.3% of patients had recurrence of pancreatitis and the overall pain score was reduced from 4 to 1, including a significant decrease in the number of days associated with pain disability. In this study, the risk of ERCP-related pancreatitis was relatively low (5.6%) compared to more typical rates of 8%–11.2%. ERCP for pancreas divisum should be performed at expert centers and preferably in the context of prospective studies.

Congenital conditions such as annular pancreas, anomalous pancreaticobiliary junction, and duodenal duplication cysts are all conditions that may be associated with RAP. Annular pancreas may be associated with pancreatitis or gastric outlet obstruction. ERCP may be performed for RAP to ensure adequate pancreatic drainage. However, ERCP has no beneficial role in patients with chronic pancreatitis or duodenal stenosis related to annular pancreas. Anomalous pancreaticobiliary junction is defined as the presence of a common biliary and pancreatic duct channel measuring more than 15 mm in length, and may be associated with a congenital dilation of the biliary tree referred to as choledochal cysts, which are classified according to their location along the biliary tree (see Chapter 91). The risk of cholangiocarcinoma and gallbladder cancer is increased in the presence of choledochal cysts. ERCP with sphincterotomy may be beneficial for RAP but in order to minimize the risk of malignancy cholecystectomy, surgical excision of the choledochal cyst is recommended [174,175]. In patients with choledochal cysts involving the main bile duct (type I and IV), a pancreatic stent can be placed prior to surgery to allow identification of the pancreatic duct at the time of the surgery and enable the surgeon to excise the bile duct as close to the pancreatic duct as possible in order to minimize the risk of malignancy and recurrent pain or infection from the retained biliary stump.

The role of ERCP in diagnosis and treatment of sphincter of Oddi dysfunction is highly controversial, and is addressed in detail elsewhere (see Chapter 93) [151,156].

Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is an inflammatory condition of the pancreas mediated by the autoimmune system associated with characteristic findings on imaging and histological assessment of the pancreas and characterized by being responsive to corticosteroid therapy (see Chapter 83). AIP has been subdivided into two types. Type 1 AIP is a manifestation of IgG4 disease, is often associated with serum IgG4 elevation, presence of IgG4 cells in pancreatic parenchyma, a characteristic pancreatic histological pattern known as lymphoplasmacytic sclerosing pancreatitis, and is often associated with involvement of other organs including salivary glands, retroperitoneal fat, and the intra- and extrahepatic biliary tree. Type 2 AIP is associated with normal IgG4 levels in the serum and pancreatic tissue, typically does not involve additional organs, and is associated with a histological pattern of neutrophils in the pancreas with characteristic granulocyte–epithelial lesions. Type 2 AIP is more common in the United States and Europe and rare in East Asia, typically occurs in younger patients, may be associated with inflammatory bowel disease, and may present with acute pancreatitis [176–183]. ERCP findings suggestive of AIP include a long (more than one-third the length of the pancreatic duct) stricture, multifocal strictures of the pancreatic duct, and mild dilation of the pancreatic duct upstream from strictures (<5 mm), whereas a focal stricture with marked dilation of the upstream pancreatic duct is more consistent with pancreatic malignancy [183]. A concomitant biliary stricture may be present in both conditions. ERCP has a reported sensitivity and specificity of 33%–91% and 80%–90%, respectively, for differentiating AIP from pancreatic cancer [184]. ERCP is
Pancreatic duct stones

Obstructing pancreatic duct stones may result in pain or disruption of the upstream duct and a pseudocyst. Stone removal can be accomplished using ERCP alone (Figure 135.37), ESWL alone, or a combination of the two. The exact approach is determined by the size and location of stones, the overall stone burden, and local expertise. Small pancreatic stones can be removed at ERCP using a stone removal basket after a pancreatic sphincterotomy. Unlike biliary stones, pancreatic stones are usually calcified and obstructing stones are typically significantly large relative to the size of the downstream duct and pancreatic orifice even after pancreatic sphincterotomy and balloon dilation of the pancreatic orifice. Therefore, the preferred approach for large stones is to perform ESWL to fragment stones in conjunction with ERCP. The success of ESWL for pancreatic stones is dependent on the equipment and operator technique, with greater success in achieving stone fragmentation reported in high-volume centers. ESWL alone has been shown to be as effective as ESWL with ERCP in removal of stones and pain relief and has been shown to be associated with shorter hospital stay and decreased cost [191]. ESWL has been reported to be effective in achieving pain relief and stone removal in a large metaanalysis, with correlation coefficients of 0.62 and 0.74, respectively (a correlation coefficient of greater than 0.5 is indicative of a large effect) and subsequently in large individual studies as well [192–194]. On the basis of these findings, European guidelines for the management of pancreatic duct stones recommend the use of ESWL as a first step in

Chronic pancreatitis

Chronic pancreatitis may be defined as a progressive inflammatory condition of the pancreas, which may lead to development of chronic abdominal pain, progressive loss of exocrine and endocrine function, and increased risk of pancreatic cancer [187] (see Chapter 84). The development of upper abdominal pain is the most debilitating symptom associated with chronic pancreatitis, the severity of which varies widely and does not correlate well with the severity of abnormalities on imaging.

ERCP offers a minimally invasive approach to treatment of chronic pancreatitis, including pancreatic sphincterotomy, stone removal, stricture dilation and stenting, and closure of duct leaks with or without associated pseudocysts [173]. Patients should be managed using a multidisciplinary approach, and the risks and benefits of all options, including surgical management, should be considered. The management of chronic pancreatitis has been addressed in two randomized prospective trials [188,189]. Both studies found significantly superior results with drainage or resection operations than with endoscopic therapy, but were limited by including only patients with very advanced disease with markedly dilated pancreatic ducts, often with a very large stone burden, and utilizing suboptimal techniques for endoscopic management. In clinical practice, such patients represent a small fraction of patients with painful chronic pancreatitis, many of whom have smaller ducts, less stone burden, and/or comorbid disease, rendering them more suitable to endoscopic than surgical therapy. In addition, drainage operations impair islet yield should the patient fail to respond and ultimately be considered for total pancreatectomy with islet autotransplantation [190].

**Pancreatic duct stones**

Obstructing pancreatic duct stones may result in pain or disruption of the upstream duct and a pseudocyst. Stone removal can be accomplished using ERCP alone (Figure 135.37), ESWL alone, or a combination of the two. The exact approach is determined by the size and location of stones, the overall stone burden, and local expertise. Small pancreatic stones can be removed at ERCP using a stone removal basket after a pancreatic sphincterotomy. Unlike biliary stones, pancreatic stones are usually calcified and obstructing stones are typically significantly large relative to the size of the downstream duct and pancreatic orifice even after pancreatic sphincterotomy and balloon dilation of the pancreatic orifice. Therefore, the preferred approach for large stones is to perform ESWL to fragment stones in conjunction with ERCP. The success of ESWL for pancreatic stones is dependent on the equipment and operator technique, with greater success in achieving stone fragmentation reported in high-volume centers. ESWL alone has been shown to be as effective as ESWL with ERCP in removal of stones and pain relief and has been shown to be associated with shorter hospital stay and decreased cost [191]. ESWL has been reported to be effective in achieving pain relief and stone removal in a large metaanalysis, with correlation coefficients of 0.62 and 0.74, respectively (a correlation coefficient of greater than 0.5 is indicative of a large effect) and subsequently in large individual studies as well [192–194]. On the basis of these findings, European guidelines for the management of pancreatic duct stones recommend the use of ESWL as a first step in
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migration and stent-induced injury of the pancreatic duct and they should therefore be used with caution, ideally in the setting of clinical trials. Patients with refractory strictures or with minimal relief of symptoms despite stent placement should be considered for surgical treatment modalities rather than repeated ERCP procedures.

Pancreatic duct leaks and disruptions
Pancreatic duct leaks or disruptions may result from acute or chronic pancreatitis, surgery involving the pancreas (e.g., after distal pancreatectomy), trauma, iatrogenic (e.g., from ductal injury during ERCP), or other causes. The injury may range from mild to complete transection resulting in a disconnected pancreatic duct. Pancreatic duct leaks can result in pancreatic ascites, pleural effusion, or early (acute fluid or necrotic collections) or late complications (pseudocyst or walled off necrosis). Management differs significantly between pseudocysts and walled off necrosis. Small pseudocysts may be treated with a transpapillary stent to drain the cyst and close the duct leak, while large pseudocysts are typically treated with transmural drainage or percutaneous drainage. In contrast, walled off necrosis often requires direct debridement as well as transpapillary or transmural drainage [144].

The role of ERCP in pancreatic ductal leaks is to place a transpapillary stent into the pancreatic duct, at least across the sphincter and preferably to bridge the area of the leak, with resolution reported in three-quarters of patients, depending on a number of factors including whether or not the site of leak could be bridged [190,200–204].

Figure 135.38 Distal main pancreatic duct stricture in patient with hereditary pancreatitis (a), and placement of four 7 Fr pancreatic stents (b).
Surgical procedures that result in alterations of the gastric, duodenal, and/or biliary anatomy may result in anatomic changes that make ERCP access to the major papilla/biliary tree technically difficult or impossible (Box 135.5). In patients with Billroth II gastrectomy and those with a short Roux limb, the major papilla can be reached with a duodenoscope or forward-viewing endoscope and ERCP completed in 67%–84% of patients [205,206]. In contrast, in patients with Roux-en-Y gastric bypass (RYGB) as currently performed, access to the major papilla with a duodenoscope is usually not possible (Figure 135.39).

**Box 135.5** Altered upper gastrointestinal anatomy in which conventional endoscopic retrograde cholangiopancreatography is challenging.

- Partial gastrectomy with Billroth II gastrojejunostomy
- Gastrojejunostomy or “bypass” performed for gastric outlet obstruction
- Pancreatoduodenectomy (Whipple procedure)
- Roux-en-Y gastric bypass for obesity
- Roux-en-Y choledochojunostomy or hepaticojejunostomy
- Roux-en-Y biliary diversion “duodenal switch”
- Total gastrectomy with Roux-en-Y esophagojejunostomy

The choice of endoscope and the associated success rate for biliary access and treatment depends primarily on the underlying surgical anatomy. A standard duodenoscope or pediatric colonoscope may be used to reach the ampullary orifice in patients with a Billroth II anastomosis or short Roux limb RYGB. For pancreatic duct access, particularly after pancreatectoduodenectomy (Whipple resection), EUS-guided rendezvous may be required to advance a wire through the stenotic anastomosis and allow retrograde access [207].

The difficulty in long Roux limb RYGB patients is that the scope may need to be inserted as much as 200 cm or more to traverse the Roux limb and jejunojejunal anastomosis to reach the major papilla or anastomosis. There are two choices in the approach to ERCP for patients with a RYGB: (1) deep enteroscopy-guided access followed by enteroscope-assisted ERCP or (2) gastric remnant access (laparoscopy-assisted or percutaneous) with conventional ERCP through the gastric remnant for ERCP. The field of deep enteroscopic ERCP is rapidly evolving. The introduction of the double-balloon enteroscope (Fujinon Corp., Saitama, Japan) in 2003, followed by the single-balloon enteroscope (Olympus, Tokyo, Japan) and the spiral enteroscopy overtube (Endo-Ease, Spirus Medical, Stoughton, MA), have provided several endoscopic options [208,209]. The long Roux limb is traversed to reach the biliary orifice, and ERCP is performed through the forward-viewing enteroscope. The double-balloon enteroscope systems require a dedicated processor and endoscope system, whereas the spiral enteroscopy overtube is compatible with both single-balloon and double-balloon enteroscopes. Balloon-assisted enteroscopy uses a balloon attached to an overtube to anchor the enteroscope and overtube as the enteroscope is advanced through the small bowel. Spiral enteroscopy makes use of a spiral overtube that is placed over the enteroscope. As the spiral overtube is rotated, the small bowel is pulled onto the overtube, and this advances the enteroscope through the small bowel, but is no longer available. Limitations of the enteroscopic approach are that the major papilla or surgical anastomosis may not be reached (because of an unfavorable surgical anatomy or adhesions), there is limited selection of accessories and devices that can be used with the enteroscope, lack of an elevator, and thus limited maneuverability of the scope in the region of papilla resulting in potentially difficult cannulation. The success rate of enteroscopy insertion to the major papilla or biliary anastomosis is 55%–100%, with successful cannulation in 63%–100% and successful therapy in 72%–100% of patients overall, though rates for RYGB patients are lower than those for Roux-en-Y hepaticojejunostomy [209].

A more invasive but direct approach to the major papilla in patients with a Roux-en-Y gastric bypass is creation of a gastrostomy, via a surgical approach (laparoscopic or open) [210–212]. According to published series, with this approach successful cannulation and therapy can be achieved in nearly 100% of cases [206,209,210]. The main advantage of a surgical approach for ERCP in patients with altered anatomy is the
ability to perform ERCP in a single-step procedure using a duodenoscope. In contrast to an enteroscopic approach, this allows a conventional approach to the papilla making biliary access easier and enables usage of all available ERCP accessories. In addition, it allows correction of any surgical problems such as internal hernias, which may not otherwise be diagnosed. In a study of patients with a Roux-en-Y gastric bypass, biliary intervention was achieved in all patients using a surgical approach compared to only 58% of patients in whom deep enteroscopy was performed, with lower success in patients with a Roux limb greater than 150 cm [211]. A novel approach for access to the gastric remnant involves EUS-assisted technique for direct percutaneous gastrostomy followed by fixation and dilation of the tract, with ERCP performed via the gastrostomy [193].

References are available at www.yamadagastro.com/textbook

Further reading

**Introduction**

The primary goal of treatment of any stenosis is luminal enlargement and amelioration of obstructive symptoms. Symptoms depend on the site and etiology of the stricture and may include dysphagia, nausea and vomiting, abdominal pain, obstipation, or frank bowel obstruction. This chapter compares the various technologies available for treatment of stenoses with regard to ease and site of application, patient tolerance, cost–benefit ratio, and available safety and efficacy data.

Historically, dilation of gastrointestinal strictures was limited to accessible anatomical areas, primarily the esophagus or anorectum. With the advent of endoscopically or radiographically placed polyethylene balloons, a variety of gastric, small bowel, and colonic strictures also became amenable to dilation. Likewise, prosthetic stent placement was initially limited to the esophagus and subsequently expanded into the pancreaticobiliary tree. However, expandable metallic stent technology and balloon enteroscopy has allowed treatment of previously inaccessible and more central (e.g., gastric, duodenal, small bowel, and colorectal) stenoses.

Whereas all the current dilating systems achieve efficacy by either stricture stretch or fracture, data are sparse regarding the specific mechanism of action by which each individual dilating system works. The few existing small prospective studies comparing the efficacy and side-effects of various dilating systems or techniques has failed to demonstrate consistent or significant differences in outcomes. Similarly, the few available randomized studies comparing different expandable prostheses in the esophagus have shown little difference in efficacy or safety between different stent brands.

However, technological improvements incorporated into some prostheses appear to reduce the risk of certain complications, such as stent migration or overgrowth, or gastroesophageal reflux. Data regarding central stent placement have been more limited, but existing randomized trials agree that prostheses compare favorably with surgery for malignant colorectal or gastroduodenal obstructions in the right clinical setting.

**Dilation**

**Theoretical considerations**

The basic goals of stricture dilation include safe and effective luminal enlargement plus the prevention of restenosis [1]. Efforts to achieve the latter goal may include proton pump inhibitors after esophageal bougienage for a reflux-induced stricture [2], intralesional steroid injection for benign strictures [3], placement of a prosthesis after dilation of a benign esophageal...
stricture, or surgical resection or bypass after dilation or stent placement for an obstructing rectosigmoid malignancy.

Although the exact mechanisms by which dilation results in luminal enlargement remain uncertain, circumferential stretch and stricture split are two likely possibilities. The former presupposes considerable elasticity in circumferential fibrous tissue, and the latter an inherent rigidity in which dilation results from one or several longitudinal tears. It is unlikely that a pylorus of 3 mm diameter can be dilated to 10 or 15 mm without significant laceration of scirrhouus tissue and, potentially, of muscle. Indeed, gross longitudinal tears and histological disruption of collagen and circular muscle have been described after esophageal bougienage for fibrous stenoses and achalasia [4]. Most perforations associated with dilation, in turn, appear to be an extension of these tears.

Among the earliest dilation techniques, bougienage was first used by Fabricius d’Acquapendente, who used a wax dilator for a food impaction [5]. The term bougienage is derived from the Algerian town of Boujiyah, the medieval capital of the wax candle trade. Cork and woven silk dilators have also been used, the latter since at least the 16th century, when Thomas Willis used a cork-tipped whalebone to treat a patient probably suffering from achalasia.

Dilating modalities can be divided into mercury bougies, guidewire-directed dilators (Figure 136.1), polyethylene balloons (Figure 136.2), and miscellaneous types (Box 136.1) [1]. Mercury-filled dilators, ranging in size from 10–60 Fr (3–20 mm), can be subdivided into the original, blunt-tipped Hurst bougies, and tapered-tip variants called Maloney bougies. Originally passed without fluoroscopic control, these dilators are now used infrequently by many practitioners.

Historically, guidewire-directed dilators have included Jackson–Plummer bougies and Eder–Puestow dilators. These include a triple olive variant, in which multiple metal olives of increasing diameter are placed on the same dilating shaft [6]. Five additional wire-guided dilating systems have subsequently been marketed: the KeyMed Advanced dilator (KeyMed Ltd, Southend-on-Sea, UK), consisting of three spindle-shaped silicone bougies on stainless steel shafts; the stepped neoplex Celestin dilator; two types of hollow-core polyvinyl systems, the Savary–Gilliard and the American; and the transparent Optical dilator. The Celestin dilating system consists of two tapered dilators that reach a maximum diameter of 12 and 18 mm respectively. The Savary–Gilliard system (CR Bard Inc., Billerica, MA) consists of bougies ranging in size from 5 to 18 mm (15–54 Fr). The American Dilating System (Cook Medical, Winston-Salem, NC) ranges in size from 7 to 20 mm (21–60 Fr). In contrast to the barium-impregnated American dilators,
Savary–Gilliard dilators are longer and have a more gradually tapered tip. The fifth type of tapered dilator, the Optical dilator (Inscope, Cincinnati, OH), is a hybrid device consisting of three separate dilators with variable diameters ranging from 14 to 20 mm, that fit over an endoscope to allow direct visualization at the time of bougienage, and thus theoretically improve procedural safety. The optical dilators, however, have not gained widespread use and have recently been withdrawn from the market.

After wire-guided bougies, the second major advance in dilation technology was the development of polyethylene balloons for use in the gastrointestinal tract [7,8]. Ranging in diameter from 4 to 40 mm [7], dilating balloons are fixed on 5–7-Fr catheter shafts that range between 100 and 200 cm in length. They can be passed over an endoscopically or radiographically placed guidewire, or directly through the scope (TTS) to allow dilation of strictures in the stomach, small bowel, and colon. A full dilation set includes balloons of variable length and diameter, 5-mL to 30-mL syringes, guidewires, and a manometer to delineate balloon pressure during inflation. A dilating gun to maintain pressure and stopcocks to ensure a constant pressure during inflation are optional. More recent advances in balloon technology have included the development of low-profile or high-compliance balloons. The latter can withstand a dilating pressure threefold to fourfold higher than previously marketed balloons, although balloon compliance has not been found to affect dilation success in achalasia [9,10]. The most recent development (over a decade ago) was the controlled radial expansion (CRE) balloon (Boston Scientific, Natick, MA) [11]. These balloons can be passed over a guidewire and inflated with variable pressure to predictably increase balloon diameter. A single CRE balloon, depending on the pressure used to inflate it, may increase in diameter from 6–8, to 8–10, to 10–12, to 15–18, or to 18–20 mm.

**Technical applications**

In general, radiologically or endoscopically directed dilation should be safer and more effective than blind dilation [8,12], particularly for sharply angulated, extremely tight, or proximal esophageal stenoses, as well as more central stenoses in the stomach, duodenum, and colon. These general principles must be balanced against the availability of fluoroscopy, the added cost of endoscopy or fluoroscopy, and the physician’s previous experience with a particular dilating modality. Endoscopically facilitated guidewire placement and subsequent bougienage of the esophagus need not always require fluoroscopic control if a sufficient length of guidewire has been placed into the stomach or a marked guidewire is used and attention is given to ensure that guidewire displacement does not occur with endoscope withdrawal [1].

There are limits to the extent to which luminal enlargement can be undertaken safely in a single dilating session [13]. There remains a maxim in esophageal bougienage that one should increase a luminal stenosis by no more than 2 mm (6 Fr) in a single dilation session [1]. Although it is based on common sense and an attempt to avoid such complications as bleeding and perforation, this adage does not necessarily hold true for most rings or webs and some pliable reflux-induced strictures. The degree of luminal enlargement should be contingent not only on the nature of the stricture itself (i.e., membranous or fibrotic) but also on the degree of associated luminal ulceration and the risks and benefits of alternative treatment modalities. These decisions cannot be made by a review of the scant existing literature discussing side-effects of dilation, but require a great deal of common sense on the part of the physician [1,12,14].

**Esophageal strictures**

Many patients who present with dysphagia have had previous esophagoscopy, although a few with lower esophageal rings may have had barium studies alone. With rings, webs, and mild reflux stenosis, mercury bougienage after a 6-h fast and pharyngeal anesthesia can often be done using a single 16–18 mm (48–54 Fr) Maloney dilator [15]. Such dilators can be passed in the upright or lateral decubitus position. Although ideally done under fluoroscopic control to avoid kinking or retroflexion of the bougie, many esophageal dilations, can be performed safely without these capabilities.

Long, angulated, or eccentric esophageal strictures, as well as severe (<7 mm) stenoses, are best handled with a guidewire dilating system [16]. Patients require an initial endoscopy to define the stricture’s cause and characteristics, for example length, diameter, pliability, eccentricity, and associated pseudodiverticula. Because a biopsy of the entire length of the stricture can be performed after dilation, it is sometimes best to delay tissue sampling until immediately after the dilation. Polyvinyl dilators, which have supplanted Eder–Puestow metal olives in most centers, always require guidewire placement [1,12,17]. This is usually done in conjunction with initial endoscopy, at which time a fluoroscopically monitored wire with a spring tip can be passed through the stricture and advanced freely into the stomach. Alternatively, the wire can sometimes be passed radiographically without endoscopy. After baseline endoscopy and stricture sizing, a dilator approximately the size of the stricture is passed, making sure the guidewire is fixed and the patient’s neck is flexed forward. This is followed by one or two additional dilators, for an increment of up to 3 or 4 mm (10–12 Fr), contingent on the stricture, before repeat endoscopy and stricture biopsy. Because of their gradual taper, polyvinyl dilators can pass through most stenoses with relative ease. The hesitation felt with these systems is more often related to dilator friction over the guidewire than to the stricture itself. Moderate stenoses (7–13 mm) can be dilated using either mercury bougies under fluoroscopic control or wire-guided polyvinyl dilators. The latter systems can be used without radiographic monitoring in some, although it is imperative that the guidewire is advanced far into the stomach and not inadvertently withdrawn at the time of endoscope removal. This is best done by feeding a marked guidewire forward in conjunction
with endoscope or bougie withdrawal and having an assistant fix the wire at the level of the patient’s mouth [1]. In addition, polyethylene balloons have been used to dilate moderate esophageal strictures [18]. The claimed advantages of balloon dilators over other systems have included ease of passage, dilation of the stricture alone, and radial as opposed to vector force applied to a stenotic wall [1], suggesting that such balloons should be safer and more effective. However, randomized trials comparing balloons to bougienage in benign esophageal strictures have demonstrated little consistent advantage to warrant the higher cost of balloon dilation in most cases [19–23]. If fluoroscopy is used to ensure waist dilation, total costs using this technology in our institution are threefold higher than dilation with polyvinyl dilators and eightfold higher than mercury bougienage (without endoscopy) [24]. Given this and the fact that such balloons are marketed as one-time use devices, balloon technology is better limited to areas of the gut not accessible to other types of dilators. One notable exception is achalasia, where forceful disruption of the lower esophageal sphincter is usually performed with a balloon to afford a larger diameter and avoid blindly passing a dilator through the redundant and often tortuous esophagus associated with this condition [25]. The technique of balloon dilation is described in Section Nongastrointestinal strictures.

**Nongastrointestinal strictures**

Most nongastrointestinal strictures require balloon dilation, although stenotic gastric stapling orifices and anastomotic strictures of the rectosigmoid can be cautiously enlarged with polyvinyl dilators or carefully incised with electrocautery (needle knife) [26–28]. Although both transcandoscopic and wire-guided balloons have shown comparable safety and efficacy for benign colonic anastomotic strictures, wire guidance allows the use of larger balloons, which appears to reduce the need for repeat dilations in this setting [29]. The use of TTS or CRE balloons provides certain theoretical advantages, including direct stricture visualization, improved placement control, and immediate evaluation of the dilated stenosis [7]. Following the same principles of dilation in the esophagus, the starting TTS or CRE dilator size should be usually 1–2 mm (3–6 Fr) larger than the diameter of the stricture. Negative pressure should be applied to the balloon using a 10- or 50-mL syringe prior to its inflation, to remove the dead-space air, when the balloon is going to be inflated with a contrast solution. The placement of the balloon across the stricture should always be centered with the help of endoscopic and fluoroscopic control, whenever feasible. This prevents the balloon from being “pulled” or “pushed” out of the stricture, during inflation. In the case of pyloric stenosis, the balloon should be centered in the pylorus with an effort to avoid any portion of the balloon being placed beyond the apex of the duodenal bulb. This could potentially help prevent a perforation of the bulb apex or C loop wall related to excessive pressure of the balloon tip or extreme balloon angulation.

Although air can be used for inflation, 10%–25% contrast solution allows better visualization fluoroscopically to demonstrate waist effacement, and more uniform balloon dilation. Placement of the endoscope tip against a transparent balloon during inflation additionally provides a transendoscopic view of the stricture from within the balloon throughout dilation. Obliteration of the balloon waist is required with pressures up to 1212 kPa (12 atmospheres). Larger balloons may increase the risk of perforation [30]. Balloon compliance has not been found to affect dilation safety or efficacy in achalasia [9,10]. Similarly, randomized trials of balloon dilation in achalasia have not found the duration of balloon inflation or number of inflations in a session to significantly impact procedural efficacy or safety [31,32]. In the case of most strictures, 30 s of dilation are sufficient and usually produces good results. Rarely is there a need to repeat dilation for a second or third time after repositioning of the balloon. After dilation has occurred, the balloon must be completely evacuated to allow balloon retrieval. Additional, larger dilating balloons can then be used, although the degree of luminal enlargement to be attempted in a single session remains a matter of common sense and is contingent on size of the initial stenosis, presence and degree of active ulceration, and patient discomfort with initial dilation. Using pyloric dilation as an example again, the ultimate goal is to dilate to 15–18 mm and follow-up with complete endoscopic inspection of the pylorus and duodenum. This goal sometimes requires two or three dilating sessions separated by an interval of several days if the obstruction is acute, or several weeks, if it is chronic.

**Indications and contraindications**

Indications for dilation are contingent on the anatomical area involved (Box 136.2). In the esophagus, symptoms are most

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**Box 136.2 Indications for gastrointestinal dilation.**

<table>
<thead>
<tr>
<th>Location</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Ring or web, Reflux stricture, Malignancy, Miscellaneous (e.g., caustic ingestion, motility disorders)</td>
</tr>
<tr>
<td>Stomach</td>
<td>Pyloric stenosis, Anastomotic stenure, Gastric stapling/bypass stenosis, Miscellaneous (e.g., caustic ingestion, proximal malignancy)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>Duodenum (web, acid peptic stricture, anastomotic)</td>
</tr>
<tr>
<td>Colon</td>
<td>Anastomotic stenosis, Inflammatory stricture (inflammatory bowel disease, diverticular, radiation induced)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Stenotic gastrostomy, enterostomy, or colostomy stoma</td>
</tr>
</tbody>
</table>
often dysphagia and food impaction, although atypical chest pain, aspiration, and odynophagia can be seen [22,33,34]. Indications for pyloric dilation are usually recurrent nausea and vomiting, weight loss, abdominal pain, and severe reflux [35,36]. Small bowel and distal colonic stenoses may require dilation for intractable obstipation, progressive diminution in stool size with constipation, pain, and recurrent bowel obstruction [26–28,37]. The causes of the above and a variety of miscellaneous stenoses are listed in Box 136.2.

The only absolute contraindication to esophageal dilation noted in guidelines for esophageal dilation published in 1998 by the American Society for Gastrointestinal Endoscopy (ASGE), which remains appropriate, was acute or incompletely healed esophageal perforation [12]. Common sense dictates that contraindications to dilation also include a lack of informed consent, an acute abdomen, or a deeply ulcerated stenosis for which the risks of dilation outweigh the benefits. Indeed, relative contraindications listed by the ASGE include bleeding disorders, cardiopulmonary instability, recent esophageal perforation or surgery, and a large aortic aneurysm, but specifically excluded concomitant radiation therapy or forceps biopsy [38]. For extraesophageal dilation, similar contraindications should apply, but there may also be lesion-specific contraindications, such as colonic stenosis associated with acute diverticulitis.

**Risks and alternatives**

There are specific risks of gastrointestinal dilation in addition to those associated with routine endoscopic procedures. These include, an increased incidence of bleeding, perforation [39], and bacteremia [40,41], although the incidence of these complications has not been well defined for gastroduodenal and colorectal dilations. Most data on gastrointestinal dilation are derived from esophageal bougienage, using a combination of Puestow and mercury dilating systems, in over 850 patients with benign esophageal strictures compiled from various series [8,15,42]. Reported complications in these patients included 16 perforations, five major bleeding episodes, two aspirations, and one death. This compares with perforation rates of 0.4% for mercury dilators and 0.6% for metal olives reported in an ASGE survey [8]. Such perforations usually occur in the cervical esophagus and relate to improper dilator introduction or in the thoracoabdominal esophagus just proximal to the stenosis, related to dilator or guidewire kinking, or falling out of the stenosis. Less frequently, the stricture itself splits, as may be seen with achalasia (1%–5% perforation rate) [1]. Overall, the reported risk of perforation with esophageal dilation ranges from 0.1% to 0.4% [43]. Factors that increase risk for esophageal perforation are listed in Box 136.3 [44–49]. While scant bleeding is relatively common after esophageal dilation, significant hemorrhage was identified in less than 0.5% of dilations historically [50] and is presumably even less common with newer techniques.

**Box 136.3 Risk factors for esophageal perforation at dilation.**

- Longer, narrower, or angulated stricture
- Malignant stricture
- Severe esophagitis
- Large hiatal hernia
- Esophageal diverticula
- Radiation stricture
- Caustic stricture
- Prior esophageal perforation
- Inexperienced operator
- Eosinophilic esophagitis

Bacteremia is quite common after esophageal dilations, occurring after 12%–22% of procedures, and occurs more frequently than with most other endoscopic procedures [41,51]. While this rate of bacteremia seems high, it is no higher than during routine activities such as brushing, flossing, or using toothpicks [52]. Therefore, the American Heart Association (AHA) and ASGE changed their recommendation in 2008, suggesting no need for the use of antibiotics, even in patients at high risk of infective endocarditis [52]. By that extension, routine use of antibiotics for dilations in other parts of the gastrointestinal tract are not recommended either. The AHA still recommends the use of antibiotics (e.g., ampicillin 2 g i.m. or i.v. or amoxicillin 2 g p.o. 30–60 min before procedure) in patients whom have had vascular grafts within the past 6 months, while the ASGE does not [53,54].

Long-term pharmacological implications of dilation must also be considered in any discussion of risks. Reflux-related esophageal strictures and many pyloric stenoses require long-term proton pump inhibition and possibly use of a prokinetic agent. Dilation of a stenosis from Crohn’s disease usually requires adjustment of immunosuppressive or biological medications to minimize the inflammatory response and stricture reformation [55,56].

The benefits and risks associated with luminal dilation must be considered in relation to alternative treatment modalities, including other endoscopic therapies (stenting or electroincision), surgery, or conservative management. Direct comparisons between dilation and these alternatives are sparse, but include several trials in which biopsy forceps or needle knife-mediated incision of Schatzki rings was at least as safe and effective as dilation [14] and possibly superior [57,58]. Furthermore, use of alternative approaches, such as electrocautery, in conjunction with dilation may enhance the latter’s clinical efficacy [59]. Dilation should not be the sole treatment in individuals who require bougienage so frequently that cumulative risk and expense become prohibitive. In this setting, intrasional steroid injection, or temporary placement of expandable esophageal stents may reduce the frequency with which dilation is required [60,61]. Alternatively, definitive management with surgical resection may be more appropriate [62].
Efficacy

Esophagus

Although dilation results in immediate symptomatic improvement in the majority of patients with benign esophageal strictures, multiple dilation sessions are often required. Strictures commonly recur, resulting in a return of dysphagia and necessitating repeat dilation. Using sequential bougies over a period of days to months, Puestow and mercury dilating systems have been associated with a 70%–100% improvement in dysphagia in a number of series [8,15,42]. Other studies have reported symptomatic improvement in excess of 90% [19,24,63].

A number of series have assessed balloon dilators for esophageal stenoses. In an early series, 93% of dilations of benign and malignant esophageal strictures in 88 patients were technically successful, with a 3% minor complication rate and 91% symptomatic improvement over a mean of 10 months [64]. Additional series and trials comparing balloon technology to Eder–Puestow or Savary dilators have demonstrated comparable efficacy between these technologies for benign esophageal stenoses [19,44,64,65]. Similarly, in a randomized prospective trial there was no significant difference between Eder–Puestow and Celestin dilators in long-term symptom relief of 72 patients, although the Celestin system was thought to be quicker and cause less pharyngeal trauma [66].

A number of series have reviewed experiences with hollow-core polyvinyl dilating systems [5,24,44,63,65,67]. Dumon and colleagues claimed efficacy in all 300 patients treated for benign or malignant esophageal stenosis, with only one perforation [67]. Our group successfully dilated 432 patients with 716 courses of dilation therapy; 89% were dilated with polyvinyl dilators and only 8% were performed with fluoroscopic monitoring [24]. Approximately 80% of the dilation sessions were undertaken with a single large dilator or employed incremental dilators of 6 mm or more in a single session. There were no complications directly related to the bougienage. Additional large series have been published with polyvinyl dilators [44]. There has been a single published series using the Optical dilator, and so claims about improved procedural safety with this device remain to be confirmed [68], but are unlikely to be published as this device has been recently withdrawn from the market.

Stomach

Large series of gastric dilation are limited to polyethylene balloon dilation, but most series with long-term follow-up report good results [69,70]. Since the initial description of successful hydrostatic dilation in a patient with pyloric stenosis and gastric outlet obstruction [71], several series have been published using this technique. McLean and colleagues dilated 94 gastrointestinal strictures in 92 patients, using radiographic guidance with a mean follow-up of 389 days in 80 patients [72]. Of these patients, 33 had various forms of gastric stenosis. Technically, 25 of the 33 were successfully dilated, and 70% were symptom free at 1 year. Perng and colleagues reviewed 42 patients with benign gastric outlet obstruction [35]. At a median follow-up of 2 years, two-thirds of patients had sustained improvement and one-third required surgery. The symptom-free rates at 1, 2, 3, and 4 years were 85%, 78%, 69%, and 69%, respectively, and the independent prognostic factor for failure was need for more than two courses of dilation for symptom relief. Lau and colleagues reviewed 45 patients who had successful gastric outlet obstruction dilation, four of whom had rapid reobstruction and were found to have malignancy [36]. At a median follow-up of 39 months, more than 50% of patients required surgery, 18 for recurrent obstruction, two for interval perforations, and one for bleeding. Nevertheless, a 60%–85% good-to-excellent symptomatic response at 1–2 years has been reported [35,36,70]. However, prospective, comparative studies between endoscopic dilation and surgery are lacking. A cost analysis comparing pyloric balloon dilation with vagotomy and pyloroplasty [73] showed balloon dilation to be cost-effective in the short term at one-tenth of the total costs of vagotomy and pyloroplasty. However, long-term acid suppression was not considered in this analysis.

Small bowel

Because of prior problems of access to the small intestine, there were few data regarding dilation of proximal small bowel strictures [74]. Since the introduction of double-balloon enteroscopy (DBE) in 2001, there has been significant progress in the diagnosis and treatment of small bowel disorders, mainly obscure gastrointestinal bleeding, but also small bowel polyps and strictures. DBE allows careful inspection of the stricture, biopsies can be performed, and contrast can be injected under fluoroscopy to better define its dimensions. Finally, balloon dilation can be performed for treatment as an alternative to surgery in the right clinical setting (e.g., nonsteroidal antiinflammatory drug-related strictures, short Crohn’s strictures, postsurgical anastomotic strictures) [75–83]. The several case series reported to date have reported success rates ranging from 58% to 100% [75]. In addition to the use of DBE to treat small bowel strictures, there are multiple series using balloon technology to dilate ileal or anastomotic ileocolonic strictures in Crohn’s disease [56]. Dilation of 27 anastomotic strictures in patients with Crohn’s disease did not result in complications, and after 7–38 months, 18 patients remained free of obstructive symptoms [84]. A prospective study of 55 patients with Crohn’s disease with 59 ileocolonic strictures noted 90% technical success with complications in 11% (six perforations) [37]. Complete long-term symptom relief was noted in 34 patients (62%). Corticosteroid injections into inflamed small bowel following anastomotic balloon dilation may decrease restenosis rates further [85–87]. However, results remain anecdotal and data should be placed in perspective of surgical resection or stricturoplasty. Comparative studies with surgery are lacking.

Colon

Most reported colonic dilations have been used for rectal or anastomotic stenoses [26,27]. Linares and colleagues dilated 33
anorectal strictures in patients with Crohn's disease with a variety of techniques; half experienced short- or long-term symptomatic relief [88]. Pietropaolo and colleagues dilated postoperative strictures in 42 patients, using either balloons or bougies, with a 2.4% failure rate but no morbidity or mortality [89]. A combination of various types of dilators with endoscopic electrosection in 39 patients with benign anastomotic strictures resulted in no complications or symptoms in any patient at a mean follow-up of 25 months [27]. Solt and colleagues performed 133 balloon dilations over 17 years in 57 patients with benign (primarily anastomotic) strictures, with a 30% eventual reoperation rate but no procedural complications [90]. Finally, Virgilio and colleagues used a 30–40 mm achalasia dilator in 18 patients with anastomotic strictures following resection for colorectal cancer [91]. A total of 45 dilating sessions was performed in 17 of the patients. Long-term symptom relief was described in 16 patients (94%) and complications were limited to one episode of bleeding and a punctiform bowel perforation. Questions remaining unanswered include the relative efficacy of balloons as opposed to polyvinyl dilators for rectosigmoid stenoses, and the rapidity with which stenoses at various sites can be safely dilated.

**Stent placement**

**Theoretical considerations**

In contrast to dilation, stent placement attempts to maintain permanent continuity to the lumen of the gastrointestinal tract. Although significant progress has been made over the last decade with stent technology and design, the search for the ideal stent continues. Gastrointestinal stents can occlude, migrate, erode, and may allow reflux of potentially noxious gastrointestinal contents depending on their location [92,93]. Symonds is credited with the first prosthesis placement in the esophagus in 1885. Initial stents were fabricated of a gum elastic material tube and a proximal funnel made of boxwood or ivory. These were then replaced with a tube and funnel made of the same gum elastic material. In the early 1900s, a French surgeon, Guisez suggested esophageal stenting over an introducer. But, it was not until 1959, when Celestin introduced a new prosthesis made of natural polythene, that the use of these rigid prostheses became popular. Since then, a variety of homemade and commercially available esophageal prostheses have been used, the latter usually constructed of latex or silicone molded over a stainless steel core (Box 136.4 and Figure 136.3). Inserted surgically or pushed into place using bougies, a small-caliber endoscope, or an expandable metal olive fixation device (Nottingham introducer), the design of these rigid stents and insertion devices precluded placement across central or sharply angulated stenoses. Their application was also primarily limited to esophageal or gastroesophageal malignancies.

The placement of the first expandable metal stent (spiral coiled stent wound around the endoscope) is attributable to Frimberger in the early 1980s [92]. A decade later, the first commercially available self-expandable metal stent (SEMS) was the Wallstent, using technology borrowed from the endovascular stents. In a seminal paper, Knyrim et al. [94], demonstrated significantly fewer complications and lower mortality associated with the placement of a self-expandable metal stent (Wallstent) versus rigid prostheses. Since then, expandable stents have largely supplanted rigid stents in the esophagus and have also made gastroduodenal and colorectal stenoses amenable to
prostheses (Box 136.4) [95]. In addition, expandable metal stents have the advantage of being able to be placed under fluoroscopic and/or endoscopic guidance, and do not require dilation prior to placement, and so are associated with a lower risk of bleeding and perforation. Their flexibility allows placement beyond acutely angulated malignancies, and their ability to imbed into the esophageal wall minimizes subsequent stent migrations. Finally, their flexibility has enabled them to be placed across obstructions in the small bowel and colon [96–98]. The initial SEMS were made of stainless steel, but have now been replaced with a shape-retaining nickel and titanium alloy called nitinol. Although they differ in expansile force and delivery systems, all these prostheses predeployment are in a compressed state, with subsequent spontaneous or balloon-assisted expansion. The initially introduced uncovered stents typically consist of a cylindrical metal mesh tube that becomes embedded in the mucosa. This permanently anchors the stent in place but can allow stent occlusion from tissue or tumor ingrowth [99]. Alternatively, stents covered with a membrane (partially covered or fully covered) reduce stent reocclusion, but may increase rates of stent migration [100]. Consequently, a wide variety of stent technologies have been developed, employing flared stent ends, double-stent design, plastic, and biodegradable stents, to name a few [101]. At least five major types of metal stents are currently marketed in the USA, and variations of these stents are marketed around the world (Figure 136.4).

The American version of the Wallstent (Boston Scientific, Natick, MA) was initially introduced as a two-layer stainless steel, dog bone prosthesis with an interposed layer of silicone. Uncovered, partially, and fully covered stents were subsequently marketed, ranging between 18 and 25 mm in diameter and constrained by an 18-Fr delivery system. A version of this prosthesis (Flamingo stent, Boston Scientific International) with a pronounced proximal taper to prevent distal migration when placed across esophagogastric junction tumors, was marketed in Europe, but never in USA due to the reports of higher rates of chest pain, and is now no longer marketed [102]. The more recent version of the Wallstent is called the WallFlex stent (Boston Scientific), and is available with diameters ranging from 18 to 23 mm in the esophagus, 22 mm in the duodenum, and 22 and 25 mm in the colon. The enteral and colonic versions of this stent have a 10-Fr delivery system, thus facilitating transendoscopic deployment, while the esophageal stent has an 18-Fr delivery system.

The Gianturco Z stent (Cook Medical, Winston-Salem, NC) is no longer manufactured other than the antireflux version of the stent (Dua Stent). This is an 18-mm diameter urethane-covered stainless steel prosthesis that flares to 25 mm at the ends. The urethane lining of the stent extends beyond its distal end to serve as an antireflux “windsock” valve designed to minimize regurgitation and reflux commonly associated with stents placed across the esophagogastric junction [103]. Ranging from 8 to 14 cm in length, the prosthesis must be back-loaded into a...
31-Fr compression catheter at the time of placement [100]. The newer esophageal, duodenal, colonic stent manufactured by Cook medical is the Evolution stent. The esophageal version is available in 18 and 20 mm diameters, the duodenal is a 22-mm stent, while the colonic is a 25-mm prosthesis.

The Ultraflex stent (Boston Scientific, Natick, MA) is a 10 or 15-cm long, 18–25-mm diameter prosthesis made of woven nitinol, available as an uncovered or partially covered stent, which is released by pulling a long suture used to constrain the stent on an insertion shaft. There is a proximal as well as a distal delivery system available.

The EsophaCoil (Medtronic Inc., Eden Prairie, MN) was a spiral nitinol coil, constrained on an insertion shaft by three trip wires, which is no longer available in the USA [104]. There were multiple problems with this stent due to its uncovered spring coil shape, once deployed, repositioning was virtually impossible. Also tissue ingrowth was a major problem and, finally, the very high expansile force led to sudden full expansion of the stent at deployment, often resulting in severe chest pain [104,105].

The Alimaxx-ES (Merit Medical Systems, Inc., South Jordan, Utah) is a laser-cut, fully covered nitinol stent with small antimigration struts on the outer part of the stent, available in 14 to 22 mm diameters. The Niti-S stent (Taewoong Medical, Seoul, Korea) is made of a single thread of 0.2 mm nitinol wire with an inner polyurethane layer, available in 16, 18, and 20 mm diameters. It is available with a 10-Fr delivery system as well, which allows through the scope delivery. The Bonastent (Standard Sci Tech., Seoul, Korea) is another nitinol SEMS available in the United States.

Additional stents not available in the United States but available in Europe and Asia include, the Hanaro, Choo, and Song stent, (M.I. Tech Co. Ltd, Seoul, Korea), the Niti-S Esophageal double-type (Taewoong Medical, Seoul, Korea), FerX-Ella and SX-Ella stent (ELLA-CS, Hardec Kralove, Czech Republic), and the ENDO-Flex stent (GmbH, Voerde, Germany) [106]. A biodegradable version of the ELLA stent is also available in Europe.

All the above differ not only in design and delivery system but also in physical characteristics. All self-expandable metal stents are more malleable than previously manufactured rigid/conventional prostheses, but there are differences in the properties of different stents. Although partially covered and uncovered stents cannot theoretically be removed, there are case series using partially covered stents to treat leaks and perforations, with excellent removability using a “stent-in-stent” technique [107,108]. Fully covered stents (currently only available for the esophagus in the United States) are removables, and although approved only for the use in malignant esophageal stenosis, they have been used extensively to treat various benign etiologies such as strictures, leaks, and perforations. Each prosthesis generates a different amount of radial force (EsophaCoil > Wallstent > Z stent ≈ covered Ultraflex stent), and different amounts of axial force (the force that wants to straighten the stent out), which may help determine the type of stent most suitable for a given application [109]. Stents with lower axial force (woven stent such as the Ultraflex stent) are most suited to be placed across tight angulations and turns, allowing the prosthesis to conform to the gastrointestinal lumen in that area and are less likely to perforate at the ends.

In addition to the various expandable metal stents described above, a self-expanding plastic stent (SEPS), called the Polyflex stent (Boston Scientific, Natick, MA) [110], is currently marketed. These 16–21-mm diameter, 9–15-cm long polyester mesh stents are fully covered by a silicone membrane. The inert nature of this coating appears to reduce the hyperplastic tissue reaction at the ends of the stent that commonly occurs within weeks to months of metallic stent placement, preventing removal of the latter. Most studies suggest these stents can be removed from patients even months after placement with relative ease. As such, their use has been expanded to include the treatment of benign or temporary problems, such as peptic strictures [111–113] or esophageal leaks [114–116]. Unfortunately, the large size (36–42 Fr) of the insertion catheter required by these stents precludes transcendoscopic placement, and thus restricts their use primarily to esophageal lesions. Additionally, their polyester mesh does not generate as much radial force as metal stents, which may limit their efficacy with tighter or stiffer stenoses, and may contribute to their documented higher rates of migration [110–113].

In 2008, a biodegradable stent SX-ELLA (ELLA-CS, Hardec Kralove, Czech Republic) was introduced, and is available currently in Europe and Asia. It is made of a woven polydioxanone monofilament, which degrades by hydrolysis at a low pH. Stent integrity and radial force are maintained usually for 6–8 weeks, with disintegration occurring at 11–12 weeks. The stent is available in diameters ranging from 18 to 25 mm. It needs to be loaded on a 28-Fr delivery system, and usually requires predilation of the stenosis since it has a lower radial force compared to nitinol stents. Although currently approved only for benign strictures, it has been used in malignant disease [117].

Considerable progress has been made toward increasing the safety, efficacy, and applicability of stent technology. What remains ill defined, however, is the role this technology should play compared with conventional treatments such as surgery or percutaneous endoscopic gastrostomy/jejunalostomy (PEG/J) placement. Moreover, where this technology fits into our therapeutic armamentarium of ablative therapies (Nd:YAG laser, bipolar cautery, caustic therapy, argon plasma coagulation, photodynamic therapy, cryotherapy, and endoscopically assisted brachytherapy) requires continued evaluation [93].

**Technical application**

Stent placement requires stricture dilation to a size that admits a conventional prosthesis or the delivery system of an expandable stent [118]. Strictures used to be commonly dilated to 30–36 Fr even with a small (18 Fr) delivery system to preclude stent dislodgement when the delivery system was retrieved through a partially expanded prosthesis. This practice, however,
stents, WallFlex, and Evolution stents are deployed by pulling back a compression catheter sleeve. Ultraflex stent (c) is released by uncoiling a suture from the proximal or distal end.

Figure 136.5 Stent deployment devices: Wallstent (a) and Z stent (b) are deployed by withdrawing a compression catheter sleeve. Ultraflex stent (c) is released by uncoiling a suture from the proximal or distal end.

Esophageal strictures
Historically, conventional esophageal prosthesis placement required adequate dilation both to allow passage of various delivery devices and to localize and measure the length of the neoplasm [118]. Necessary dilator sizes ranged from 48 to 51 Fr for conventional prostheses. It is no longer commonly necessary to dilate a malignant stricture prior to placement of a self-expandable stent. Preoperative bronchoscopy may be required, particularly for bulky extrinsic, proximal/midesophageal neoplasms, as stent placement may be associated with airway compression and acute respiratory distress. At minimum, review of a cross-sectional imaging study such as a computed tomography (CT scan) should be undertaken. Collaboration with a pulmonologist or thoracic surgeon familiar with the placement of airway stents may be required. Defining the stricture for accurate stent placement can be done using external radiopaque markers taped to the patient’s chest but is more commonly accomplished by injecting water- or lipid-soluble contrast material into the proximal or distal tumor margins [118]. Alternatively, endoscopic placement of radiopaque through-the-scope clips can be used.

For most accurate deployment, prosthesis placement usually requires fluoroscopic control, although some of the smaller delivery systems (Ultraflex, WallFlex, Evolution, Niti-S, etc.) allow simultaneous endoscopic visualization during delivery [118]. Stents should be 4–6 cm longer than the neoplasm, contingent on local anatomy (e.g., placement relative to the esophagogastric junction, cricopharyngeus, contralateral gastric wall, and stricture angulation). Conventional prostheses were pushed into place over a guidewire using a variety of devices to stabilize the stent (e.g., small-caliber endoscope, Savary-type dilator, Nottingham expandable olive fixation shaft) and various types of pusher tubes. These devices encounter considerable resistance at the level of the cricopharyngeus and may require neck hyperextension for passage. After conventional stents are pushed into place, the pusher tube and delivery system are retrieved and a repeat endoscopy should be performed immediately to document correct prosthesis position. Expandable prostheses have variable delivery systems (Figure 136.5). Polyflex stents, Z stents, WallFlex, and Evolution stents are deployed by pulling back a compression catheter. Ultraflex stents are constrained by a single long suture that can be pulled off the delivery shaft. Nonbraided stents such as the Z-stent, Alimaxx-ES) have minimal to no foreshortening and essentially retain their pre-expansion length after deployment. In contrast, all the other available esophageal stents, including the Polyflex stent and the biodegradable SX-ELLA stent, have significant foreshortening, making proper placement crucial.

Despite the plethora of prostheses now available, certain practices are followed after placement of all prostheses. The most important is the need for immediate endoscopy after insertion to assure that the prosthesis has accomplished the treatment goal, for example correct location, full expansion, or occlusion of tracheoesophageal fistula. Problems occur when the prosthesis is too long or short, abuts into the cricopharyngeus or contralateral gastric wall, or has inadequate radial force to open a tight stricture. The latter may preclude retrieval of the delivery system. Airway compression and immediate migration at the time of placement are additional potential problems. The
endoscopist has to be prepared to deal with these problems with balloon dilators, as well as additional prostheses to correct problems associated with inadequate length, acute angulation, or migration. Excessive stent material extending too far beyond a stricture's margin may cause occlusion or mucosal injury, although it may be trimmed from metallic stents with an argon plasma device [120]. Once SEMS have fully deployed, most prostheses, including uncovered stents, have the potential to be repositioned soon after placement. The uncovered Ultraflex prosthesis can be completely removed, at least in theory, up to several weeks after placement.

Nonesophageal strictures
Expandable prostheses can be placed in the proximal stomach and distal colorectum using conventional delivery systems and techniques similar to those described for the esophagus [121]. Some of the original stents that were approved in the United States specifically for colonic application included the colonic Z stent (Cook Medical), Enteral Wallstent (Boston Scientific), and colonic Memotherm stent (CR Bard). The colonic Z stent is no longer manufactured and has been replaced by the Evolution colonic and enteral stent (Cook Medical) [122]. Although the Enteral Wallstent, made of stainless steel, is still manufactured, it has been largely replaced by the WallFlex colonic and enteral stent (Boston Scientific), a nitinol stent. The enteral and colonic stents have a wider diameter, ranging from 20 to 25 mm, to reduce the risk of obstruction, and are currently only available as uncovered stents. Strictures in the more proximal colon, as well as those in the duodenum or proximal jejunum, require either a longer insertion system or a stent mounted on a 3–4 mm delivery system that can be placed through a large-channel endoscope or colonoscope [93]. Additional stents available in Europe and Asia include the Niti-S (uncovered, partially covered, and fully covered) stents (Taewoong Medical, Seoul, Korea), Bonastent (Standard Sci Tech., Seoul, Korea), Hanaro (uncovered and partially covered) stent (M.I. Tech), Egis (single and double-covered) stent (S&G Biotech, Seongnam, Korea), SX-ELLA stent (ELLA-CS, Hradec, Czech Republic), and the Endo-Flex stent (ENDO-FLEX GmbH, Voerde, Germany). These stents require delineation of stricture length, localization with contrast injection at the tumor margins, and concomitant fluoroscopic and or endoscopic control to ascertain proper placement and prosthesis expansion. If biliary and duodenal stents are both required, as may be the case in locally advanced pancreatic cancer, the permanent biliary stent should be placed first whenever possible, as it is technically challenging to cannulate the biliary system through the fenestration of a duodenal stent.

Indications and contraindications
For the most part, conventional and uncovered metal expandable prostheses are difficult or dangerous to remove once placed, and thus should be reserved for obstructing or fistulizing neoplasms that cannot be cured by resection, or in potentially curable patients with prohibitive operative risk (Box 136.5) [95,118,123,124]. The most experience has accrued in the proximal gut for malignant dysphagia or esophago-airway fistulae. The latter can be a consequence of primary esophageal carcinoma, lung cancer, or mediastinal metastases. Gastric outlet obstruction from widespread pancreatic cancer has traditionally been treated by gastrojejunostomy or a percutaneous endoscopic gastrostomy with jejunal tube (PEG!) in infirm patients [97,125]. With increasing experience using enteral stents, their role in malignant gastric outlet obstruction has become more common. Enteral stents should probably be the first choice in patients with expected survival shorter than 3–4 months, potentially predictable by a WHO (World Health Organization) score [126,127]. Likewise, patients who present with malignant colon obstruction usually have far advanced disease (stage III [40%] or IV [60%]) [98]. Traditionally treated with palliative resection or bypass, colorectal prosthesis placement appears to be a useful alternative, both to allow adequate preoperative bowel preparation in surgical candidates [128–131] and as long-term palliation in a subset of patients with malignant ascites or liver metastases, and thus a higher operative risk [132–134].

While removable stents, such as the plastic Polyflex stent and fully covered metal stents, can also be used for malignant stenoses [110,113,135], their ability to be removed months after deployment expands the indications for prostheses to include benign conditions. In the esophagus, temporary placement of a
Polyflex stent for 6 weeks to 13 months has been successfully used to provide durable relief from a variety of benign causes of esophageal stenosis, including peptic, caustic, anastomotic, and radiation-induced strictures [111,112]. Additionally, this covered stent allows temporary occlusion of nonmalignant esophageal perforation [114], particularly postsurgical anastomotic leaks [115,116]. SEPS have been associated with migration rates ranging from 6% to 84% [111,113,114]. Self-expandable metal stents have been used for the same indications as SEPS with similar to higher success rates and migration rates reported upwards of 30% [136–139]. Although minimal literature exists on the extraesophageal application of removable stents, these prostheses may become indicated for benign strictures of the colorectum, stomach, or even small bowel in the near future.

With the notable exception of removable stents, prostheses are generally contraindicated in the low-risk and potentially curable patient [93,118], as permanent stents have a long-term potential for erosion, occlusion, and migration. Conventional prostheses should not be placed in the setting of a tracheoesophageal fistula unless there is an adequate shelf to seat the stent. Esophageal stents should not be used if placement of a dilator approximating the stent diameter results in significant airway compression by a bulky neoplasm. Stents may be contraindicated if placement cannot be undertaken without impingement on the cricopharyngeus muscle or anal sphincter, or if the opening of a placed stent would abut a contralateral luminal wall, thus occluding it. An absolute contraindication for prosthesis placement is an inability to endoscopically or radiographically define both the proximal and distal stricture margins.

**Risks and alternatives**

**Esophageal strictures**

Complications with the early rigid esophageal stents were not uncommon, and so provide a paradigm for possible complications with today’s self-expandable stents. Acute procedure-related complications included perforation, bleeding, tracheal compression, and tube malposition. Total complications with these conventional stents approximated 20%, with a mean procedure-related mortality of 8.6% [118]. Subacute complications include erosion with bleeding or fistula development, stent migration, food bolus impaction, and tumor overgrowth. Variable degrees of reflux are inevitable if the esophagogastric junction has been stented. Patients who have delayed gastric emptying as a consequence of vagal denervation or gastric infiltration by tumor may experience florid regurgitation or aspiration.

Complications of expandable prostheses are variable and contingent on prosthesis design and endoscopist experience, but are generally similar to those of conventional prostheses, except less common [94,102,140,141]. For example, a Swedish nationwide review of 152 recipients of expandable metal esophageal stents revealed such complications as transient chest and pharyngeal discomfort (in nearly all patients), stent migration (5% of cases), bleeding (1%), incomplete stent expansion (1%), perforation (1%), and stent occlusion (10%) from food impaction or tumor overgrowth or ingrowth [142]. The latter is a complication unique to expandable stents, and can be reduced with covered stents, although this increases the risk of stent migration [143–145]. As with conventional stents, gastroesophageal reflux can complicate expandable stents placed across the lower esophageal sphincter, prompting some manufacturers to incorporate valves or sleeves into versions of their prostheses. While some of these modifications have appeared ineffective in randomized trials [146], others have demonstrated as much as an eightfold lower rate of subjective [147] or objective reflux [103,148] compared to unmodified prostheses. Rare cases of potentially fatal reflux aspiration pneumonia have been seen only with the valveless stents in these studies. The ability to place expandable esophageal stents more proximally than conventional prostheses [149] has also associated them with rare complications such as cervical discitis [150] and stent perforation into the common carotid artery [151].

The risk of life-threatening complications from both conventional and expandable stents may be increased in esophageal cancer patients with prior chemotherapy and radiation. Indeed, the initial retrospective series showed increased rates of bleeding, perforation, sepsis, or tracheoesophageal fistula formation in such patients [152–156]. However, other reports have found no significant association between these complications and chemoradiation therapy [157–159], raising the question of whether these patients are particularly sensitive to variations in stent design, physician technique, or institutional experience. Two randomized controlled trials found that combination of stent and radiation therapy was effective and safe. In one trial, 84 patients were randomized to an Ultraflex stent combined with external beam radiotherapy (30 Gy in 10 sessions) versus Ultraflex stent alone [160]. The combination group experienced a more sustained relief of dysphagia and prolonged overall survival. Another study compared a conventional SEMS with a SEMS loaded with iodine-125 seeds for brachytherapy and similarly noted a survival advantage and longer stent patency in the SEMS group loaded with iodine seeds [161].

Tumor ablative technologies have also been studied as alternatives to stent placement. In randomized trials, endoscopic laser therapy by itself was less effective than covered or uncovered expandable stents at relieving dysphagia [143], although it increased median survival and quality of life, as well as treatment cost, in one study [162]. However, the cost and survival with laser therapy were found to be comparable, and the quality of life actually worse relative to stents [164]. The addition of external beam radiotherapy to laser increased serious complications, hospitalization time, and cost, but did not result in more long-term efficacy than stents [164]. In addition to the above, another major limitation of laser therapy was the need for repeated endoscopic treatments.

In contrast, single-dose esophageal brachytherapy has compared favorably with partly covered Ultraflex stent placement in
a randomized trial of 209 patients [165]. Although stents resulted in more immediate relief of dysphagia, dysphagia relief was better in brachytherapy recipients after 5 months. Cost, survival, and quality of life were not significantly different between the two groups. Similar results have also been reported with multiple sessions of endoluminal brachytherapy compared to Ultraflex stent placement [166].

Nonesophageal strictures

Although few randomized trials have been conducted with extraesophageal stents, a plethora of case series have been assessed in metaanalyses of gastroduodenal [167] and colorectal [168,169] malignancies. These analyses found that stent migration and occlusion are among the most common complications, each occurring in 5%–17% after enteral or colonic SEMS placements. While occlusion was usually from tumor ingrowth or overgrowth, 10%–25% of colonic stent obstructions were the result of fecal impaction. With the introduction of partially covered and fully covered self-expandable enteral and colonic stents, lower occlusion rates have been offset by higher migration rates. A randomized prospective trial by Kim et al. in 80 patients with malignant pyloric obstruction, reported a stent occlusion rate of 3% for covered stents versus 44% for uncovered stents [170]. However, migration rates were significantly higher for the covered stents versus uncovered stents (32% vs 8%). The negative features of these two types of stents compensated each other resulting in similar patency rates for both types of stents. In order to overcome the shortcomings of uncovered and covered stent design, investigators have tried to combine the best features of both by development of a double-type expandable nitinol prosthesis with an inner uncovered and partially covered outer stent. In a large prospective series, when placed fluoroscopically these hybrid prostheses showed promising results with a migration rate of 4% and obstruction rate of 14% [171].

Life-threatening complications, namely perforation or severe bleeding, are rare, occurring in less than 1% of gastroduodenal stent placements [170,172–174]. However, the rate of perforation is higher (up to 5%) with colorectal stent placement, particularly if balloon predilation or excessive wire manipulation is employed, and it constitutes the major cause for the 0.5%–1% mortality observed with this procedure [134,175,176]. In the current literature, more than 80% of perforations occur within 30 days of placement (half within 1 day of the procedure) and the mortality for patients experiencing a perforation is 16%. Bevacizumab-based chemotherapy is emerging as a major risk factor for poststent placement perforation and this may be secondary to its antiangiogenic effect. Some studies have demonstrated a threefold increase in risk of perforation [134,177,178].

Biliary obstruction, with jaundice or cholangitis, complicates 1.3% of gastroduodenal prostheses placements [170,172–174]. Pain is less commonly a complication with extraesophageal stent placements than with esophageal stents, being reported in only 2.5%–5% of cases, and is usually minor or transient.

Surgery is the principal alternative to stent placement for extraesophageal obstructions, and has historically been indicated for emergency colorectal obstructions, even in patients for whom a surgical cure is not possible. Randomized trials and case series have demonstrated that while stents and surgery for malignant colorectal obstruction have comparable morbidity and mortality, colectomy is associated with longer hospitalization and usually necessitates colostomy [128,129,133,163,179]. Similarly, surgical treatment of malignant gastric outlet obstruction is comparable to stent placement in terms of morbidity, mortality, and ultimate clinical efficacy, but takes longer to achieve that efficacy and results in longer hospitalization [133]. Thus, reports have suggested that prostheses are a more attractive approach to malignant extraesophageal obstruction than surgical alternatives. There are few data that compare prostheses to less invasive palliative alternatives such as a jejunal feeding tube or a diverting cecostomy.

Efficacy

Esophagus

Conventional stents can be successfully placed in approximately 90%–95% of patients with malignant esophageal obstruction, with mean patient survival of 2–4 months [118]. Terminal events frequently include tumor cachexia or subacute stent-related problems such as aspiration or stent erosion into major vessels.

Numerous series reporting long-term results of expandable stent placement for malignant dysphagia have been published, documenting technical and clinical success rates comparable or superior to conventional stents [102,118,180–182]. As noted above, these results are contingent, in part, on both stent design and initial successful palliation of dysphagia, but usually patients experience fewer complications and shorter hospitalization with expandable stents. Nevertheless, in most series, survival appears identical to that following conventional prosthesis insertion [102], underscoring the degree to which mortality is dictated more by the underlying malignancy than the complications of these palliative prostheses. Our study comparing 85 patients in whom conventional versus expandable prostheses were placed for malignant dysphagia found comparable levels of poststent dysphagia (0.4 vs 0.9), fistula occlusion (13/15 vs 13/14), and survival (87 vs 90 days) [157]. Similar palliation and complication rates have been reported in studies comparing Z, Ultraflex, and Flamingo prostheses for malignant dysphagia [183,184].

Benign esophageal strictures have been treated with temporary SEPS and fully covered SEMS (FCSEMS), with response rates varying from 20% to 80% [111,112,185]. In a metaanalysis (eight studies published from 1965 to 2010, 199 patients) of the efficacy of SEPS and FCSEMS for the treatment of refractory esophageal strictures, overall 46% patients had improvement of dysphagia at an average follow-up of 74 weeks [186]. FCSEMS and partially covered SEMS (PCSEMS), and SEPS have also successfully occluded esophageal leaks, perforations, and fistulae with less mortality and shorter hospitalization than surgical
or conservative management [114,115]. In a pooled analysis of 25 studies, which included 267 patients, clinical success was achieved in 85% of patients and there was no difference among stent types (FCSEMS 85%, PCSEMS 86%, and SEPS 84%) [187]. Furthermore, placement of a SEPS or FCSEMS inside a previously placed metal stent has facilitated the removal of the latter [107,108,112]. FCSEMS have more uncommonly been used to treat patients with variceal bleeding, and postband induced and post sclerotherapy ulcer-induced bleeding [188,189]. A few series demonstrate the efficacy of temporary placement of large-diameter SEMS for the treatment of achalasia with comparable results to pneumatic dilation [190,191].

Nonesophageal strictures
Numerous reports of stent placement in malignant stenoses of the stomach, small bowel, and colon have been summarized in the aforementioned metaanalyses [167–169]. Technically successful stent deployment was reported in 97% of gastroduodenal strictens. About 88% of enteral prostheses achieved clinical success, namely improved oral intake [167]. The majority (61%) of gastroduodenal stent failures were due to disease progression, with most of the remainder reflecting stent migration (20%) or incorrect deployment (15%) [167]. The data for the use of FCSEMS to treat patients with gastric outlet obstruction from benign strictures, who are not surgical candidates, and are refractory to balloon dilation, is sparse. Kim et al. [192] reported on a small series of patients who underwent placement of fully covered \((n = 4)\) and partially covered \((n = 3)\) SEMS for benign anastomotic gastric strictures. Clinical success was achieved in 71% of these patients, with stent migration occurring in three out of the four patients with FCSEMS.

Technically successful stent deployment has been reported in 93% of colorectal placements, with most failures due to inability to cannulate a high-grade obstruction with a guidewire [168]. Technical success was not increased in colorectal strictures when predilation was performed to facilitate guidewire passage [169], suggesting that predilation [168,169] may not be warranted. Factors that predict a lower likelihood of technical success with colorectal prostheses include lesions proximal to the rectosigmoid, in which only about 85% of placements were successful [168]. Extrinsic colorectal compression from non-colorectal primary malignancies have also been found to be less amenable to stent placement, with only 78% of these cases achieving technical success [168]. Clinical success (i.e., colorectal decompression) has been approximately 88% with colonic prostheses [168,169]. Although stent malposition or migration caused about half the clinical failures of colorectal prostheses, perforation was a significant limitation, accounting for 15%–30% of failures in this group [168,169]. In a subset of patients who received a colorectal prosthesis as a bridge to surgery, 72%–78% were able to undergo a single-stage colectomy, avoiding colostomy [168,169]. Furthermore, in a large, systematic review (29 studies, 2286 patients), the stent group had a lower mortality, complication rate, and shorter hospital stay than the surgical group [193]. Data on the use of SEMS to treat benign colonic strictures are limited and disappointing. In an extensive literature review using 53 uncovered SEMS, six SEPS, and four FCSEMS, the overall patency rate at a mean follow-up of 18 months was 71%, with a migration rate of 43%, and a major complication rate of 21% [194].

**Future applications**

The future of gastrointestinal dilation is contingent on further experience with the available dilating systems, such as CRE balloons, in comparison to polyvinyl dilators. Both expanded experience and controlled clinical trials should allow improved delineation of the indications, benefits, procedure costs, and risks with individual dilating systems, for specific stenotic lesions. More recently developed technologies, such as the transparent over-the-scope Optical dilators, may facilitate endoscopic guidance and visualization during dilation to improve the safety of dilation, and extend the applicability of solid dilators beyond esophageal and anorectal stenosis. However, there remains minimal data on their use. The future of gastrointestinal dilation may also include the development of dilators that can detect a fall in wall tension or resistance within a tissue during dilation to confirm that the dilation is adequate, thus conceptually improving safety [195].

There are also likely to be additional technological combinations of dilators and various thermal modalities for malignant stenoses. Just as bipolar tumor probes have conjoined Eder–Puestow dilators with multipolar electrocautery to treat concentric esophageal or rectal neoplasms, similar electrodes have been implanted on balloons or polyvinyl dilators. A new approach is to take a quartz laser fiber and surround the tip with a balloon so that the balloon keeps the fiber tip in the center of the lumen. These catheters may ultimately allow treatment of nonresectable biliary, gastroesophageal, or rectal neoplasms using laser energy. Photodynamic therapy, in turn, may play an increasing role in the treatment of malignant stenoses, while argon plasma coagulation or endoscopic cryotherapy may be used in lieu of Nd:YAG laser to open a lesion or facilitate stent placement.

Finally, as noted already, dilation will be increasingly used in conjunction with expandable stent technology. Permanent expandable stents hold the potential promise of prolonged stricture patency and decreased stent migration [196]. A covered esophageal stent impregnated with a \(\beta\)-emitting radionuclide has been demonstrated to combine the benefits of brachytherapy and stent technology in a single device [161]. Z stents covered with small intestinal submucosa have facilitated reepithelialization of vascular and airway stents in animal models [197,198] and may hold similar potential in the alimentary canal. A lumen-apposing dual anchor, transluminal stent (AXIOS, XLumena Inc., Mountain View, California, USA), has recently been developed for transluminal drainage. The stent is
designed to provide robust anchorage of nonadherent luminal surfaces such as a pancreatic fluid collection and the gastrointestinal wall by preventing tissue ingrowth and track leakage. This stent has been used to establish a gastrojejunostomy [199,200]. As the technology improves for removable prostheses, their role in the treatment of benign conditions may expand to obviate repeated dilation sessions, and potentially provide treatment for benign and malignant central stenoses and leaks.

References are available at www.yamadagastro.com/textbook

Further reading


CHAPTER 137

Endoscopic approaches to enteral nutrition

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Introduction

Enteral nutrition is used in a variety of settings and is preferred to parenteral nutrition whenever possible in patients who have intact gastrointestinal function. Enteral nutrition support is utilized in patients unable to obtain adequate peroral nutritional intake related to permanent neurological impairment, short gut syndrome, malnutrition prior to surgical intervention, major trauma or severe burns, severe acute pancreatitis, and patients undergoing chemotherapy prior to bone marrow transplantation [1].

Enteral feeding through nasal routes is a mainstay of short-term feeding. Transnasal tube delivery can be achieved using endoscopic methods, especially when blind and even radiologically guided passage is not possible. The delivery of enteral nutrition was revolutionized in 1980 after the description of percutaneous endoscopic gastrostomy (PEG). Prior to the development of PEG, a variety of surgical gastrostomy techniques had been employed, including both open (“Stamm”) and laparoscopic (“Janeway”) methods [2]. Now virtually ubiquitous, PEG placement, pioneered by Gauderer and Ponsky [3], provides a long-term alternative to surgical gastrostomy in patients requiring enteral nutrition. When compared to its predecessors, PEG is less invasive and can be performed without general anesthesia. Thus PEG is now the most commonly used method for gastrostomy worldwide. PEG tubes are placed using a variety of methods. Additionally, PEG tubes and PEG tracts can be used to provide jejunal feeding. Finally, direct percutaneous endoscopic jejunoostomy (PEJ) is increasingly being performed. In this chapter, we will review the endoscopic approaches to enteral feeding (see Podcast 137.1).

Types of endoscopic enteral feeding

Enteral nutrition can be provided using a variety of endoscopic methods (Box 137.1). These include short-term feeding using nasogastric (NG) and nasojejunal (NJ) tubes, and long-term options via percutaneous placement. The type of feeding used depends on whether feeding is required short term or long term, prior surgical anatomy, gastric emptying, and presence of luminal obstruction.

Transnasal feeding

Transnasal feeding tubes are generally used for short-term feeding (up to several weeks) in patients unable to consume

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adequate oral nutrition. This option can be used in patients who
only require short-term feeding or as a bridge to a long-term
feeding option such as a PEG or PEJ feeding. The placement of
a transnasal feeding tube such as NJ, is necessary to assess toler-
ability of enteral nutrition prior to placement of a long-term
percutaneous tube, when small bowel function has not been
established. Simple NG tubes can be placed nonendoscopically
at the bedside, with or without fluoroscopy. Endoscopic place-
ment is usually undertaken when other measures fail, particu-
larly when there is anatomical obstruction or difficulty in blind
placement of a feeding tube.

Endoscopic NG tube placement entails the passage of an
endoscope into the stomach, placement of a guide wire into the
antrum, removal of the endoscope, and passage of the tube over
the guide wire. It may be done with or without fluoroscopy. If
the endoscope is passed transorally the wire must be exchanged
from the mouth to the nose before tube placement. This can be
uncomfortable for the patient and risks injury to the operator.
Thus, at many institutions, a small-caliber endoscope (4.9–
5.5 mm outer diameter) is passed transnasally for delivery of the
guide wire into the stomach.

Endoscopic NJ tube placement is performed in a manner
similar to that described for NG tube feeding. Fluoroscopy is
more frequently used during NJ placement to ensure that guide
wire placement is well beyond the pylorus, ideally beyond the
ligament of Treitz as evidenced radiographically. Fluoroscopy is
also used to monitor the wire for looping and to prevent wire
loss during endoscope removal and tube placement. When tran-
snasal endoscopes are used, looping often occurs in the stomach
and thus the endoscope tip may not advance much beyond the
second duodenum. Aggressive air aspiration during entry and
exit from the stomach can also help prevent looping, as does the
use of a stiff guide wire.

Percutaneous options for feeding
Percutaneous endoscopic gastrostomy
In patients with a functional stomach who will likely require
enteral feeding for more than 30 days, placement of a PEG tube
is usually the most appropriate method to deliver nutrition. The
most common indications (>70%) for PEG placement are ina-
Bility to swallow due to neurological impairment (i.e., cerebrov-
ascular accident, dementia, motor neuron disease, Parkinson
disease, central nervous system tumors) and malignancy [4]. In
addition, nonnutrition-related applications have been described,
most commonly to facilitate gastric decompression in patients
with gastrointestinal dysmotility (i.e., diabetic gastroparesis) or
uncorrectable small bowel obstruction, such as in the setting of
peritoneal carcinomatosis.

Placement of PEG tubes is now a routine procedure. As expe-
rience with the placement of PEG tubes has grown, the number of
absolute contraindications to placement has dwindled. The
inability to pass an endoscope transorally into the stomach, or
inability to locate a suitable tube site using transillumination
should be considered absolute contraindications related to tech-
ical aspects of the procedure. Patient-related factors which are
considered contraindications to a feeding gastrostomy include
gastric outlet obstruction, severe intestinal dysmotility, intratho-
racic stomach, and peritonitis. In patients with coagulopathy or
ascites, placement of a PEG tube is possible though the endo-
scopist should proceed with caution as these confer high risks.
Ascites is not an absolute contraindication; however, large-
volume paracentesis before and after placement is recom-
ended to allow adherence of the anterior gastric wall to the
abdominal wall [5].

Though endoscopic placement of percutaneous feeding tubes
is considered safe, endoscopists need to be aware of the ethical
and medicolegal aspects of tube placement in patients with
diminished life expectancy [6]. The perceived benefits must out-
weigh the risks of the procedure and in certain circumstances
this remains difficult to discern. Placement of a PEG tube is
certainly indicated in patients with acute insults, such as dys-
phagia following a cerebrovascular accident, as the potential for
recovery of function is substantial [7]. However, major contro-
versy persists regarding the beneficence of PEG tube placement
in patients with incurable malignancies and advanced dementia
as these patients are unlikely to benefit from enteral nutrition.

Patient preparation
Several key preprocedural evaluation essentials can minimize
intra- and postprocedural adverse events (AEs). The patient
should refrain from clear liquids several hours prior to the pro-
cedure and solids for at least 6 h prior to the procedure. In
patients with known impaired motility, these intervals may need
to be lengthened to prevent aspiration. A brief focused physical
examination and assessment of vital signs should be performed
with consideration given to procedural postponement in febrile
patients and those with hemodynamic compromise. Prior to
procedural intervention, routine laboratory testing consisting of
a complete blood count and coagulation profile (i.e., pro-
thrombin time [PT], activated partial thromboplastin time
[aPTT], and international normalized ratio [INR]) is usually
obtained to elucidate coagulopathies and/or thrombocytopenia.
A platelet count of ≥50 000/μL and INR of ≤1.5 are considered
satisfactory for gastrostomy tube placement, but these values

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Box 137.1 Types of enteral access provided via endoscopy.

- Nasogastric
- Nasojugal
- Percutaneous endoscopic gastrostomy (PEG)
- PEG with jejunal extension
- Transgastric jejunal feeding
- Direct percutaneous endoscopic jejunostomy (DPEJ)
may vary between physicians and institutions. PEG placement is considered a higher risk procedure than diagnostic endoscopy and foresight for management of antithrombotic agents will also minimize procedure-related bleeding [8]. Pertinent radiological imaging, such as computed tomography (CT), if performed, should be reviewed prior to the procedure. Finally, informed consent detailing the risks, benefits, and alternatives to PEG placement should be obtained from the patient or healthcare proxy with power of attorney prior to intervention.

The patient should be positioned supine with the head of the bed slightly elevated to minimize aspiration risk. Supplemental oxygen should be provided to all patients and a suction setup should be readily available for the management of oropharyngeal secretions. Blood pressure and oximetry should be monitored throughout the entirety of the procedure. In patients with American Society of Anesthesiologists (ASA) physical classification system score of 3–4, strong consideration should be given to having anesthesia assistance, especially in those patients with neurological disease such as amyotrophic lateral sclerosis (ALS).

A single-dose intravenous antibiotic aimed at coverage of Gram-positive organisms should be given 30 min prior to the procedure in patients not already on a scheduled antibiotic regimen [9,10]. Data suggests that antibiotic prophylaxis with cephalosporins or penicillin-based agents results in a >60% relative risk reduction in PEG site wound infections [9]. Esophageal intubation can be challenging in the supine position, thus patients may be placed in the left lateral decubitus position initially and moved supine after passage of the gastroscope.

Supplies for percutaneous endoscopic gastrostomy placement

Several complete PEG kits are commercially available. The kits generally contain a sterile drape, povidone-iodine solution (Betadine), three needles of various sizes, injectable local anesthetic (lidocaine), a disposable grasping snare, a Teflon-coated guide wire, and the gastrostomy tube itself. The smallest needle (25 g) is used to anesthetize the skin with lidocaine. The 21-gauge needle is considered a “finder” needle and is used to locate the gastrointestinal lumen while the largest needle (18 gauge) is housed within an outer sheath which permits guide wire passage after needle removal. Additional pre- and postprocedural supplies such as gauze pads and a scalpel are also included in most kits.

Pull (Ponsky–Gauderer) technique

Following adequate sedation, a full endoscopic evaluation of the upper gastrointestinal tract should be performed prior to gastrostomy placement. The gastroscope is then withdrawn into the stomach for siting of the gastrostomy. The room lights are dimmed to enhance detection of the endoscopic transillumination directed at the anterior gastric wall. Liberal use of air insuf-
needle is then used as a “finder” needle to identify the gastric lumen. The needle is preloaded onto a water-filled syringe and introduced through the abdominal wall while suction is applied to the syringe barrel to ensure that air bubbling in the syringe coincides with visualization of the needle in the stomach (Figure 137.1b). This is termed the “safe-track” technique and ensures that a nongastric lumen has not been entered. This needle is removed and an 18-gauge needle (trocar) with plastic sheath is passed in the same path as the finder needle. Upon entry into the stomach, the needle catheter is ensnared to maintain its position. The trocar is removed and a long (260 cm) plastic guide wire is passed through the needle and into the gastric lumen. The sheath is peeled away from the catheter and repositioned to grasp the guide wire (Figure 137.1c) that has a loop on one end to allow attachment to the gastrostomy tube. The gastroscope, snare, and guide wire are then withdrawn through the mouth. The guide wire exiting via the mouth is fastened to the drainage end of the gastrostomy tube (Figure 137.1d). After adequate lubrication is applied to the tube, the guide wire exiting the abdominal wall is grasped and the gastrostomy tube is pulled through the esophagus and into the stomach before exiting the abdominal wall (Figure 137.1e). The gastrostomy tube is shortened and an external disk is loosely approximated to the skin allowing for easy rotation and ~1 cm of anterior-posterior movement. This is important since excessive apposition of the bumper is associated with the buried bumper syndrome and likely increases the risk of infection and ischemia as well as the rare but possibly fatal complication of necrotizing fasciitis. Repeat endoscopy following PEG tube placement to assess the position of the internal bumper is not necessary and should only be considered when a technical error is suspected [12].

**Push (Sacks–Vine) technique**

Placement of a PEG tube utilizing the push technique shares many procedural similarities to the pull technique. Identification of a suitable site, puncture through the abdominal wall, and control of the guide wire with removal through the patient’s mouth are performed in the same manner (Figure 137.2a). While maintaining tension on both ends of a standard guide wire (enclosed within the kit), a long, tapered-tip gastrostomy tube is pushed over the guide wire until it exits the abdominal wall (Figure 137.2b). The gastrostomy tube is then grasped at the exit site and pulled into the final position while applying forward (push) pressure from the oral side. An external disk is placed over the tube joining the gastric and abdominal wall in a similar fashion to the pull technique.

**Direct introducer (Russell) technique**

The introducer method permits gastrostomy tube placement via percutaneous access, without the need for tube passage through the oropharynx and esophagus. This is particularly important in patients with untreated head and neck, and esophageal cancers, as well as some oroesophageal infections to prevent tumor implant and infection [13], respectively, at the gastrotomy site. Similar to the prior techniques, the gastroscope is withdrawn into the stomach after full endoscopic survey. Transillumination and finger indentation of the anterior gastric wall are used to identify a puncture site. The skin is prepped, draped, and anesthetized before the skin is incised. An 18-gauge needle catheter is introduced into the gastric lumen and a guide wire is passed. The needle is removed and a sequence of dilators are passed over the wire (Figure 137.3a), similar to the modified Seldinger technique utilized for venous catheter placement [14]. After adequate dilation, an introducer with a peel-away sheath is passed over the guide wire. The guide wire and introducer are then removed leaving the sheath behind. A balloon-bumper gastrostomy tube is placed through the sheath and inflated. The sheath is peeled away and the gastrostomy tube is pulled into position (Figure 137.3b). Finally, the external skin disk is applied to approximate the gastric and abdominal walls.

Though not in the original description by Russell et al. [15], T fastener gastropexy can be placed prior to tract dilation. This prevents wall separation during the remainder of the gastrotomy procedure and limits complications in the event of inadvertent tube dislodgement [16]. T fasteners are composed of a suture affixed to the center of a metal bar. This apparatus is introduced through a needle catheter after site localization and gastric puncture. The T fastener is then deployed through the needle catheter and positioned in its T configuration. A suture and external bolster are anchored to the external abdominal
the gastric and abdominal wall anastomosis, though with the advent of T fasteners and suture anchors this may no longer be a distinguishing benefit. In the event of endoscopic and radiological failure, a primary surgical gastrostomy with an open [19] or minimally invasive approach [20] can be employed. Alternatively, a combined laparoscopic–endoscopic technique has been described and can be used to facilitate gastrostomy placement [21]. This method begins with placement of a small (≈5 mm) trocar into the peritoneal cavity which allows for laparoscopic evaluation and investigation into reasons for prior PEG failure. Adhesiolysis and repositioning of overlying organs can be performed, if necessary. A gastroscope is then passed into the stomach with the laparoscope remaining in place. PEG placement using the pull-type method is then performed in standard fashion under direct laparoscopic visualization.

**Comparison of gastrostomy techniques**

There are very few studies comparing the various methods for gastrostomy tube placement. It appears that for most patients, and in most situations other than those outlined above, there is little difference in outcome between the different endoscopic methods (i.e., pull-type, push-type, introducer). In the current era, most gastrostomy tubes are placed using the endoscopy, though this may be center dependent. Moreover, most gastroenterologists prefer the pull-type endoscopic method over the push-type, likely due to enhanced control with this method. As mentioned, surgical gastrostomy is generally not performed given the high success rate of the endoscopy and radiological methods; however, surgical placement may be most appropriate in some patients with extenuating circumstances.

There are two other clinical scenarios which bear mentioning. Severe esophageal obstruction can be seen in a variety of clinical scenarios (i.e., advanced malignancy, lye stricture, etc.) and is
not an absolute contraindication to PEG placement. However, dilation of the stricture may be necessary to allow passage of the endoscope and/or the internal mushroom bumper of the gastrostomy tube. Radially incising the internal bumper to improve collapsibility during passage through the esophagus may be helpful in this circumstance. Endoscopists must also exercise caution when placing a PEG tube after previous placement of an esophageal self-expandable metal stent (SEMS). This is most important in the setting of recent SEMS placement when the stent is not yet fully expanded or when fully covered SEMS are used as this may result in stent dislodgement and distal migration [22]. Utilization of the introducer method has advantages in patients with severe esophageal obstruction and indwelling esophageal SEMS; however, this technique still requires intubation of the esophagus and stomach with the endoscope, and thus it is best to proceed cautiously in these patients.

**Postprocedural management**

Standardized care of the gastrostomy tube is effective in preventing skin breakdown and AEs such as PEG site infections and buried bumper syndrome which can result from excessive tension on the external bumper. Enteral feeding is generally initiated 24 h of placement, though some centers have demonstrated safe initiation 3 h postprocedure assuming no periprocedural AEs occurred [23].

Following tube placement, the PEG site should be cleansed daily with mild soap and water but water immersion (i.e., bathing, swimming, etc.) should be strictly avoided for the following 6 weeks. After cleansing, a split, sterile gauze dressing should be placed between the external disk and the skin for the initial 5 days postprocedure, and as needed thereafter. This sponge should be changed routinely once it becomes moist. The PEG tube should be freely mobile within the tract as mentioned above. The site may be tender for 2–3 days following placement and pain control with acetaminophen or, rarely, narcotic analgesics may be indicated; however, aspirin and nonsteroidal anti-inflammatory agents (i.e., ibuprofen, naproxen, etc.) should be strictly avoided. After 2–3 days, the site tenderness and procedure-related erythema should resolve; persistent symptoms thereafter require physician evaluation.

Most manufacturers recommend tube removal 3–6 months after placement, though PEG tubes can last for up to 1 year with proper care. All commercially available PEG tubes are traction removable. This can be performed as an outpatient, though it is painful and patients may prefer parenteral analgesia during removal. Replacement tubes are generally balloon tubes which are less robust and must be replaced every 3 months. Although nearly any balloon tubes can be placed (e.g., Foley catheters), commercially available replacement tubes have an external bumper to prevent inward migration. After removal of the original PEG, the balloon catheter is placed through the mature (>4 weeks after placement) gastrostomy tract and the balloon inflated. One must be certain that the tube has entered the stomach as false passage may occur into the peritoneum. Some authors advocate for fluoroscopic confirmation using water-soluble contrast instillation via the percutaneous tube.

**Complications**

Two recent large retrospective studies have demonstrated an overall AE rate of ∼13% following PEG tube placement [4,24]. The specific frequency of minor and major AEs varies widely in the literature (Box 137.2). Current evidence suggests an overall procedure-related mortality of 0.2% [4]. The 30-day mortality following PEG placement varies in the literature and is largely related to underlying comorbidities [4,25]. Recent evidence suggests that patients with a low serum albumin, and possibly, elevated C-reactive protein have an increased 30-day mortality risk [4,26,27].

**Aspiration**

Aspiration of oropharyngeal secretions or gastric contents remains a major AE following PEG placement, occurring in 1.5% of cases [4]. Pneumonitis can occur during the procedure or in the postprocedural setting once tube feeding is initiated. Patients with aspiration-related pneumonia or pneumonitis may exhibit a productive cough, fever, or become dyspneic. An overt infiltrate on standard chest X-ray or leukocytosis may accompany this symptom. Procedure-related aspiration can be mitigated by avoiding oversedation, raising the head of the bed, minimizing air insufflation, performing aggressive intraprocedural suctioning of oropharyngeal secretions, and complete aspiration of gastric contents prior to PEG placement. The

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**Box 137.2 Adverse events following percutaneous endoscopic gastrostomy (PEG) placement.**

**Minor**
- Peristomal infection, pain, leakage
- Prolonged ileus
- Gastric ulcer
- Inadvertent tube removal
- Tube dysfunction

**Major**
- Peritonitis
- Hemorrhage
- Aspiration
- Perforation
- Buried bumper/tube migration
- Gastrocolocutaneous fistula
- Neoplastic seeding
- Necrotizing fasciitis
placement of a direct PEJ or a PEG tube with a jejunal extension (PEG/J) is thought to decrease the risk of reflux-induced tube feeding aspiration but has no effect on oropharyngeal aspiration, which often occurs in patients who require PEG placement. One large series documented the risk of aspiration in patients undergoing PEJ placement at 3 cases per 1000 procedures [28]. Most gastroenterologists believe that direct PEJ (DPEJ) is a more reliable option than a PEG/J; however, direct PEJ is a complex procedure which may require balloon-assisted enteroscopy for placement [29].

**Wound infection**

Local wound infection is a common minor complication following tube placement. Current microbiological data suggests that that *Candida* species, methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Pseudomonas aeruginosa* are the most frequent organisms leading to PEG site infection [30]. Gossner and colleagues [31] previously reported that a single dose of cefazolin covered >70% of organisms encountered and was effective in reducing PEG site infections by 20%. A systematic review and metaanalysis have since substantiated the benefits of prophylactic antibiotics in this setting [9,10]. Other organisms often identified include *Streptococcus* species, *Klebsiella pneumoniae*, and methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA wound infections have been observed in certain cohorts with some advocating for screening, decontamination, and MRSA-directed antibiotic prophylaxis prior to PEG placement [32,33]. The use of the “direct introducer method” has also demonstrated a significantly lower incidence of peristomal infection when compared to the standard “pull method” [34,35]. It has been hypothesized that the “direct introducer method” mitigates gastrostomy tube contamination by the inherent lack of exposure to oral flora during placement. A small skin incision during PEG placement was previously thought to increase the incidence of post-PEG wound site infections; however, data from Sedlack and colleagues suggests no increased risk of infection even after incisionless PEG placement [11].

Most wound infections are superficial and can be managed with conservative measures, though necrotizing fasciitis following PEG placement has been rarely reported [36]. Patients typically present several days after the procedure with erythema and pain surrounding the PEG site. Induration with abscess formation requiring incision and drainage occurs less frequently. Fever and leukocytosis are additional objective findings which may be present. The most common cause of peristomal infection is excessive tension between the inner bumper and outer bolster, leading to tissue ischemia and, possibly, necrosis. A correctly placed tube with unimpeded rotation and 1 cm of anterior-posterior movement is unlikely to produce local infection. Oral antibiotics should be started upon presentation and continued for the subsequent 5–7 days. The need for intravenous antibiotics is unlikely, but may be considered in patients with severe infections, bacteremia, or after identification of resistant bacteria.

**Pneumoperitoneum and peritonitis**

Pneumoperitoneum is a frequent finding after PEG placement but is usually clinically insignificant in the absence of symptoms. Recent data suggests that benign intraperitoneal air following PEG can be observed in approximately 5%–15% of all cases; however, emergent procedural intervention is necessary in less than 20% of patients with this finding [37,38]. A minority of patients (less than 2%) will go on to develop overt evidence of peritonitis (i.e., fever, hypotension, or abdominal pain) in the setting of extraluminal air [24]. A new leukocytosis or bacteremia should prompt immediate clinical evaluation and intervention, if necessary. A fluoroscopic tube injection study using water-soluble contrast is the test of choice to identify intraperitoneal extravasation. Patients with confirmed extraluminal contrast extravasation secondary to tube malfunction or wall separation should be started on broad-spectrum antibiotics and undergo immediate endoscopic or surgical repair [39].

**Gastrocolocutaneous fistula**

Gastrocolocutaneous fistula is a rare complication of PEG tube placement which occurs when the colon is interposed between the gastric and abdominal wall and inadvertently traversed during gastric puncture. The presence of air or stool within the syringe in conjunction with the lack of endoscopic needle visualization is suggestive of entry into the colon or small bowel. The “safe-tract technique” aims to minimize this complication by ensuring that syringe entry through the gastric wall coincides with endoscopic visualization of the needle in the stomach during initial placement [40]. Many patients remain asymptomatic with the error only noted during the subsequent tube exchange when the new tube is noted within the colon. Symptomatic patients typically present in one of three ways: (1) acute intestinal or colonic obstruction; (2) severe diarrhea related to direct infusion of tube feedings into the colon; or (3) feculent leakage from the stoma site. The fistula generally resolves spontaneously following tube removal; however, newer endoscopic techniques such as the over-the-scope clip [41] and endoscopic suturing [42] may be utilized for closure. In rare instances, surgical intervention or radiological drainage may be required in patients with peritonitis or abscess formation.

**Buried bumper syndrome**

Buried bumper syndrome is a late complication which occurs most frequently in the setting of excessive tension between the outer bolster and inner bumper. These circumstances lead to localized ischemia, eventual tissue necrosis, and partial or complete regrowth of the gastric mucosa over the internal bumper with subsequent migration into the subcutaneous tissues. Similar to PEG site infections, appropriate tube placement is critical to prevent this complication. Patients most frequently present with difficulty feeding, tube fixation, and/or peristomal leakage [43]. Peristomal wound pain or external bulging from the migrated bumper may also be evident on examination. The optimal management strategy for buried bumper syndrome is
less evident. Removal of a buried bumper can be performed by external traction [43], advanced endoscopic techniques [44], or laparoscopic intervention [45] after failure of less invasive options.

Neoplastic seeding of the stoma
Metastatic disease arising at the stoma site is a rare, but devastating, complication following PEG placement using pull or push techniques. The pathogenetic mechanisms of this phenomenon remain controversial with direct transfer of malignant cells from the tumor origin to the abdominal wall, the leading hypothesis. The risk of neoplastic seeding is highest in patients with PEG placement utilizing the pull or push technique; however, cases of stomal metastases following surgical [46] and radiological [47] gastrostomy have also been reported. These reports implicate additional mechanisms which may be involved, such as hematogenous or lymphogenous spread. A recent literature review identified less than 50 cases of stomal seeding from 1962 to 2011 in patients with upper aerodigestive tract cancers [48]. Though a rare complication, this should be considered in patients undergoing PEG placement prior to neoadjuvant radiation or chemotherapy as evidence of widespread metastases would make future curative surgical intervention unlikely. Gastrostomy placement using surgical, radiological, or endoscopic introducer methods should be strongly considered in this subset of patients.

Use of gastrostomy tubes and sites for endoscopic jejunostomy
In patients who require jejunal feeding there are two general approaches when a gastrostomy tract is used. The first option is to use a jejunal extension tube placed through the original PEG tube. This can be done at the time of initial PEG placement or subsequent to it. These tubes are passed through the lumen of the existing PEG tube and contain one port for jejunal feeding and one port for gastric aspiration, if needed (e.g., in the setting of delayed gastric emptying). Placement of a jejunal extension tube can be performed in a variety of ways. One method frequently employed involves passing the extension tube through the PEG tube which is then grasped and advanced into the duodenum using a transorally delivered endoscope. This technique is somewhat limited as the extension tube may drag back into the distal stomach upon withdrawal of the endoscope and, even if placed successfully, the extension tube frequently slips back into the stomach. Alternatively, a single-piece jejunal tube can also be placed by passing a small-caliber pediatric gastroscope through a mature gastrostomy tract [49]. Using this method, the PEG tube is removed and the gastrostomy site serves as the access point. The endoscope enters the stomach and is advanced to the distal duodenum. A guide wire is then passed and the gastroscope is withdrawn, thus allowing placement of the single-piece jejunostomy tube over the guide wire and into the small bowel. A similar technique using a pediatric bronchoscope has also been reported [50].

Direct percutaneous endoscopic jejunostomy tube placement
Direct PEJ placement was initially described in 1987 [51] as a method to provide enteral nutrition to patients with prior partial or total gastrectomy, but is now utilized in a variety of clinical scenarios. Direct PEJ placement is indicated in patients requiring long-term jejunal feeding who are unable to tolerate gastric feedings (i.e., diabetic gastroparesis, history of aspiration, etc.). In addition, a DPEJ can be placed in patients when the stomach is not easily accessible (e.g., Roux-en-Y gastric bypass, prior distal esophagectomy with gastric pull-up [Ivor Lewis procedure]). When successful, DPEJ placement mitigates many of the limitations described above for PEG/J; however, there is greater risk for AEs [28]. Direct PEJ ensures stable placement beyond the ligament of Treitz, has no risk for proximal tube migration, decreases the risk for aspiration pneumonia [52], and allows for placement of large-bore feeding tubes that are less prone to blockage and dysfunction. When compared to PEG/J the patency and need for reintervention after the index procedure is quite low [53,54].

Direct PEJ is a technically challenging procedure that is performed by placing a percutaneous tube directly into the small bowel using similar techniques and principles as PEG placement. A few key procedural differences bear mentioning. In contrast to PEG placement, a site within or near an abdominal surgical scar often provides an optimal location for DPEJ placement. During DPEJ placement adherence of small bowel to the abdominal wall is advantageous and facilitates anchoring of the tube. After site identification, the “finder” needle is introduced into the bowel and firmly grasped with a standard colonoscopy snare to fix the small bowel to the abdominal wall [54]. A colonoscopy snare must be utilized during DPEJ placement since the snare provided in the commercially available kits is of insufficient length. Next, the 18-gauge needle catheter is then delivered alongside and in the similar trajectory as the finder needle. The snare is released and repositioned around the needle catheter. The remainder of the procedure then proceeds similar to PEG placement. The DPEJ procedure is often performed only in tertiary referral centers and frequently requires anesthesia support, two additional differences when compared to the PEG procedure.

In patients with native (nonsurgically altered) gastrointestinal anatomy, or prior history of Whipple or Billroth II procedure, long-length endoscopes are necessary. Historically, these included adult and pediatric colonoscopes as well as push enteroscopes. In 2005 Maple et al. [28] reported a series of 307 DPEJ attempts, in which nearly one-third failed due to lack of transillumination and/or inability to gain entry to the jejunum.
More recently, balloon enteroscopes (single- and double-balloon) have demonstrated success rates of 90%–100% and are especially useful in patients with surgically altered anatomy [29,55]. When compared to traditional colonoscopes, balloon enteroscopes achieve an increased depth of insertion within the small bowel and minimizes instrument looping within the stomach and proximal small bowel. In patients with surgically altered anatomy which includes both an efferent and afferent limb (i.e., Whipple or Billroth II), the DPEJ tube should be placed into the efferent limb or at the level of the anastomosis [54]. In contrast, placement of a DPEJ in patients with a Roux-en-Y anatomy (gastrojejunostomy) and/or surgically altered anatomy (total gastrectomy with esophagojejunostomy) can often be successfully performed using a standard gastroscope.

**Conclusion**

Placement of enteral access tubes should be individualized based upon long- and short-term patient needs. Transnasal routes are preferred when short-term feeding is needed. PEG or jejunostomy tube placement requires careful patient selection, strict adherence to the procedural protocol, and an awareness of potential AEs. Overall, these commonly performed procedures are safe and effective for patients requiring supplemental enteral nutrition, or those requiring gastric decompression.

References are available at www.yamadagastro.com/textbook

To access the podcast for this chapter, please go to www.yamadagastro.com/textbook

**Podcast 137.1** The podcast discusses enteral access and tube management in several challenging cases. Dr. Todd Baron outlines the presentation and management strategy in each case and provides tips and tricks for the practicing endoscopist.

**Further reading**


CHAPTER 138
Management of upper gastrointestinal hemorrhage related to portal hypertension

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Introduction

Portal hypertension is defined as the pathological increase in portal venous pressure, in which the pressure gradient between the portal vein and inferior vena cava (IVC) is increased above the normal value of approximately 5 mmHg. Portal hypertension becomes clinically significant when the portal venous pressure gradient exceeds a threshold value of 10 mmHg, as this gradient predicts the development of complications of portal hypertension, including the development of gastroesophageal varices (GOVs) and clinical decompensation [1]. Gastroesophageal variceal bleeding is a direct consequence of portal hypertension that leads to significant mortality and morbidity among patients with cirrhosis. This chapter will discuss the anatomy of the portal venous system and the causes of portal hypertension, the pathophysiology of portal hypertension, and the prevention and management of upper gastrointestinal hemorrhage secondary to portal hypertension. Upper gastrointestinal bleeding secondary to portal hypertension can result from a spectrum of conditions including GOVs, portal hypertensive gastropathy (PHG), and ectopic varices. The management of variceal gastrointestinal hemorrhage is centered on three principles: primary prophylaxis to prevent the first episode of bleeding, treatment of acute hemorrhage, and secondary prophylaxis to prevent recurrent bleeding.

Anatomy of portal venous system (see Chapter 10)

The portal vein drains blood from the stomach, intestines, spleen, pancreas, and gallbladder. The anatomy of the portal venous system is illustrated in Figure 138.1. The portal vein is formed by the union of the superior mesenteric vein (SMV) and splenic vein (SV) posterior to the head of the pancreas. The portal vein enters the liver at the porta hepatitis and divides into the right and left branches of the portal vein. The SMV is formed by tributaries draining the duodenum, head of the pancreas, jejunum, ileum, cecum, ascending colon, proximal two thirds of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2]. The inferior mesenteric vein, which drains the distal third of the transverse colon, and stomach via the right gastroepiploic vein [2].
pancreas. The left gastroepiploic vein and pancreatic veins also enter the SV. The left and right gastric veins, which run along the lesser curvature of the stomach, usually drain into the portal vein immediately after the junction of the SV and SMV. The paraumbilical veins and remnants of the umbilical vein drain into the left portal vein [3].

Portal venous flow is approximately 1000–1200 mL/min [2]. The portal vein supplies about 75% of the blood flow to the liver, while the hepatic artery provides the remainder of hepatic blood flow. Three hepatic veins drain blood from the liver into the IVC. The caudate lobe drains directly into the IVC.

When the portal venous pressure gradient exceeds a certain threshold, collaterals develop at sites of communication between the portal and systemic circulations, and blood will flow in a reverse direction to reach systemic circulation. The five areas of portosystemic anastomoses are as follows (Figure 138.2) [2]:

1. At the lower end of the esophagus, where the left gastric vein of the portal system anastomoses with the azygous system of veins which drains the middle third of the esophagus into systemic circulation.
2. In the paraumbilical region, where the paraumbilical veins in the falciform ligament anastomose with the superficial veins of the anterior abdominal wall.
3. At the anal canal, where the superior hemorrhoidal vein of the portal system anastomoses with the middle and inferior hemorrhoidal veins of the caval system.
4. In the splenic venous bed and the left renal vein.
5. In the retroperitoneum.

Gastroesophageal collaterals are of important clinical significance due to the risk of rupture and variceal hemorrhage.

**Causes of portal hypertension**

Causes of portal hypertension can be categorized as presinusoidal, sinusoidal, and postsinusoidal, based on the site of increased resistance to portal venous flow. Cirrhosis is the most common cause of portal hypertension, in which the resistance to flow occurs at the sinusoidal level. Presinusoidal causes include portal vein occlusion and SV thrombosis. In many parts of the world including sub-Saharan Africa, the Middle East, and Asia, schistosomiasis is a common cause of presinusoidal portal hypertension. Infection with *Schistosoma mansoni* or *S. japonicum* leads to deposition of eggs in the presinusoidal portal venules, which results in granulomatous inflammation. Postsinusoidal portal hypertension results from impaired outflow of blood from the liver. Causes include occlusion of the hepatic veins, i.e., Budd–Chiari syndrome, which can result from spontaneous thrombosis due to an underlying hypercoagulable state. Right-sided heart failure with passive congestion of the liver is a common cause of postsinusoidal portal hypertension. Rare causes of portal hypertension include nodular regenerative hyperplasia, congenital hepatic fibrosis, and sarcoidosis. The causes of portal hypertension are summarized in Table 138.1.

**Portal venous imaging techniques and measurement of portal pressure**

The portal vein can be imaged by several modalities including ultrasonography with Doppler, 3D computed tomography (3D-CT) scan (Figure 138.3), magnetic resonance imaging (MRI), and angiography. Ultrasonography with Doppler is the preferred initial test of choice due to its low cost and high accuracy. The use of Doppler allows for determination of the presence, direction, and velocity of portal blood flow. The patency of the hepatic veins can also be assessed. However, accuracy is dependent on the technical expertise of the operator [4]. 3D-CT and MRI scans with intravenous contrast are valuable tests to evaluate liver echotexture and assess for liver masses, portal vein patency, splenomegaly, and the presence of portosystemic collaterals. Indeed, the presence of portal hypertension is frequently first detected when noninvasive imaging reveals a dilated portal vein or the existence of ascites, splenomegaly, or portosystemic collaterals [4]. Diagnostic angiography is rarely needed for portal vein assessment given the high accuracy of noninvasive imaging.

The measurement of portal venous pressure is not routinely performed in clinical practice but can provide valuable information about the severity of portal hypertension and the risk of clinical decompensation including variceal hemorrhage. The most commonly used method is an indirect measurement of portal pressure via a transjugular approach in which the hepatic venous pressure gradient (HVPG) is calculated. A balloon catheter is introduced into the internal jugular vein and then into
Figure 138.2 Sites of portosystemic collateral circulation in portal hypertension and cirrhosis. Source: Dooley and Sherlock 2011 [2]. Reproduced with permission of John Wiley & Sons, Ltd.

Table 138.1 Causes of portal hypertension.

<table>
<thead>
<tr>
<th>Presinusoidal</th>
<th>Sinusoidal</th>
<th>Postsinusoidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis</td>
<td>Cirrhosis from most causes</td>
<td>Budd–Chiari syndrome</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Severe hepatitis</td>
<td>IVC malformation/web</td>
</tr>
<tr>
<td>Portal vein thrombosis/stenosis/compression</td>
<td>Nodular regenerative hyperplasia</td>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Splenic vein thrombosis</td>
<td>Congenital hepatic fibrosis</td>
<td>Right heart failure</td>
</tr>
<tr>
<td>Splanchnic arteriovenous fistula</td>
<td>Sarcoïdosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hereditary hemorrhagic telangiectasia</td>
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</table>

IVC, inferior vena cava.
The normal HVPG is approximately 3–5 mmHg. Portal hypertension is defined as an HVPG greater than 5 mmHg. An HVPG of 10 mmHg or more defines clinically significant portal hypertension, as studies have shown that this gradient predicts the clinical course in patients with cirrhosis, including the development of varices [5] and clinical decompensation, i.e., variceal hemorrhage, ascites, or encephalopathy [1]. The risk of variceal bleeding is low when the HVPG is less than 12 mmHg. The reduction of HVPG to $\leq 12$ mmHg or by $\geq 20\%$ of baseline has been shown to significantly reduce the risk of variceal bleeding [6]. A reduction in HVPG by $\geq 20\%$ of baseline has also been shown to decrease mortality [6]. Furthermore, in acute variceal bleeding, the HVPG has been found to predict prognosis and clinical outcome, with patients with an HVPG $>16$ mmHg having a higher likelihood of rebleeding and death [7].

Pathophysiology of portal hypertension

In the early stages of cirrhosis, patients have a normal portal venous pressure gradient. As disease progression occurs, portal venous pressure increases and portal hypertension develops. The pathophysiology of portal hypertension is complex and remains incompletely understood. Portal venous pressure is directly related to portal venous blood flow and
vascular resistance (Ohm’s law). In cirrhosis, there is increased resistance to portal flow due to vascular obliteration by the architectural distortion of the liver secondary to the development of fibrosis and regenerative nodules [8]. This increased resistance occurs at all levels of the intrahepatic vascular bed, i.e., the intrahepatic branches of the portal vein, hepatic sinusoids, and hepatic venous outflow tract [9]. Furthermore, in cirrhosis, activated hepatic stellate cells, which are located in the space of Disse between sinusoidal endothelial cells and hepatocytes, proliferate and deposit collagen in this space, which leads to the loss of fenestrae between endothelial cells and the formation of a subendothelial basement membrane. This is referred to as the capillarization of hepatic sinusoids and increases intrahepatic resistance [10]. Hepatocyte swelling and enlargement also contribute to increased resistance to portal flow [11,12].

**Endothelial dysfunction in intrahepatic circulation**

In addition to fixed structural defects, an increase in intrahepatic vascular tone is a dynamic component that contributes to the increase in intrahepatic vascular resistance. This reversible component accounts for about 20%–30% of the increase in intrahepatic resistance and is amenable to pharmacological modification [9]. In cirrhosis, endothelial dysfunction in the intrahepatic vasculature involves an interplay of multiple factors, including nitric oxide (NO) [13,14], cyclooxygenase (COX)-1 [15], angiotensin II [16,17], and oxidative stress [18]. Inflammation has also been implicated as a cause of endothelial dysfunction in cirrhosis [19,20]. Furthermore, there is evidence that the Toll-like receptor 4 (TLR4) which is present on sinusoidal endothelial cells and recognizes bacterial endotoxin plays a role in mediating angiogenesis [21]. This is important as angiogenesis is thought to contribute to portal hypertension by promoting fibrogenesis [22]. Tissue hypoxia may also stimulate angiogenesis via production of vascular endothelial growth factor (VEGF). Hypoxia may occur due to sinusoidal remodeling with loss of sinusoidal endothelial cell fenestrae and formation of a basement membrane with subsequent impairment in oxygen diffusion [22].

**Endothelial dysfunction in splanchnic and systemic circulations**

The increase in portal pressure triggers vascular changes in the splanchnic and systemic circulations which lead to arterial vasodilatation and the development of a hyperdynamic circulatory state [13]. Splanchnic vasodilation results in increased portal venous flow and worsens pre-existing portal hypertension. It appears that NO is the most important mediator of splanchnic vasodilatation [23,24]. The systemic circulation in cirrhosis is a hyperdynamic one which is characterized by increased cardiac output and plasma volume and decreased peripheral resistance and mean arterial pressure [25]. The decrease in mean arterial pressure and effective hypovolemia results in activation of baroreceptors and upregulation of neurohumoral systems with antinatriuretic and vasoconstrictive effects, such as the renin angiotensin system (RAS) and sympathetic nervous system, that cause sodium and water retention and an increase in plasma volume, which further exacerbates portal hypertension [25–27].

A major consequence of increased portal pressure is the development of portosystemic collateral vessels once the pressure gradient between the portal vein and the hepatic vein exceeds a certain threshold. Although this initially diverts blood flow away from the liver and decompresses the portal system, it becomes inadequate due to the increased portal venous flow caused by increasing splanchnic vasodilatation and the increased resistance in the collateral circulation [27]. It was previously thought that collaterals only resulted from dilatation of pre-existing vascular channels. However, studies have shown that the process of angiogenesis is also a critical component in the formation of portosystemic collaterals [28].

Figures 138.5 and 138.6 summarize the changes that occur in the intrahepatic and splanchnic/systemic circulations in cirrhosis that lead to the development of portal hypertension.

**Strategies for the long-term treatment of portal hypertension**

An increased understanding of the pathophysiology of portal hypertension has led to the discovery of newer pharmacological therapies that may ameliorate portal hypertension in the long term. The two main goals of pharmacological therapy are to: (1) reduce splanchnic and portal venous flow; and/or (2) decrease intrahepatic vascular tone. Currently, nonselective β-blockers (propranolol, nadolol, and timolol) are the most widely used drugs for the prevention of variceal bleeding and the reduction of portal venous pressure in the long term. They work by
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approximately 20% [34,35]. However, nitrates also cause vasodilation in the systemic and portosystemic collateral circulations, which leads to arterial hypotension that is often symptomatic [33,36]. Studies have shown that there is a direct correlation between the decrease in arterial pressure and the reduction in HVPG, which suggests that nitrates primarily decrease portal venous blood flow via a reflex splanchnic vasoconstriction that occurs secondary to arterial hypotension [9,33]. Peripheral vasodilation also results in activation of endogenous vasoactive systems which cause sodium and water retention due to the decrease in effective arterial blood volume [9].

Carvedilol is a potent nonselective $\beta$-blocker that also has anti-$\alpha_1$-adrenergic activity. It thus reduces portal pressure both by decreasing portal venous blood flow (via $\beta$-blockade) and reducing intrahepatic and portocollateral resistance (via $\alpha_1$-blockade) [9]. Randomized controlled trials (RCTs) have shown that carvedilol has a greater portal hypotensive effect than propranolol in cirrhotic patients [37–40]. The reduction in HVPG reported in the literature ranges from 8% to 43% [41]. However, carvedilol also causes a greater decrease in mean arterial pressure, with subsequent fluid retention and an increase in plasma volume, which may have a negative impact on long-term outcomes in cirrhotic patients [9,39,40].

Another strategy in the treatment of portal hypertension is to decrease intrahepatic vascular resistance via the use of drugs that increase the delivery of NO to the intrahepatic circulation. Organic nitrates such as isosorbide mononitrate (ISMN) serve as NO donors and have been shown to lead to significant reductions in HVPG [32,33]. The use of nitrates in combination with nonselective $\beta$-blockers results in a greater reduction in HVPG compared to $\beta$-blockers alone, with a median reduction of approximately 20% [34,35]. However, nitrates also cause vasodilation in the systemic and portosystemic collateral circulations, which leads to arterial hypotension that is often symptomatic [33,36]. Studies have shown that there is a direct correlation between the decrease in arterial pressure and the reduction in HVPG, which suggests that nitrates primarily decrease portal venous blood flow via a reflex splanchnic vasoconstriction that occurs secondary to arterial hypotension [9,33]. Peripheral vasodilation also results in activation of endogenous vasoactive systems which cause sodium and water retention due to the decrease in effective arterial blood volume [9].

Carvedilol is a potent nonselective $\beta$-blocker that also has anti-$\alpha_1$-adrenergic activity. It thus reduces portal pressure both by decreasing portal venous blood flow (via $\beta$-blockade) and reducing intrahepatic and portocollateral resistance (via $\alpha_1$-blockade) [9]. Randomized controlled trials (RCTs) have shown that carvedilol has a greater portal hypotensive effect than propranolol in cirrhotic patients [37–40]. The reduction in HVPG reported in the literature ranges from 8% to 43% [41]. However, carvedilol also causes a greater decrease in mean arterial pressure, with subsequent fluid retention and an increase in plasma volume, which may have a negative impact on long-term outcomes in cirrhotic patients [9,39,40].

The limitations of $\beta$-blocker and nitrate therapies have prompted research to develop newer pharmacological therapies for the long-term treatment of portal hypertension. Experimental and clinical studies have shown that the administration of statins improves liver sinusoidal endothelial dysfunction and decreases...
portal pressure in cirrhotic livers [42–45]. This occurs via upregulation of endothelial nitric oxide synthase (eNOS) activity and increased NO production in the liver microcirculation, which decreases intrahepatic vascular resistance [45]. A recent RCT demonstrated that simvastatin significantly decreases HVPG and improves liver perfusion and function in patients with cirrhosis and portal hypertension [44]. Of note, 32% of patients had an HVPG reduction of 20% or greater to less than 12 mmHg, a value which has been shown to significantly reduce the risk of variceal bleeding and mortality [6]. An additive effect of HPVG reduction was observed in patients who were also receiving β-blocker therapy, which provides further evidence that statins act via a different mechanism of action than β-blockers. Importantly, there were no changes in mean arterial pressure or systemic vascular resistance after initiation of statin therapy. Thus, statins appear to induce a liver-selective vasodilatory effect and do not have deleterious effects on the hemodynamics of systemic circulation. In addition, there were no differences in adverse events between the groups who received simvastatin vs placebo, which suggests an excellent safety profile for statin use in patients with cirrhosis [44]. A recent study using an animal model has provided further insight into molecular mechanisms by which statins lead to improvement in endothelial dysfunction and decreased intrahepatic resistance [46]. Larger prospective clinical studies are needed to confirm the beneficial effects of statin therapy and determine its impact on long-term clinical outcomes in patients with cirrhosis and portal hypertension.

The evidence from experimental studies establishing the role of angiotensin II in the development of increased intrahepatic resistance in portal hypertension have led to clinical trials assessing the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with cirrhosis [17]. In addition, there is experimental evidence that the RAS is involved in the pathogenesis of hepatic fibrosis via the activation of hepatic stellate cells and resulting production of the profibrotic cytokine transforming growth factor (TGF)-β [47]. A recent meta-analysis using individual patient data demonstrated that patients with Child–Pugh A cirrhosis receiving ARBs/ACE inhibitors had a similar reduction in HVPG to those with Child–Pugh A cirrhosis receiving β-blockers (−17% vs −21%, respectively) [48]. There was no statistically significant reduction in HVPG in patients with Child–Pugh B or C cirrhosis receiving ARBs/ACE inhibitors [48]. Furthermore, there was a higher rate of adverse side effects in patients with Child–Pugh B or C cirrhosis, including hypotension and renal dysfunction. Thus, ARBs/ACE inhibitors appear to have the most benefit for patients with early cirrhosis. Further prospective studies are needed to investigate the long-term outcomes of RAS blockade in patients with compensated cirrhosis.

Other possible novel therapeutic targets for the amelioration of portal hypertension in cirrhosis include blockade of pathways leading to angiogenesis and fibrosis such as VEGF signaling [22]. The pharmacological therapy used for the reduction of portal hypertension in the control of acute variceal bleeding is discussed in detail in a subsequent section in this chapter on the management of acute variceal hemorrhage.

**Gastroesophageal varices**

The development of GOVs is the most serious consequence of portal hypertension due to the risk of rupture and variceal hemorrhage, which is the most common lethal complication of cirrhosis [8]. Varices develop mainly at the gastroesophageal junction (GEJ) due to the unique anatomy of the venous drainage there [49]. The veins draining the esophagus are classified as intrinsic, extrinsic, and venous comitantes of the vagus nerve [4]. The intrinsic veins consist of a subepithelial and submucosal plexus which starts at the gastric cardia and runs along the length of the esophagus. The intrinsic veins drain via perforating veins into the extrinsic veins, which drain into the inferior thyroid and brachiocephalic veins in the neck, azygos veins in the thorax, and left gastric vein in the abdominal part of the esophagus [4]. Flow through the perforating veins is normally unidirectional due to the presence of valves.

The intrinsic veins of the GEJ are comprised of four distinct zones, known as the gastric, palisade, perforating, and truncal zones (Figure 138.7). The gastric zone is a 2–3 cm zone distal to...
the GEJ and is composed of longitudinal veins in the submucosa and lamina propria. The palisade zone starts at the GEJ and is a direct extension of veins in the gastric zone. It extends 2–3 cm cranially and is composed of longitudinal veins which run in parallel primarily in the lamina propria. Flow is bidirectional in the palisade zone. It is the main site of communication between the portal venous system and the azygous system of veins, and thus is the most common site of variceal bleeding [4,49]. Above the palisade zone is the perforating zone where the intrinsic veins drain into the extrinsic veins via perforating veins. It extends 2–3 cm cranially. The truncal zone extends 8–10 cm above the perforating zone and consists of 4–5 large venous trunks in the submucosa which drain via perforating veins into the extrinsic veins [49]. As portal hypertension develops, there is increased flow through portosystemic anastomoses which causes dilation of the intrinsic veins at the GEJ and the formation of gastroesophageal varices (Figure 138.8). In addition, the valves of the perforating veins become incompetent and reversal of flow from the extrinsic to intrinsic veins occurs [4].

Gastroesophageal varices typically fall into four basic categories: (1) varices in the gastric and palisade zones; (2) varices in the perforating zone; (3) paraesophageal varices which involve the extrinsic esophageal veins; and (4) varices in the fundus of the stomach. In clinical settings, GOVs are classified as esophageal or gastric varices [4]. Esophageal varices are graded according to their form, i.e., size and shape, into four groups as follows [4,50] and illustrated in Figure 138.9:

- F0: no varicose appearance.
- F1: small straight varices.
- F2: moderately enlarged tortuous varices, occupying less than one-third of the lumen.
- F3: large tortuous varices, occupying more than one third of the lumen.

Gastric varices are classified by their location, size (small vs large), and whether they are in continuity with esophageal varices. Gastric varices are called GOVs when they occur in continuity with esophageal varices but called isolated gastric varices (IGVs) when they are found in isolated clusters in the stomach. Sarin et al. described the most commonly used classification for gastric varices [51] summarized below (Figure 138.10):

- GOV1: esophageal varices that extend along the lesser curvature of stomach.
- GOV2: esophageal varices that extend along the greater curvature into the fundus of the stomach.
- IGV1: isolated gastric varices in the fundus of stomach.
- IGV2: isolated gastric varices in the other parts of the stomach.

GOV1 arise when a branch of the left gastric vein anastomoses with the deep submucosal veins in the gastric zone. They are in direct continuity with the veins in the palisade zone and most often occur in association with large esophageal varices [4]. GOV1 are the most common type of gastric varices. Fundal varices arise from the short gastric and posterior gastric veins, and are the most common source of gastric variceal bleeding.

Figure 138.8 Development of gastroesophageal varices in portal hypertension.
Figure 138.9  Endoscopic grading of esophageal varices. Varices are graded from F0 to F3 based on size and shape (F0 not shown here). Source: Maruyama and Arun 2012 [4]. Reproduced with permission of John Wiley & Sons, Ltd.

(Figure 138.10). They are often seen as large collaterals on imaging studies such as 3D-CT scan or MRI (Figure 138.12). IGVs are often seen in association with SV thrombosis.

Natural history and epidemiology of gastroesophageal varices
The development of GOVs is a common sequelae of portal hypertension in patients with cirrhosis. GOVs are present in approximately 50% of cirrhotic patients [52]. The highest prevalence occurs in patients with more advanced liver disease, i.e., Child–Pugh B or C class disease (Table 138.2). A large study utilizing data from a national endoscopic database found that varices were present in 72% of patients with Child–Pugh class B or C cirrhosis compared to 43% of patients with Child–Pugh A cirrhosis [52]. Furthermore, patients with Child–Pugh B or C cirrhosis are more likely to have large varices.

Patients with cirrhosis without GOVs develop them at a rate of approximately 8% per year [5,53]. The strongest independent predictor for the development of varices is an HVPG >10 mmHg [5]. The rate of progression from small to medium or large varices in cirrhotic patients is about 10% per year [53]. Factors which are associated with the progression from small to large varices include Child–Pugh class B or C cirrhosis, alcoholic cirrhosis, and the endoscopic presence of red wale marks, which are longitudinal dilated venules on the surface of varices [53].
Predictors of first variceal bleeding

The 1-year incidence of variceal hemorrhage in patients with GOVs is about 5%–15% [54]. One of the most important predictors of first variceal hemorrhage is the size of varices, with patients with large varices having the highest risk of hemorrhage (15%) [54]. There are also endoscopic features of esophageal varices which have been shown to predict the risk of hemorrhage, which are referred to as red signs. The red color correlates with blood flow through dilated subepithelial and perforating veins [2]. Red signs include red wale marks (described previously) and cherry red spots, which are dilated subepithelial veins that appear as discrete flat red spots overlying varices. Hematocystic spots are raised red spots that overlie varices and resemble blood blisters (Figure 138.13) [55]. They develop when blood from the extrinsic veins of the esophagus flows via perforating veins into the more superficial submucosal veins [2]. Another important risk factor for the development of variceal bleeding is the presence of advanced liver disease, i.e., Child–Pugh B or C cirrhosis [54].

Variceal wall tension is the primary factor that determines the probability of variceal rupture. Wall tension is directly proportional to transmural pressure and the radius of the blood vessel, and inversely proportional to wall thickness (Laplace’s law). Transmural pressure is equal to the product of flow rate and resistance to flow through the varix. Resistance to flow is directly proportional to the length of the vessel and inversely proportional to the fourth power of the radius. Thus, long large varices with high flow rates and thin walls have the highest risk of rupture [4].

In addition, the pressure within a varix is directly related to HVPG. Thus, a reduction in HVPG decreases variceal wall tension and the risk of variceal rupture [8]. Indeed, patients have a low risk of bleeding if the HVPG is less than 12 mmHg [6]. The risk of variceal bleeding is markedly diminished if the HVPG is reduced to less than 12 mmHg or more than 20% of baseline [6].

Mortality and risk of rebleeding

Despite the advances in the management of variceal bleeding which have led to a significant decline in mortality over the past

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**Table 138.2** Modified Child–Turcotte–Pugh score.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Child–Turcotte–Pugh (CTP) class</td>
<td>Points</td>
</tr>
<tr>
<td>A</td>
<td>5–6</td>
</tr>
<tr>
<td>B</td>
<td>7–9</td>
</tr>
<tr>
<td>C</td>
<td>10–15</td>
</tr>
</tbody>
</table>

INR, international normalized ratio.
Primary prophylaxis refers to the prevention of the first episode of variceal bleeding in cirrhotic patients at high risk of bleeding. The high mortality associated with an episode of acute variceal bleeding highlights the importance of the need for primary prophylaxis. The risk factors that determine which patients are at increased risk for first time variceal bleeding were detailed in the previous section, and include patients with large varices, varices with red wale signs, and/or advanced cirrhosis. Thus, cirrhotic patients can be stratified into two groups according to their risk of variceal hemorrhage: (1) high-risk patients, i.e., patients with medium/large varices that have red wale signs or patients with Child–Pugh B or C cirrhosis; and (2) low-risk patients, i.e., patients with small varices without red wale signs or occurring in patients with Child–Pugh A cirrhosis. The goal of primary prophylaxis is to treat high-risk patients using a low-risk, cost-effective approach that reduces the incidence of variceal bleeding and the mortality associated with it.

Gastric varices

Gastric varices are less prevalent than esophageal varices in patients with portal hypertension, with an estimated prevalence of about 5%–33% [8]. Secondary gastric varices may occur after the obliteration of esophageal varices. The reported incidence of bleeding from gastric varices is approximately 25% in 2 years [51]. The risk of bleeding from gastric varices according to location. Although GOV1 comprise about 75% of gastric varices, they account for only a small proportion of the cases of gastric variceal bleeding. Fundal varices appear to have a higher risk of bleeding, with an incidence of bleeding that may exceed 50%. The highest risk is for IGV1 varices. The important independent predictors of bleeding from gastric varices are the size of the varix, the endoscopic presence of red spots on the mucosal surface of the varix, and Child–Pugh class [60]. Patients with large gastric varices, i.e., size greater than 10 mm, and Child–Pugh class C have the highest risk of bleeding. A significant proportion of patients with gastric varices develop bleeding with a HVPG <12 mmHg [61]. This is likely due to the high prevalence of spontaneous gastrorenal shunts in patients with gastric varices. Gastric variceal bleeding is associated with increased severity of hemorrhage and a higher mortality compared to esophageal variceal bleeding. Indeed, the mortality from bleeding gastric varices has been estimated to be about 45% [51].

Primary prophylaxis of variceal hemorrhage

Primary prophylaxis refers to the prevention of the first episode of variceal bleeding in cirrhotic patients at high risk of bleeding. The high mortality associated with an episode of acute variceal bleeding highlights the importance of the need for primary prophylaxis. The risk factors that determine which patients are at increased risk for first time variceal bleeding were detailed in the previous section, and include patients with large varices, varices with red wale marks, and/or advanced cirrhosis. Thus, cirrhotic patients can be stratified into two groups according to their risk of variceal hemorrhage: (1) high-risk patients, i.e., patients with medium/large varices that have red wale signs or patients with Child–Pugh B or C cirrhosis; and (2) low-risk patients, i.e., patients with small varices without red wale signs or occurring in patients with Child–Pugh A cirrhosis. The goal of primary prophylaxis is to treat high-risk patients using a low-risk, cost-effective approach that reduces the incidence of variceal bleeding and the mortality associated with it.

Endoscopic screening

Esophagastroduodenoscopy (EGD) remains the gold standard for the diagnosis of varices. The current recommendation is for all patients with cirrhosis to undergo an EGD for screening for varices at the time of diagnosis [8]. The size of the varices and the presence of red wale marks should be assessed. The use of esophageal capsule endoscopy has been explored as a less invasive method to screen for esophageal varices. Although the initial preliminary studies were promising [63,64], larger subsequent studies have shown that the accuracy of capsule endoscopy in the detection of esophageal varices and red signs is not sufficient to replace EGD at the present time [64–67]. In addition, the lack of an ability to insufflate air hinders the grading of esophageal varices [67].
In low-risk patients with cirrhosis and small varices, there is limited evidence that treatment with nonselective β-blockers may slow the progression to large varices [69]. A large multicenter placebo-controlled single-blinded trial showed that administration of nadolol to low-risk patients with cirrhosis significantly decreased the risk of growth to large varices, with a cumulative risk of growth at 5 years of 20% in patients receiving nadolol compared to 51% in the placebo group [69]. The risk of variceal bleeding was also lower in patients receiving nadolol vs placebo. However, the difference in survival between the two groups was not statistically significant [69]. Similar to the results of other studies, a higher proportion of patients receiving nadolol had to discontinue treatment due to adverse effects (including hypotension, asthma, and heart failure) compared to placebo (11% vs 1%, respectively). Thus, the use of β-blockers in low-risk patients with small varices may be considered, but further studies are needed to confirm the long-term benefits of treatment. Such patients who are not started on β-blocker therapy should undergo repeat EGD in 2 years or at the time of decompensation and annually thereafter if they develop decompensated disease [8].

β-blockers A large multicenter randomized double-blind placebo-controlled trial showed that nonselective β-blockade therapy (i.e., timolol) was not effective in preventing the development of GOVs or variceal hemorrhage in unselected patients with cirrhosis and portal hypertension with no varices at baseline [5]. In addition, there was a higher incidence of serious adverse events in patients receiving timolol vs placebo. These side effects included bradycardia, severe fatigue, wheezing or shortness of breath, and syncope [5]. Thus, the initiation of nonselective β-blocker therapy is not recommended in patients with cirrhosis who do not have varices [8]. Based on the natural history of varices, repeat surveillance endoscopy is recommended in such patients in 3 years in those with compensated disease or annually in the setting of decompensated disease [8].

In patients with medium or large varices, there have been many trials that have shown that the use of nonselective β-blockers significantly reduces the risk of first variceal bleeding by approximately 50% compared to placebo [71,72]. A large meta-analysis of 11 trials demonstrated that patients with medium or large varices who received β-blockers had a risk of first variceal hemorrhage of 14% vs 30% in patients who received placebo over a median follow-up period of 2 years (Table 138.3a) [73]. Furthermore, these trials have shown that treatment with
β-blockers results in a significant reduction in mortality by 25%–45% [74,75].

Endoscopic variceal ligation Several RCTs have established the efficacy of EVL in the primary prophylaxis of variceal bleeding in high-risk patients with medium or large esophageal varices. A meta-analysis of five such RCTs showed that prophylactic EVL compared to no treatment significantly decreases the risk of first variceal bleeding by 64% and mortality by 45% in patients with medium or large esophageal varices (Table 138.3a) [76]. The ethics of these studies are in question, as patients in the control group were not treated despite the recognized efficacy of β-blockers.

There have been many RCTs that have compared EVL to nonselective β-blocker therapy (propranolol and nadolol) for the treatment of patients with medium or large esophageal varices. A recent meta-analysis of 19 RCTs which included 1483 patients demonstrated that the risk of first variceal hemorrhage was significantly lower in the EVL group compared to the group receiving β-blockers [77]. However, there were no significant differences in bleeding-related mortality or overall mortality between the groups. Furthermore, when only high-quality trials were taken into account, the difference in the rates of variceal bleeding between the two groups was no longer significant. This finding is similar to the results of an earlier meta-analysis which showed that there was no significant difference in bleeding rates when only trials with reported adequate bias control were analyzed (Table 138.3b) [78]. Meta-analyses have also shown that although the frequency of adverse events was lower among patients undergoing EVL, the adverse events in this group were of increased severity and included bleeding episodes from ligation-induced esophageal ulcers which led to death in a few cases [77,79,80]. Esophageal perforation has also been reported. In contrast, there were no fatal side effects among patients who received β-blocker therapy, and the majority of side effects resolved upon discontinuation of therapy. A small RCT showed that a short course of pantoprazole therapy (40 mg i.v. followed by 40 mg orally daily for 9 days) after elective EVL significantly decreased the size of ligation-induced ulcers, with a trend towards a lower risk of bleeding [81]. Thus, short-term proton pump inhibitor (PPI) use after EVL can be considered.

### Summary of advantages and disadvantages of β-blockers and endoscopic variceal ligation

The main advantages of nonselective β-blockers are their low cost and ease of administration. Furthermore, they cause a reduction in portal venous pressure, which may prevent other complications of cirrhosis and portal hypertension, such as bleeding from PHG, ascites, and spontaneous bacterial peritonitis [82,83]. In addition, there is no need for repeat EGD once a patient is initiated on β-blocker therapy. The primary disadvantage is that adverse effects are common, as detailed previously. The most common adverse effects are fatigue, lightheadedness, and shortness of breath. In clinical trials, adverse effects requiring treatment discontinuation occurred in approximately 15% of patients receiving β-blockers [78]. Another disadvantage is that prophylactic therapy with β-blockers must be continued indefinitely, as there is evidence that the risk of variceal bleeding returns once treatment is discontinued which leads to increased mortality [84].

The advantages of EVL include that it can be performed at the same time as screening endoscopy. In addition, side effects are less frequent with EVL compared to β-blocker therapy. The disadvantages include that specific expertise is required to

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### Table 138.3a

Summary of meta-analyses for primary prophylaxis of variceal bleeding. Rate of first variceal bleeding for patients receiving β-blocker or endoscopic variceal ligation (EVL) vs control patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>Control (%)</th>
<th>β-blocker (%)</th>
<th>EVL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Amico et al. (1999) [73]</td>
<td>11</td>
<td>1189</td>
<td>30</td>
<td>14</td>
<td>–</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Imperiale et al. (2001) [76]</td>
<td>5</td>
<td>601</td>
<td>18</td>
<td>–</td>
<td>4%</td>
<td>&lt;0.04</td>
</tr>
</tbody>
</table>

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### Table 138.3b

Summary of meta-analyses for primary prophylaxis of variceal bleeding. Relative risk of first variceal bleeding and overall mortality for patients receiving endoscopic variceal ligation (EVL) vs β-blocker therapy.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>RR for variceal bleeding (95% CI)</th>
<th>RR for mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluud et al. [78]</td>
<td>16</td>
<td>1167</td>
<td>0.80 (0.50–1.28)*</td>
<td>1.22 (0.84–1.78) (2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.57 (0.38–0.85)*</td>
<td>1.02 (0.75–1.39)</td>
</tr>
</tbody>
</table>

CI, confidence interval. RR for EVL vs β-blocker.

a For three trials with adequate bias control.

b For trials with inadequate bias control.
perform EVL. Furthermore, repeat EGD must be performed every 2–4 weeks until obliteration of varices occur. Surveillance EGD is then recommended 1–3 months after obliteration and then every 6–12 months to monitor for recurrence of varices [8]. Endoscopy is also associated with a higher cost compared to β-blocker therapy. The risks include that of the endoscopic procedure and administration of sedation. Finally, the severity of side effects is greater with EVL and includes the risk of bleeding from EVL-induced esophageal ulcers and possibly death as well as esophageal perforation. Less severe side effects include chest pain and transient dysphagia.

**Recommendations and future directions** Current evidence suggests that either nonselective β-blockers or EVL are effective in the primary prophylaxis of variceal hemorrhage in patients with medium or large varices. The decision on which treatment to use should be based on local resources, expertise, and patient preference [8]. EVL should be considered in patients who have contraindications to β-blockers or are intolerant of them due to side effects. Recent evidence has shown that the nonselective β-blocker carvedilol, which has weak vasodilating properties due to anti-c1-α-adrenergic activity, is effective in the primary prophylaxis of variceal hemorrhage in such patients. An RCT of carvedilol versus EVL showed that cirrhotic patients with medium or large varices receiving carvedilol had a significantly lower rate of first variceal bleed (10% vs 23%), with no differences in bleeding-related mortality or overall mortality [41]. Another recent study showed that the use of carvedilol in patients with esophageal varices who were nonresponders to propranolol therapy resulted in a greater decrease in HVPG with significantly lower bleeding rates and lower mortality compared to the propranolol or EVL groups [85]. Thus, carvedilol appears to be a promising new drug for the primary prophylaxis of variceal hemorrhage, but further studies are needed before its widespread use can be recommended.

The routine use of HVPG measurement in primary prophylaxis to assess the hemodynamic response to β-blocker therapy has been proposed as a method to identify nonresponders who are at higher risk of variceal hemorrhage. The rationale arises from studies that have shown that patients with a good hemodynamic response to medical therapy, defined as a reduction in HVPG to \(\leq 12\) mmHg or by \(\geq 20\%\) of baseline, have a significantly decreased risk of variceal bleeding, compared to patients with a poor response [86,87]. However, the invasive nature of this approach, the need for specific expertise, and its cost may prohibit its use in routine clinical practice. Thus, there is a need for the development of less invasive, less expensive methods for the measurement of portal pressure, which will help guide the treatment approach in primary prophylaxis.

The algorithm for primary prophylaxis of variceal hemorrhage in cirrhotic patients with esophageal varices is illustrated in Figure 138.15. The doses of β-blockers, therapeutic goals, and follow-up and maintenance recommended for each strategy are summarized in Table 138.4.

**Figure 138.15** Algorithm for primary prophylaxis of esophageal variceal bleeding. F ratings – see Figure 138.9. EGD, esophagogastroduodenoscopy; EVL, endoscopic variceal ligation; HR, heart rate.

**Therapies not recommended for primary prophylaxis**

**Nitrates**

Given about one-third of patients with cirrhosis cannot tolerate β-blockers due to contraindications or side effects, nitrates such as ISMN have been studied for primary prophylaxis. Their mechanism of action in reducing portal hypertension was discussed previously. Garcia-Pagan et al. conducted a multicenter prospective double-blind RCT in which 133 cirrhotics with varices and contraindications or intolerance to β-blockers were randomized to receive ISMN vs placebo [88]. There were no significant differences in the rates of variceal bleeding at 1 year and 2 years or any difference in survival between the two groups. Another study comparing ISMN to propranolol showed that patients older than 50 years of age receiving ISMN had a higher mortality in long-term follow-up [89]. Therefore, the use of nitrates alone is not recommended in cirrhotic patients.

**Combination therapies**

The combination of nonselective β-blockers and ISMN has been studied for primary prophylaxis given their synergistic effects in reducing portal pressure. Merkel et al. performed a nonblinded RCT which showed that the addition of ISMN to nadolol significantly reduced the rate of first variceal bleeding in patients with cirrhosis and varices after a median follow-up of 30 months, with no difference in survival [90]. Long-term follow-up of these patients confirmed that this beneficial effect was still seen after 7 years [91]. However, a subsequent larger multicenter prospective double-blind RCT which compared combination therapy with propranolol and ISMN to propranolol and placebo found that there were no significant differences in
the rates of variceal bleeding or survival at 1 and 2 years [92]. Furthermore, there was a higher rate of adverse effects in the group receiving combination therapy due to the increased incidence of headache. Thus, the combination of a nonselective β-blocker and ISMN is not recommended as primary prophylaxis, but can be considered in patients who require a dose reduction of β-blocker due to side effects [8].

The combination of nonselective β-blocker therapy and EVL for primary prophylaxis was evaluated in an RCT in patients with high-risk varices [93]. This showed that there were no differences in the risk of first variceal hemorrhage or mortality between patients who received treatment with both EVL and propranolol compared to EVL alone. Although the risk of recurrence of varices was lower in the group who received combination therapy, this group also had a higher incidence of side effects. Such combination therapy is thus not recommended for primary prophylaxis.

### Portosystemic shunts
In the era before the advent of endoscopy, a number of trials of surgical shunts were performed for the primary prophylaxis of variceal hemorrhage. These trials showed that although surgical shunts were quite effective in the prevention of first variceal hemorrhage, they were associated with a higher incidence of hepatic encephalopathy and mortality [74]. Thus, prophylactic shunt surgery is not recommended for primary prophylaxis of variceal hemorrhage. Transjugular intrahepatic portosystemic shunt (TIPS) has not been studied for primary prophylaxis, but given that the physiology is similar to surgical shunts, it is also not recommended for primary prophylaxis [94].

### Sclerotherapy
Endoscopic sclerotherapy is a local therapy to obliterate varices by the injection of sclerosing substances into varices which cause vascular thrombosis and endothelial damage that leads to scarring. The most commonly used sclerosants are ethanol, the synthetic chemical sodium tetradeyl sulfate, and the fatty acid derivatives sodium morrhuate and ethanolamine oleate. The performance of sclerotherapy requires a skilled endoscopist and is associated with serious complications in 10%–20% of patients [73]. The use of sclerotherapy has been studied for primary prophylaxis. Although early studies showed promising results, later studies did not find a benefit [74,95]. A large randomized multicenter clinical trial found a significantly higher mortality in patients receiving prophylactic sclerotherapy vs sham therapy despite a decrease in the rate of variceal hemorrhage, which required early termination of the study [96]. Hence, sclerotherapy is not recommended for the primary prevention of variceal hemorrhage.

### Primary prophylaxis for gastric varices
Based on the studies for variceal hemorrhage due to esophageal varices, it is recommended that all patients with large gastric varices receive treatment with nonselective β-blockers as primary prophylaxis. There has been only one RCT that has assessed primary prophylaxis strategies for gastric varices which included 89 patients [97]. This study showed that patients with large gastric fundal varices (IVG1 and GOV2 with eradicated esophageal varices) who received endoscopic cyanoacrylate injection had a significantly lower incidence of variceal bleeding (13%) compared to patients who received β-blockers (28%) or no treatment (45%) over a median follow-up period of approximately 2 years. In addition, patients who underwent cyanoacrylate injection had increased survival compared to those who received no treatment (90% vs 72%, \( P = 0.048 \)). There were no differences in the frequency of complications among the three groups. Larger RCTs are needed to confirm these results before the use of cyanoacrylate injection can be formally recommended for primary prophylaxis.

### Management of acute variceal hemorrhage
Acute variceal hemorrhage is a medical emergency that requires optimal management to prevent mortality. Over the past two

### Table 138.4 Management strategies for primary prophylaxis of variceal bleeding.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Starting dose</th>
<th>Therapeutic goal</th>
<th>Follow-up/maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>20 mg orally twice daily, adjust every 2–3 days until therapeutic goal achieved, maximal daily dose 320 mg</td>
<td>Maximum tolerated dose, goal HR &lt; 55–60 beats/min or 25% reduction from baseline</td>
<td>Continue indefinitely, no need for follow-up EGD</td>
</tr>
<tr>
<td>Nadolol</td>
<td>40 mg orally daily, adjust every 2–3 days until therapeutic goal achieved, maximal daily dose 160 mg</td>
<td>As for propranolol, as for propranolol</td>
<td>As for propranolol</td>
</tr>
<tr>
<td>EVL</td>
<td>Every 2–4 weeks until obliteration of varices</td>
<td>Obliteration of varices</td>
<td>First surveillance EGD 1–3 months after obliteration and then every 6–12 months subsequently</td>
</tr>
</tbody>
</table>

EGD, esophagogastroduodenoscopy; EVL, endoscopic variceal ligation; HR, heart rate.
decades, there have been significant advances in the management of variceal bleeding that have resulted in a decrease in mortality from approximately 40%–50% to 15%–20% [57,58]. These advances include the use of short-term antibiotic prophylaxis, vasoactive drugs, endoscopic treatment with variceal ligation and sclerotherapy, and TIPS. The current recommended management strategies for acute variceal bleeding and the supportive evidence for them are detailed in the following sections. The general management is centered on the goals of resuscitation, specific treatment to control acute hemorrhage, and the prevention of early rebleeding that is defined as any bleeding that occurs after initial hemostasis is achieved in the time period from 48 h up to 6 weeks. The incidence of early rebleeding is approximately 30%–40%, with the highest risk occurring in the first 5 days [98].

**Resuscitation and initial management**

Patients with suspected acute variceal bleeding require admission to an intensive care unit for resuscitation and management. Resuscitation is centered on the basic medical principles of establishing airway, breathing, and circulation. Patients with active hematemesis or altered mental status due to hepatic encephalopathy should be intubated for airway protection to decrease the risk of aspiration, which is a significant cause of morbidity and mortality in patients. Volume resuscitation should be performed promptly to achieve hemodynamic stability and protect the function of vital organs such as the kidneys. The ideal fluid of choice for resuscitation is blood, but crystalloids may be used for immediate resuscitation until blood product becomes available. Blood transfusion should be performed conservatively to achieve a target hemoglobin level of 7–8 g/dL [70], as experimental evidence has shown that excessive blood volume restitution increases portal pressure and thus leads to increased bleeding and mortality [99,100]. Similarly, aggressive resuscitation with crystalloids should be avoided. The target hemoglobin may be higher in patients with ischemic heart disease or rapid ongoing hemorrhage with hemodynamic instability.

Transfusion of fresh frozen plasma or platelets can be considered in patients with significant coagulopathy or thrombocytopenia, but no formal studies have assessed this. An RCT of recombinant factor VIIa in patients with advanced cirrhosis and active variceal bleeding did not show any differences in the rates of failure to control 24-h bleeding or failure to prevent rebleeding or death at day 5 compared to placebo [101].

**Antibiotic prophylaxis**

Cirrhotic patients with upper gastrointestinal hemorrhage have been shown to have a high prevalence of bacterial infections including spontaneous bacterial peritonitis (SBP), bacteremia, pneumonia, and urinary tract infections [102]. Studies have demonstrated that the presence of bacterial infection is an independent prognostic factor of the failure to control bleeding as well as early rebleeding in acute variceal hemorrhage [102,103]. The use of short-term prophylactic antibiotics in patients with cirrhosis and gastrointestinal bleeding, independent of the presence of ascites, has been found to significantly decrease the rate of bacterial infections as well as increase the survival rate [104]. A randomized trial showed that a 7-day course of prophylactic antibiotics in patients with acute variceal bleeding decreased the risk of bacterial infections as well as early rebleeding compared to those who received antibiotics only when an infection became evident [105]. Thus, antibiotic prophylaxis is recommended for all patients with cirrhosis who present with acute variceal bleeding and should be initiated upon admission to hospital [70]. The antibiotic of choice is norfloxacin 400 mg twice daily for 7 days [106]. However, a more recent study showed that in patients with advanced cirrhosis and gastrointestinal hemorrhage, intravenous ceftriaxone was more effective than oral norfloxacin in preventing bacterial infections, although no difference in hospital mortality was seen [107]. Of the seven Gram-negative bacilli isolated in the norfloxacin group, six were found to be quinolone resistant. Hence, ceftriaxone should be used for prophylaxis in patients with advanced cirrhosis, especially if they are receiving quinolone prophylaxis for SBP.

**Pharmacological therapy**

The advantages of pharmacological therapy are that it can be initiated as soon as variceal bleeding is suspected, even before upper endoscopy is performed, as it does not require any special expertise for administration. Vasoactive drugs that cause splanchnic vasoconstriction and thus decrease portal venous flow and pressure are the mainstay of treatment. These include vasopressin and its analog terlipressin and somatostatin and its analogs, octreotide and vapreotide. Only vasopressin and octreotide are currently available for use in the US, and octreotide is considered the only safe vasoactive agent for the treatment of acute variceal hemorrhage due to the increased frequency and severity of side effects associated with vasopressin use. A meta-analysis of 30 RCTs including 3111 patients demonstrated that the use of vasoactive medications is significantly associated with decreased acute mortality, lower blood transfusion requirements, shorter duration of hospital stay, and increased control of bleeding compared to placebo [108]. There appears to be no significant differences among the different vasoactive agents in the control of hemorrhage or early rebleeding based on the results of meta-analyses [108,109]. Vasoactive drugs have been shown to improve the efficacy of endoscopic therapy (sclerotherapy or band ligation) in obtaining control of hemorrhage compared to endoscopic therapy alone [110,111].

Vasopressin is a peptide hormone that is a potent splanchnic vasoconstrictor. Its clinical utility is limited by serious side effects which result from nonselective arterial vasoconstriction, including bowel ischemia, myocardial ischemia, hypertension, left heart failure, and arrhythmias. Because of its poor safety profile and the availability of safer alternatives, vasopressin is not recommended in the management of acute variceal bleeding. Terlipressin is a synthetic analog of vasopressin which is longer acting and has fewer side and less severe effects.
compared to vasopressin or the combination of vasopressin and nitroglycerin [112,113]. It is given in bolus i.v. injections at doses of 2 mg every 4 h for up to 48 h. After initial control of bleeding is achieved, the dose is decreased to 1 mg every 4 h and continued as maintenance treatment for 5 days. Terlipressin is the only vasoactive agent which has been shown to reduce mortality in acute variceal bleeding. A double-blind randomized trial showed that early administration of terlipressin to patients with cirrhosis and gastrointestinal bleeding resulted in improved control of bleeding and decreased bleeding-related mortality rates at 15 and 42 days compared to placebo [114]. A subsequent meta-analysis of RCTs of terlipressin use in acute variceal hemorrhage showed a 34% relative risk reduction in overall mortality compared to placebo [113]. The use of terlipressin also significantly reduced the risk of failure of initial hemostasis and the number of procedures per patient required for uncontrolled bleeding or rebleeding. Severe side effects occur in about 2%-4% of patients receiving terlipressin and include arrhythmias, angina, and limb ischemia [113,115].

Somatostatin and its analogs cause splanchnic vasoconstriction by a direct effect on vascular smooth muscle and also by inhibiting the release of vasoactive hormones such as glucagon [116]. A recent meta-analysis including 21 trials and 2588 patients comparing somatostatin and its analogs to placebo or no treatment found that the use of these drugs was associated with a small reduction in the need for blood transfusion and a decreased risk of failing initial hemostasis [117]. Another meta-analysis of 8 trials showed that the addition of pharmacological therapy with somatostatin or its analogs to endoscopic therapy (sclerotherapy or EVL) increased the ability to achieve initial control of bleeding and 5-day hemostasis compared to endoscopic therapy alone, with no differences in mortality or the frequency of severe adverse events [111]. A major advantage of somatostatin and its analogs is that they have an excellent safety profile and have fewer side effects than terlipressin and vasopressin [118–120]. The side effects which are usually mild include sinus bradycardia, hyperglycemia, diarrhea, and abdominal cramping. Thus they can be used as a continuous infusion for 5 days or even longer. Somatostatin treatment (250 μg bolus injection followed by a continuous i.v. infusion at 250 μg/h) has been shown to result in a sustained decrease in HVPG in cirrhotic patients with acute variceal bleeding and prevent the rise in HVPG that occurs in response to a meal or blood transfusions [121]. The bolus injection can be repeated in the first hour if bleeding is uncontrolled. A higher dose of continuous infusion (500 μg/h) should be considered in patients found to have active bleeding at endoscopy, as it is associated with increased control of bleeding and improved survival compared to standard dosing [122].

Octreotide is a synthetic somatostatin analog that has a longer half-life than somatostatin. It is generally administered as a 50 μg i.v. bolus followed by a continuous infusion of 50 μg/h for 5 days. Unlike somatostatin, octreotide infusion does not cause a sustained decrease in portal pressure, but results in a transient reduction [123]. Studies of the efficacy of octreotide have yielded conflicting results, perhaps in part due to the phenomenon of desensitization which can occur rapidly. A meta-analysis of 13 trials showed that the addition of octreotide improves the control of bleeding in patients receiving initial endoscopic therapy (sclerotherapy or EVL) compared to placebo, with a similar side effect profile. In addition, fewer complications were seen in patients receiving octreotide vs vasopressin or terlipressin. Thus, octreotide appears to be beneficial as an adjunct to endoscopic therapy in the control of variceal bleeding [118]. Vapreotide is another analog of somatostatin which has been shown to be efficacious in controlling varical hemorrhage. The importance of early administration of vasoactive drugs was illustrated by a randomized double-blind trial which showed that administration of vapreotide (50 μg i.v. bolus followed by a continuous infusion of 50 μg/h for 5 days) before endoscopic treatment to patients with cirrhosis presenting with acute upper gastrointestinal hemorrhage resulted in a significant reduction in the rates of active bleeding seen at endoscopy and increased control of bleeding and survival at 5 days compared to placebo [124]. Furthermore, patients in the vapreotide group received significantly fewer blood transfusions. Thus, patients with suspected variceal hemorrhage should have vasoactive drug therapy initiated promptly as they are being resuscitated. Vasoactive drug therapy should be continued for 5 days after the bleeding episode. Table 138.5 summarizes the pharmacological therapy used in the management of acute variceal hemorrhage.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard dosing</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin*</td>
<td>Initial 250 μg i.v. bolus followed by continuous infusion of 250–500 μg/h (bolus can be repeated in the first hour if bleeding uncontrolled)</td>
<td>Splanchnic vasoconstriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of release of vasoconstrictor hormones (e.g., glucagon)</td>
</tr>
<tr>
<td>Somatostatin analogs</td>
<td></td>
<td>Same as somatostatin, longer duration of action</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Initial 50μg i.v. bolus followed by continuous infusion of 50μg/h (bolus can be repeated in the first hour if bleeding uncontrolled)</td>
<td></td>
</tr>
<tr>
<td>Vapreotide*</td>
<td>Initial 50μg i.v. bolus followed by continuous infusion of 50μg/h</td>
<td></td>
</tr>
<tr>
<td>Terlipressin* (vasopressin analog)</td>
<td>2 mg i.v. every 4 h for first 48 h followed by 1 mg i.v. every 4 h</td>
<td>Splanchnic vasoconstriction</td>
</tr>
</tbody>
</table>

*Not available for use in the US.
**Endoscopic therapy**

Patients with cirrhosis and suspected variceal bleeding should undergo upper endoscopy as soon as safely possible after admission (i.e., within 12 h) to confirm the diagnosis and perform endoscopic therapy [125]. The diagnosis of variceal bleeding is confirmed if one of the following signs is observed during endoscopy: (1) active bleeding (i.e., spurting or oozing of blood) from a varix; (2) white nipple sign or clot adherent to a varix; or (3) the presence of varices without other potential sources of bleeding [98]. Both sclerotherapy and EVL are effective in achieving initial control of bleeding in about 75%–90% patients with variceal bleeding [126,127]. EVL is now the preferred treatment of choice for esophageal variceal bleeding, as randomized trials have shown that it is associated with decreased rebleeding rates, mortality, bleeding-related mortality, and fewer complications compared to sclerotherapy [126,128,129]. In addition, the number of endoscopic treatment sessions required to achieve variceal obliteration has been found to be lower with EVL [126,128]. A study demonstrated that although both EVL and sclerotherapy produced an increase in HVPG immediately after treatment in patients with cirrhosis and bleeding esophageal varices, HVPG returned to baseline within 48 h in patients who underwent EVL but remained persistently elevated during the 5-day period of the study in patients who underwent sclerotherapy [7]. This correlated with a higher rate of rebleeding in the sclerotherapy group. An RCT including 179 patients showed that the use of EVL vs sclerotherapy as emergency endoscopic therapy added to pharmacological therapy with somatostatin significantly improved the efficacy and safety of treatment, with a lower incidence of therapeutic failure (10% vs 24%, \(P = 0.02\)), failure to control bleeding (4% vs 15%, \(P = 0.02\)), and serious side effects (4% vs 13%, \(P = 0.01\)) [56]. Furthermore, the 6-week probability of survival without therapeutic failure was higher in the EVL group (83% vs 67%, \(P = 0.01\)).

The risks of endoscopic therapy during acute variceal bleeding include the usual risks of upper endoscopy, with an increased risk of aspiration due to active bleeding. Studies have shown that sclerotherapy is associated with serious complications in 10%–20% of patients, with an overall mortality of 2% [73]. Complications include the development of esophageal strictures, bleeding from treatment-induced esophageal ulcers, aspiration pneumonia, bacterial peritonitis, and sepsis. Table 138.6 summarizes the complications that can occur with the endoscopic treatment of varices.

**Summary and recommendations**

The first-line treatment for acute variceal hemorrhage is the combination of vasoactive drugs, started prior to upper endoscopy, and emergency endoscopic therapy. The endoscopic therapy of choice is EVL, as it is associated with increased therapeutic efficacy with fewer serious side effects compared to sclerotherapy. Sclerotherapy may be used in the acute setting if EVL is technically difficult [125]. Short-term antibiotic management is an integral part of management as it decreases the incidence of bacterial infections, early rebleeding, and mortality.

**Salvage therapy for patients with treatment failure**

Despite appropriate pharmacological and endoscopic therapy, failure to control bleeding occurs in about 10%–20% of patients with acute variceal hemorrhage. Studies have shown that the main predictors of failure are Child–Pugh class C disease, HVPG >20 mmHg, and active bleeding at endoscopy [130–132]. Patients with failure to control bleeding have a high risk of exsanguination and the development of complications related to active hemorrhage [4]. If the patient is stable, a second attempt to achieve endoscopic hemostasis may be performed. However, if this is unsuccessful or the bleeding is severe, more definitive therapy should be pursued immediately.

Balloon tamponade is a highly effective method of achieving short-term hemostasis in acute variceal bleeding. Immediate control of bleeding is achieved in over 80% of patients [133]. However, the rebleeding rate is very high once the balloon is deflated. In addition, it is associated with frequent and serious complications including aspiration, migration, and esophageal necrosis or perforation, with mortality rates as high as 20% [8]. Endotracheal intubation should be performed in all patients for airway protection prior to balloon tamponade. Balloon tamponade should not be applied for more than 24 h consecutively to avoid the risk of ischemic mucosal ulceration. Thus, the use of balloon tamponade should be restricted to patients with massive bleeding as a temporary bridge to more definitive treatment within 24 h of placement, i.e., endoscopic therapy or shunt therapy. Recently, there have been several studies that have described an innovative approach using removable covered

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**Table 138.6 Complications of endoscopic treatment of varices.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Common complications</th>
<th>Uncommon complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotherapy</td>
<td>Retrosternal chest pain</td>
<td>Esophageal perforation</td>
</tr>
<tr>
<td></td>
<td>Ulcers</td>
<td>Bacterial peritonitis/sepsis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Bleeding from ulcers</td>
<td>Motility disorder</td>
</tr>
<tr>
<td></td>
<td>Mediastinitis</td>
<td>Portal/mesenteric vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Transient dysphagia</td>
<td>Aspiration pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stricture&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Band ligation</td>
<td>Retrosternal chest pain</td>
<td>Stricture</td>
</tr>
<tr>
<td></td>
<td>Ulcers</td>
<td>Perforation</td>
</tr>
<tr>
<td></td>
<td>Transient dysphagia</td>
<td>Aspiration pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacterial peritonitis/sepsis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleeding from ulcers</td>
</tr>
</tbody>
</table>

<sup>a</sup>More common in acute variceal bleeding.

<sup>b</sup>Late complication.
self-expanding metal esophageal stents to achieve hemostasis in patients with uncontrolled variceal bleeding as a safer alternative to balloon tamponade [134–136]. These small preliminary studies have shown that the deployment of such stents in the lower esophagus is highly effective in achieving immediate hemostasis and is associated with fewer complications despite use for periods of time up to 14 days. In addition, new stents have been devised that allow placement without the use of radiographic or endoscopic guidance [134]. Further studies with larger numbers of patients are needed to confirm these findings.

Shunt therapy with TIPS or shunt surgery is highly effective in achieving control of variceal bleeding in patients who have failed pharmacological and endoscopic therapy. TIPS is a radiological procedure in which a stent is placed between the portal vein and the hepatic vein to relieve portal hypertension (Figure 138.16). Studies have shown that salvage TIPS or surgical shunt therapy is successful in achieving hemostasis in over 90% of patients [137–140]. A recent landmark study showed that the early use of TIPS (within 72 h after endoscopy) in patients at high risk of treatment failure who had been treated with vasoactive drugs and EVL was associated with a significant reduction in the failure to control bleeding, rebleeding, and mortality, compared to standard therapy [141]. The main complications of shunt therapy are the development of hepatic encephalopathy or worsening liver function. The incidence of new or worsening hepatic encephalopathy post-TIPS is approximately 20%–30% [142]. A meta-analysis showed that nonselective surgical shunts were more effective than endoscopic therapy in achieving control of acute hemorrhage at the expense of higher mortality rates of 31%–77% [74]. TIPS is preferred over surgical therapy in patients with Child–Pugh class B or C cirrhosis given the excessive mortality associated with surgical intervention. The mortality associated with salvage TIPS remains high, with an estimated 30-day mortality of 25%–50% [137] and a 1-year mortality of 50% [138]. This reflects the fact that the majority of patients in whom failure to control bleeding occurs have advanced liver disease.

Surgical intervention is now rarely performed as salvage therapy for the control of acute variceal bleeding. Its use should be reserved for patients with Child–Pugh class A cirrhosis or patients with an anatomical preclusion to TIPS such as complete portal vein thrombosis. The options for surgical shunts include nonselective surgical shunts (portocaval or mesocaval shunts) or the selective distal splenoportal shunt (Figure 138.17). The distal splenoportal shunt is associated with lower rates of hepatic encephalopathy but requires more operating time which makes it less suitable as an emergency surgery [143].

**Gastric varices**

Although no studies have specifically evaluated this, the initial management of patients with acute gastric variceal bleeding is similar to the strategy for esophageal variceal bleeding. Specifically, volume resuscitation using a restrictive transfusion policy, the use of short-term prophylactic antibiotics, and the early administration of vasoactive drugs are recommended. About 40% of patients with bleeding from IGV1 varices who receive treatment with vasoactive drugs only will require rescue therapy with TIPS to achieve control of bleeding [144]. Thus, the combination of vasoactive drugs with endoscopic therapy is recommended.
Management of upper gastrointestinal hemorrhage related to portal hypertension

CHAPTER 138

Two RCTs have compared cyanoacrylate injection to banding ligation in acute gastric variceal bleeding. The first trial which included 60 patients showed that the cyanoacrylate group had a significantly higher rate of initial hemostasis compared to the EVL group (87% vs 45%, \( P = 0.03 \)), with a decreased rate of rebleeding (31% vs 54%, \( P = 0.0005 \)). The rate of significant complications was also lower in the cyanoacrylate group (19% vs 38%, \( P < 0.05 \)), including the frequency of treatment-induced ulcer bleeding (28% vs 7%, \( P = 0.03 \)). The second study of 97 patients showed that both treatments were equally effective in controlling active bleeding, but rebleeding rates were lower in the cyanoacrylate group compared to EVL (22% vs 44%, \( P = 0.044 \)) over a follow-up period of 1.6–1.8 years [152].

One of the most feared complications of gastric variceal obliteration using cyanoacrylate is the development of thromboembolic phenomena including splenic, renal, pulmonary, cerebral, spinal, and coronary emboli [154,155]. These are rare occurrences which may lead to infarction and/or septic complications, and possibly death. A recent retrospective review of 735 patients with gastric variceal hemorrhage who received N-butyl-2-cyanoacrylate for EVO found that distal embolism occurred in 5 patients (0.7%) [156]. Other complications included...
rebleeding due to early-onset extrusion of the glue cast (4.4%), sepsis (1.3%), gastric ulcer formation (0.1%), major gastric variceal bleeding (0.1%), and mesenteric hematoma associated with hemoperitoneum and bacterial peritonitis (0.1%). Three patients died from sepsis and one from rebleeding after glue cast extrusion, with an overall complication-related mortality of 0.53%. Other studies have reported a higher incidence of distal embolism of 2%–3% [157,158].

A standardized injection technique and regimen for the treatment of gastric fundal varices using cyanoacrylate has been proposed to minimize the risk of complications and rebleeding [159]. The first step involves dilution of 0.5 mL of N-butyl-cyanoacrylate with 0.8 mL of lipiodol. Dilution with lipiodol is necessary to prevent early glue polymerization from occurring which may result in entrapment of the needle in the varix. Conversely, overdilution prolongs the polymerization process and increases the risk of embolism. Also, the volume of the glue mixture is limited to 1.0 mL per injection to minimize the risk of embolism. Repeat intravariceal injections of 1.0 mL are performed until hemostasis is achieved. Next, complete obliteration of all tributaries of the fundal varix is performed to prevent early recurrent bleeding. As mucosal necrosis may develop around the site of injection several days after treatment, rebleeding may occur from the remaining patent varix if complete obliteration is not achieved. The adequacy of variceal obliteration is assessed by probing the treated varix with the tip of the injection catheter. Complete obliteration is indicated by a firm consistency of the varix. If the varix remains soft, repeat treatment is applied. Repeat EGD is performed 4 days later to confirm obliteration of all visible varices, with further cyanoacrylate injection if needed to achieve this. A study of 131 patients with bleeding fundal varices who underwent obliteration using this standardized technique and regimen showed that initial hemostasis and variceal obliteration was achieved in 100% of patients, with no occurrence of early rebleeding, procedure-related complications, or bleeding-related deaths. The cumulative rebleeding-free rates at 1, 3, and 5 years were 94.5%, 89.3%, and 82.9%, respectively.

The use of endoscopic ultrasonography (EUS) and Doppler imaging to guide the treatment of gastric varices with cyanoacrylate injection has also been studied as a method to increase the effectiveness and safety of treatment (Figures 138.18, 138.19, 138.20, 138.21, and 138.22). A pilot study of five patients showed that EUS-guided injection of cyanoacrylate into the perforating veins feeding gastric varices was successful in eradicating gastric varices in all patients, without recurrent bleeding or any procedure-related complications observed during the mean follow-up period of 10 months [159]. A more recent pilot study evaluated the outcomes of transesophageal EUS-guided therapy with combined coiling and cyanoacrylate injection in 30 patients with bleeding from large gastric fundal varices [160]. It was theorized that coils with attached synthetic fibers would function as a scaffold to retain cyanoacrylate within the varix, thus increasing efficacy and reducing the risk of embolization. Immediate injection of 1 mL 2-octyl-cyanoacrylate was performed after a coil was delivered into a varix. Color Doppler was used to evaluate the flow in the varix after treatment. If persistent flow was identified, further treatment was applied. Immediate hemostasis was achieved in the two patients with active bleeding at the time of endoscopy. Complete obliteration of varices was found at follow-up endoscopy after a single treatment session in 96% of patients. The mean volume of cyanoacrylate injected was 1.4 mL per varix. Rebleeding from gastric varices occurred in only one patient, which was successfully...
thrombin is between 1500 and 2000 U. Uncontrolled studies have shown that thrombin is effective in achieving initial hemostasis in 70%–100% of patients with gastric variceal bleeding, with rebleeding rates of 0–50% [161–164]. However, no RCTs of thrombin injection for the treatment of gastric variceal bleeding have been performed. Further studies are needed before its widespread use can be recommended.

A hemostatic powder has recently been shown to be effective in the management of nonvariceal upper gastrointestinal bleeding due to peptic ulcer disease, cancer-related bleeding, and arterial bleeding [165–167]. Two case reports have described the successful use of hemostatic powder to achieve control of gastric variceal bleeding, including a case of refractory bleeding [166,168]. A prospective pilot study of nine patients with acute variceal bleeding from esophageal varices demonstrated that the application of hemostatic powder from the cardia to 15 cm above GEJ resulted in hemostasis in all patients, with no rebleeding observed in any patients within 24 h and no mortality within a 15-day follow-up period [169]. Thus, larger RCTs are needed to determine the role and efficacy of hemostatic powder in the management of acute variceal bleeding, as primary therapy or rescue therapy for refractory or severe bleeding.

A major limitation of the use of tissue adhesives for gastric variceal obliteration is that they are not widely available. Indeed, tissue adhesives such as cyanoacrylate are not approved by the US Food and Drug Administration for use in the treatment of gastric varices. If tissue adhesives are not available, EVL can be performed for the treatment of GOV1, as they are a continuation of esophageal varices and share the same vascular anatomy.

In patients with massive gastric variceal bleeding with hemodynamic instability, balloon tamponade can be used as a...
temporizing measure until more definitive treatment can be performed. TIPS is the treatment of choice for salvage therapy in patients with failure to control bleeding from gastric varices despite pharmacological and endoscopic treatment [170–172]. It is effective in achieving control of bleeding in over 90% of patients. Studies have shown that salvage TIPS for gastric varices has similar rates of hemostasis, rebleeding, and mortality as for esophageal varices [170,173]. In patients with isolated fundal varices secondary to SV thrombosis, the recommended treatment is splenectomy or splenic embolization. The algorithm for the management of acute variceal bleeding is summarized in Figure 138.23.

Figure 138.21 The adequacy of gastric variceal obliteration after treatment can also be assessed by probing the varix with the tip of the injection catheter. Complete obliteration is indicated by a firm consistency of the varix. Source: Courtesy of Dr Payal Saxena and Dr Marcia Canto.

Secondary prophylaxis
Patients with cirrhosis who survive an episode of variceal bleeding are at high risk of rebleeding. The median rebleeding rate in untreated patients is about 60% at 1–2 years, with a mortality of 33% [59,73]. The highest risk for rebleeding is within the first 6 weeks after the acute bleeding episode. Thus, the prevention of rebleeding is a critical component of the management of variceal bleeding. Secondary prophylaxis should be initiated as soon as possible from day 6 of the index hemorrhage after resolution of acute bleeding occurs [70].

β-blockers
Many RCTs have established the efficacy of nonselective β-blocker therapy in the secondary prevention of variceal bleeding. Several meta-analyses of these studies have shown that nonselective β-blockers significantly reduce the rate of rebleeding to approximately 40% from 60% in untreated controls [73]. Furthermore, the use of β-blockers is associated with a significant reduction in mortality and bleeding-related mortality. The efficacy of β-blockers correlates with the reduction in portal pressure, as studies have shown that a reduction of HVPG of at least 20% of baseline or to below 12mmHg substantially decreases the risk of recurrent bleeding [82,174].

Endoscopic variceal ligation vs sclerotherapy
Endoscopic variceal ligation has now replaced sclerotherapy as the endoscopic treatment of choice for the prevention of variceal rebleeding, as it has been found to have increased efficacy in reducing the risk of rebleeding, with less frequent and severe complications [175]. In addition, fewer endoscopic sessions are required to achieve variceal eradication with EVL compared to sclerotherapy. The incidence of recurrence of varices after eradication ranges from 8% to 48% for EVL and 2% to 50% for sclerotherapy [175].

Figure 138.22 Endoscopic ultrasonography (EUS) revealing large gastric varix and perforating veins feeding gastric varix. Source: Courtesy of Dr Payal Saxena and Dr Mouen Khashab.
Endoscopic variceal ligation vs pharmacotherapy
Four RCTs have compared the efficacy of pharmacological treatment with a nonselective β-blocker (nadolol or propranolol) ± nitrates to EVL for the secondary prevention of variceal bleeding [176–179]. These studies have had conflicting results, but a meta-analysis of them found no differences in the risk of rebleeding or mortality between the two treatment groups. The results of long-term follow-up of patients in one of these studies showed that the combination of nadolol and ISMN was less efficacious than EVL in preventing variceal rebleeding, but was associated with increased survival after a median follow-up period of 6.8 years [180].

Combination of endoscopic variceal ligation and pharmacotherapy
Two RCTs have demonstrated that the combination of EVL and β-blockers is more efficacious in decreasing the risk of rebleeding and variceal recurrence after obliteration than EVL alone, with no difference in mortality rates [181,182]. These results were corroborated by the findings of a meta-analysis of 25 clinical trials including 2159 patients, which showed that the combination of pharmacotherapy (β-blocker ± nitrates) and endoscopic intervention (EVL or sclerotherapy) significantly reduced the incidence of all-cause rebleeding and variceal rebleeding, with no difference in mortality, compared to endoscopic treatment alone [183]. A recent meta-analysis of 9 clinical trials including 955 patients confirmed the similar findings [184]. Thus, the combination of a nonselective β-blocker and EVL is the recommended therapy for the secondary prophylaxis of variceal bleeding [70]. EVL should be performed every 2–3 weeks until variceal obliteration is achieved.

Transjugular intrahepatic portosystemic shunt and surgery
In patients who fail pharmacological and endoscopic treatment for the prevention of rebleeding, TIPS with
polytetrafluoroethylene-covered stents is the recommended treatment to prevent rebleeding [125]. Several RCTs have compared the efficacy of endoscopic therapy vs TIPS in secondary prophylaxis. A meta-analysis of 12 high-quality RCTs showed that TIPS significantly decreased the incidence of variceal rebleeding and bleeding-related mortality, at the cost of a higher incidence of post-treatment encephalopathy, compared to endoscopic treatment [185]. Furthermore, there was no difference in overall mortality between the two groups. An RCT also demonstrated that although TIPS resulted in a lower rebleeding rate in patients with advanced cirrhosis compared to pharmacotherapy with propranolol and ISMN (13% vs 39%, \( P = 0.007 \)), it was associated with increased rates of encephalopathy (38% vs 14%, \( P = 0.007 \)), less improvement in Child–Pugh class, higher costs, and equivalent survival [186]. Thus, TIPS has not been recommended as a first-line treatment to prevent rebleeding, but as salvage therapy for patients who fail endoscopic and pharmacological therapy. However, as discussed above, the results of a landmark RCT challenged this concept, as it showed that the use of early TIPS in patients who presented with variceal bleeding with Child–Pugh class C cirrhosis (with a score of 10–13) or class B cirrhosis with active bleeding at endoscopy, markedly decreased the risk of rebleeding and increased survival at 1 year, compared to standard therapy [141]. In addition, there was no increase in the incidence of hepatic encephalopathy. Thus, TIPS should be considered for secondary prophylaxis in such patients. Shunt surgery is also very effective in preventing variceal rebleeding. However, as with TIPS, a major limitation is the development of hepatic encephalopathy. A multicenter RCT of 140 patients comparing TIPS to distal splenorenal shunt in patients with Child–Pugh class A or B cirrhosis with refractory variceal bleeding found no differences in the rates of rebleeding, mortality, or encephalopathy [185]. However, the rates of thrombosis, stenosis, and reintervention were significantly greater in the TIPS group. A substantial majority of patients in the TIPS group (82%) required dilation to maintain patency compared to only 11% of patients who underwent distal splenorenal shunt therapy (\( P < 0.001 \)). It is important to note that covered stents, which reduce the frequency of TIPS occlusion, were not used in this study. Thus, in patients with Child–Pugh class A or B cirrhosis, the choice between TIPS vs shunt surgery depends on available expertise.

All patients with cirrhosis who survive an episode of variceal bleeding should be evaluated for orthotopic liver transplantation, as the development of variceal bleeding marks the progression to decompensated disease with a 1 year rate of mortality of approximately 57% [187]. Liver transplant is the most definitive treatment for end-stage liver disease and its complications, and has excellent long-term outcomes. Figure 138.24 shows the algorithm for secondary prophylaxis of esophageal variceal bleeding.

**Figure 138.24** Algorithm for the secondary prophylaxis of esophageal variceal bleeding. EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt.
Gastric varices prevention
Nonselective β-blockers have been used as first-line therapy to prevent gastric variceal rebleeding, although there is limited evidence to support this practice. A retrospective study showed that the use of propranolol or ISMN in patients who presented with acute gastric variceal bleeding and underwent EVO with cyanoacrylate injection did not decrease the incidence of rebleeding or improve survival [188]. An RCT comparing cyanoacrylate injection to β-blockers in 67 patients with eradicated GOV2 or IGV1 showed that cyanoacrylate injection was associated with a significantly lower incidence of gastric variceal rebleeding (15% vs 55%, \( P = 0.004 \)) and decreased mortality (3% vs 25%, \( P = 0.026 \)) during a median follow-up of 26 months [189]. A second RCT of 95 patients with fundal varices showed that addition of β-blocker therapy to EVO with cyanoacrylate injections did not change the risk of rebleeding or survival compared to cyanoacrylate injections alone [190].

Endoscopic variceal obturation with cyanoacrylate injection has also been compared to TIPS for secondary prophylaxis of gastric variceal bleeding. An RCT found that TIPS was more efficacious in preventing variceal rebleeding than cyanoacrylate injection (rate of bleeding 11% vs 38%, \( P = 0.014 \)), with no differences in survival or frequency of complications [191]. However, gastric variceal obliteration was only achieved in 51% of patients receiving cyanoacrylate injection, which is lower than the rates found in subsequent studies as described previously. The majority of patients in the study had GOV1 or GOV2. These findings were in contrast to a retrospective analysis which showed that there were no differences in rebleeding or survival in patients receiving cyanoacrylate injection vs TIPS [192]. However, patients receiving TIPS had a higher rate of long-term morbidity requiring hospitalization that those in the cyanoacrylate arm (41% vs 1.6%, \( P < 0.0001 \)). A cost-effectiveness analysis using retrospective data found that although TIPS was associated with a lower incidence of rebleeding compared to cyanoacrylate injection (20% vs 35%, \( P = 0.005 \)) in patients with GOV1 and GOV2, it was less cost-effective in the management of gastric variceal bleeding. A limitation of these studies is that bare stents were used for TIPS placement. Thus, further RCTs with covered stents and which include more patients with IGV1 varices are needed to clarify whether TIPS should be used as first-line treatment or salvage therapy after failure of EVO with tissue adhesives.

Balloon-occluded retrograde transvenous obliteration (BRTO) is a radiological technique introduced by Kanagawa in 1996 as a treatment method to obliterate gastric fundal varices [193]. It has become widely accepted as a highly effective treatment for gastric varices in Japan. It requires the presence of a gastrosystemic shunt, i.e., gastrorenal or gastrocaval shunt, in association with gastric varices. A prior CT scan or MRI is needed to outline the anatomy. The technique involves inserting a balloon catheter into the outflow shunt via the femoral or internal jugular vein. The balloon catheter is then inflated to occlude blood flow, and a retrograde venogram is obtained. A mixture of 5% ethanolamine olate and a contrast agent such as iopamidol is injected to fully visualize and obliterate gastric varices. Uncontrolled studies have shown that BRTO results in very high rates of variceal eradication (75%–100%) and exceptionally low rates of variceal rebleeding (0–9%) [194]. A small study comparing BRTO to TIPS showed no significant differences in the rates of rebleeding, mortality, or encephalopathy between the two treatment groups [195]. A small retrospective study found that BRTO was associated with lower rebleeding rates than cyanoacrylate injection [196]. RCTs are thus needed to compare the efficacy and safety of BRTO to other treatment strategies in the management of gastric variceal bleeding.

In summary, EVO with cyanoacrylate injection is an effective method to prevent rebleeding in patients who have experienced bleeding from gastric varices. After initial hemostasis by EVO with tissue adhesives is achieved, repeat sessions should be performed every 2–4 weeks until complete obliteration of gastric varices is achieved. Unlike the case of esophageal variceal bleeding, the addition of β-blocker therapy provides no benefit for the prevention of rebleeding or mortality in patients with fundal varices. In patients with GOV1, the use of band ligation of esophageal varices or β-blocker therapy may be considered [125]. TIPS is very effective in preventing gastric variceal rebleeding and is the treatment of choice if cyanoacrylate injection is not available or for patients who fail endoscopic therapy. Shunt surgery may also be considered in patients with Child–Pugh class A cirrhosis. Figure 138.25 illustrates the algorithm for secondary prophylaxis of gastric variceal bleeding.
shown to be effective in the treatment of both acute and chronic bleeding from PHG [200]. In acute bleeding, vasoactive drugs should be used, as two small studies have established the efficacy of octreotide [204] and terlipressin [205] in the control of acute bleeding. In chronic bleeding, iron supplementation should be administered to avoid depletion of iron stores. An RCT established the efficacy of β-blockers in preventing recurrent bleeding in cirrhotic patients with acute or chronic bleeding from severe PHG [206]. Of patients who received propranolol, 52% remained free of rebleeding at 30 months compared to only 7% of controls (P < 0.05). Patients treated with propranolol also had fewer episodes of acute bleeding compared to untreated patients. Thus, nonselective β-blockers are recommended for secondary prophylaxis of rebleeding in patients with PHG, at the same doses used in the treatment of esophageal varices. In patients with recurrent severe bleeding requiring frequent blood transfusions despite pharmacological therapy, TIPS should be considered as a treatment option, as it has been shown to improve the endoscopic appearance of lesions within 6 weeks and reduce transfusion requirements [207,208]. Shunt surgery may also be considered in patients with Child–Pugh class A cirrhosis. Figure 138.27 shows the algorithm for the management of bleeding from PHG.

Gastric antral vascular ectasia (GAVE) is characterized by the presence of red marks in the stomach without a background mosaic-like pattern (Figure 138.28). The red marks may be arranged in a linear pattern in the antrum or occur more diffusely. Although 30% of patients with GAVE have liver cirrhosis, portal hypertension is not associated with the development of GAVE [209]. Unlike PHG, the mainstay of treatment for symptomatic GAVE is endoscopic ablation by argon plasma coagulation or laser photocoagulation. Reducing portal pressure via TIPS placement is not effective for the treatment of patients with gastrointestinal bleeding from GAVE. Severe PHG may resemble GAVE as the red marks become confluent and

**Portal hypertensive gastropathy and gastric antral vascular ectasia**

Portal hypertensive gastropathy is a gastric mucosal lesion seen in patients with cirrhotic or noncirrhotic portal hypertension that is characterized by ectatic gastric mucosal capillaries and submucosal veins [197]. It is typically seen in the fundus and body of the stomach. The diagnosis is established by endoscopy. The mucosa typically has a mosaic-like pattern of erythema resembling “snake skin.” More severe forms have red marks such as cherry red spots and black-brown spots that represent submucosal hemorrhage [198]. PHG is categorized as mild when only the mosaic-like pattern is present or severe if red marks are observed [199] (Figure 138.26). A similar pattern may be seen in other parts of the gastrointestinal tract such as the small intestine and colon.

The prevalence of PHG in patients with portal hypertension has been reported to range from 20% to 80% [200]. A higher prevalence is associated with more advanced Child–Pugh class, the presence of GOVs, and previous endoscopic treatment with sclerotherapy or EVL [200]. The pathogenesis of PHG is not well defined. In addition to the role of portal hypertension, it appears that the gastric mucosa has increased susceptibility to injury by noxious factors and impaired healing [201].

The majority of patients with PHG are asymptomatic. Primary prophylaxis of bleeding in patients with PHG is not recommended as there are no clinical studies that have established its clinical benefit. In symptomatic patients, the most common presentation is chronic gastrointestinal blood loss resulting in anemia. The incidence of chronic bleeding in patients with PHG is approximately 10%–15% at 3 years [202]. Acute bleeding from PHG is rare, with an incidence of less than 3% at 3 years [203]. The highest incidence is observed in patients with severe PHG [200].

The treatment of bleeding from PHG is centered on the goal of reducing portal pressure. Nonselective β-blockers have been
have a striped appearance. A background mosaic-like pattern is consistent with PHG but not GAVE.

**Ectopic varices**

Ectopic varices originate from pre-existing veins of the gastrointestinal mucosa that are portosystemic collaterals between the portal vein and the IVC [202]. They typically occur in the duodenum, small intestine, colon, rectum, or ileostomy stoma. The prevalence of duodenal and small bowel varices is approximately 0.4% [197]. Bleeding from ectopic varices is rare, occurring in about 1%-4% of patients with cirrhosis and 30%-40% of patients with extrahepatic portal hypertension due to causes such as portal vein thrombosis [197]. Bleeding ectopic varices may be challenging to identify and treat because of their location. Injection with cyanoacrylate or sclerotherapy can be used to treat bleeding small bowel varices within the reach of an endoscope [210,211]. Band ligation is a treatment option for duodenal varices [212]. No controlled studies are available that compare treatment strategies. Case reports have shown that TIPS is an effective treatment for refractory bleeding from ectopic varices [213].

**Acknowledgments**

We thank Dr Payal Saxena, Dr Marcia Canto, and Dr Mouen Khashab in the Division of Gastroenterology/Hepatology at Johns Hopkins Hospital for providing multiple images for this chapter.

References are available at [www.yamadagastro.com/textbook](http://www.yamadagastro.com/textbook)

**Further reading**


Endoscopic diagnosis and treatment of nonvariceal upper gastrointestinal hemorrhage

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CHAPTER 139

Introduction

Upper gastrointestinal bleeding (UGIB) represents a significant entity for all clinicians. UGIB is defined as any source of gastrointestinal hemorrhage proximal to the Ligament of Treitz. In the United States, it is the cause of 300,000 hospitalizations per year, and approximately 2.5 billion dollars are spent annually on UGIB care [1,2]. Annual incidence has been reported to range from 48 to 160 per 100,000 adults [3–6]. Some reports have suggested that the incidence is decreasing [3,7]. The mortality rate is approximately 10% to 14% [6,8]. Despite advances in Helicobacter pylori detection and eradication, education on the effects of nonsteroidal antiinflammatory drugs (NSAID) use, and the use of proton pump inhibitors (PPIs), peptic ulcer disease remains the most common cause of nonvariceal UGIB. Endoscopic evaluation remains the gold standard for definitive diagnosis and therapy.

Initial assessment

The initial evaluation and risk assessment of the patient are the most important steps in the management of acute gastrointestinal bleeding. The clinical history can help identify factors that increase the risk for gastrointestinal bleeding. These include male gender, older age, current use of anticoagulation agents, NSAIDS, advanced chronic obstructive pulmonary disease, end stage renal disease, underlying cirrhosis, complicated neurological diseases, malignancies, and history of gastrointestinal surgeries [2,9–11].

Assessing the hemodynamic status of the patient at the time of presentation and prior to any intervention is critical. The clinician needs to determine whether airway protection by endotracheal intubation is necessary, the urgency of resuscitation, and the appropriate level of care. A minimum of two large bore (18 gauge) intravenous catheters for vascular access is required to ensure that immediate and effective volume resuscitation can be delivered. Evidence of hypovolemia such as tachycardia, hypotension, tachypnea, should be sought. Volume resuscitation should not be delayed pending availability of blood products. Aggressive fluid resuscitation has been shown to significantly decrease overall mortality [12]. Isotonic intravenous fluids such as normal saline or lactate ringers should be transfused immediately. The volume and speed of blood product transfusions should be determined based on the patient’s condition, estimated magnitude of on-going blood loss,
Identifying the source of bleed

UGBI typically presents with hematemesis (vomiting of bright red blood), coffee ground emesis (black blood/clots), or melena (black tarry stools). Ten percent of patients may present with hematochezia, a clinical suggestion of a brisk and massive bleed [16]. Taking an appropriate history to identify any underlying risk factors for gastrointestinal bleeding including past medical history, family history, medications including herbal supplements (which may contain salicylates) is essential. In certain circumstances a history may not be readily available because of the patient’s unstable condition and/or lack of cooperation, and lack of eye-witnesses, or family members. Clinicians must rely on physical examination to identify signs and symptoms of hypovolemic shock, evidence of trauma, and stigmata of chronic liver disease. A digital rectal exam should be performed to identify presence of melena, or hematochezia. If overt signs of gastrointestinal bleeding are not present, a fecal occult blood test (FOBT) can be helpful.

The routine use of nasogastric tube (NGT) lavage remains controversial. The main concern for the NGT is the pain and discomfort experienced by the patients. The clinical indication for placement of a NGT is twofold. In theory the NGT should assist the clinician in the triage of the acuity of blood loss and help determine whether urgent endoscopy is warranted. Secondly, the NGT lavage may aid in the clearance of the stomach in order to optimize endoscopic visualization. In a large retrospective study, Huang et al. demonstrated that NGT lavage did not affect overall mortality, length of hospital stay, or predict the need for surgery, or blood transfusions [17]. This study confirmed that the presence of a bloody or coffee ground material in the NGT lavage helps predict the presence of high-risk lesions, as shown in a 2004 study involving the Canadian registry of patients with UGBI [18]. However, a clear or bilious NGT aspirate does not imply the absence of a serious UGIB. In a metaanalysis looking at the sensitivity and specificity of the NGT lavage, the authors concluded that NGT aspiration has a sensitivity of 42% to 84%, and a specificity of 54% to 91% [19].

The presence of large amount of blood clots or coffee ground material often impairs endoscopic examination. However, the routine use of prokinetic agents such as erythromycin or metoclopramide is not recommended [6]. However, when large amounts of blood or clots are suspected, or there is a history of gastroparesis, and recent food ingestion, prokinetic agents may aid in endoscopic visualization. The metaanalysis found that both erythromycin and metoclopramide reduced the need for repeat endoscopy [20]. On the other hand, the use of these agents did not affect the duration of hospital stay, requirements for blood transfusions, or surgery [20–22].

Proton pump inhibitor (PPI) use

Preendoscopic PPI use is associated with a lower rate of high-risk stigmata seen on endoscopic exam, and decreases the need for subsequent endoscopic intervention. A Cochrane review involving 2223 patients from six randomized control trials using either oral or intravenous PPIs compared to placebo or a histamine 2 receptor (H2R) antagonist, found that PPI therapy given 24 to 48 hours before endoscopy, reduced the frequency of findings of high-risk stigmata (OR, 0.67; 95% CI, 0.54 to 0.84) and the need for endoscopic intervention (OR, 0.68; 95% CI, 0.50 to 0.93) [23]. Clinical outcomes such as rebleeding, mortality rates, and need for surgical intervention were not affected by PPI therapy.

A cost analysis study on the use of intravenous (IV) PPI’s before endoscopy found that its use was more costly but effective in the United States [24]. In Canada, intravenous PPI use before endoscopy became more effective and less costly with longer hospital stays (greater than 6 days) in high-risk patients and hospital stays less than 3 days in low-risk patients.

Post endoscopic use of PPI’s has also been studied in detail. Both the International Consensus Recommendations and American College of Gastroenterology guidelines, strongly recommend the use of high dose IV PPI after endoscopic hemostasis in patients with high-risk stigmata [6,25]. In 2005, a metaanalysis of randomized controlled trials with confirmed peptic ulcer bleeding and the primary endpoint of 30 day mortality, reported that the use of PPI’s, whether oral or in varying doses intravenously, did not affect mortality [26]. However, the use of PPI’s when compared to placebo or H2R antagonists, was associated with a reduction in rebleeding (OR, 0.46, number needed to treat [NNT], 12), and the need for surgery (OR, 0.59; NNT, 20).

A randomized control trial compared IV PPI (esomeprazole) dosed at 80mg bolus followed by 8mg/h for 71.5 hours, to placebo, in patients with documented single ulcer displaying high-risk stigmata [27]. All patients had undergone successful endoscopic hemostasis. The results support administration of IV PPI after endoscopic therapy to reduce rebleeding rates (from 10.3% to 5.9%) and reduce the need for repeat endoscopic therapy (placebo 11.6% vs. PPI 6.4%).

In contrast, multiple studies from Asia have not found any benefit from high dose PPI or requirement for IV administration to decrease rebleeding [28–32]. H. pylori infection was associated with lower rates of rebleeding [29,32]. The differences in response to PPI therapy observed between Asian populations and other ethnicities have been thought to be due to genetic polymorphisms in CYP2C19 genotype affecting PPI metabolism, differences in parietal cell mass, and prevalence of H. pylori infection [33–36]. A post hoc analysis of Cochrane
study also found that benefits of PPI therapy in the Asian population was much greater [37]. PPI use was associated with a decrease in mortality from all causes (OR, 0.35; NNT, 33) only in the Asian population. Moreover, a quantitatively greater decrease in rebleeding and surgery were observed in Asia.

### The role of endoscopy

Prognostic scales aid the clinician in risk stratification. There are multiple prognostic scales, most incorporating endoscopic findings that aim to identify those patients that require admission and have a higher risk of mortality [38–42]. Commonly used scores include the Rockall score, Glasgow-Blatchford score, Baylor College, and Cedars-Sinai Medical Center predictive index.

The Rockall Score was developed in 1996 as the result of a large multicenter prospective study with the primary goal to identify patients and specific clinical characteristics that increase mortality risk [42]. The Rockall score is a simple scoring system based on age, comorbidities, hemodynamic status such as pulse and blood pressure, endoscopic diagnosis, and bleeding stigmata [42]. A score of less than three signifies a low-risk patient, whereas a score of eight or greater identifies a patient with high mortality risk (Table 139.1).

The Glasgow-Blatchford Score (GBS) is similar to the Rockall Score in that it uses existing comorbidities and hemodynamic measurements. However it was developed to identify patients that need transfusions and endoscopic therapy to treat the bleeding [43]. In order to identify high-risk patients, the score also incorporated the presence of syncope and melena, hemoglobin levels, and blood urea levels (Table 139.2).

There are two American scores: The Baylor Score, which aims to risk stratify patients at high-risk for rebleeding, and the Cedars-Sinai predictive index, which takes into account the time from initial bleed as well as commonly used factors of comorbidities, endoscopic findings, and hemodynamics, to identify patients that can be discharged early from the hospital [38,45].

The GBS and the Rockall are the most user friendly and well-validated scores. The Rockall Score is superior in predicting

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**Table 139.1** Rockall classification of risk in acute upper gastrointestinal (UGI) bleeding.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Points for this variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;60</td>
<td>≥60 and &lt;79</td>
<td>≥80</td>
<td></td>
<td>Maximum 2</td>
</tr>
<tr>
<td>Shock</td>
<td>HR &lt; 100</td>
<td>Systolic BP ≥ 100</td>
<td>HR ≥ 100</td>
<td>Systolic BP &lt; 100</td>
<td>Maximum 2</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td>Maximum 3</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Mallory-Weiss tear, no lesion</td>
<td></td>
<td></td>
<td>Malignancy of UGI tract</td>
<td>Maximum 2</td>
</tr>
<tr>
<td>Endoscopic stigmata</td>
<td>Clean base or flat spot</td>
<td></td>
<td>Active bleeding, adherent clot or nonbleeding visible vessel</td>
<td></td>
<td>Maximum 2</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maximum 11</td>
</tr>
</tbody>
</table>

BP, blood pressure (mmHg); HR, heart rate.
Source: Adapted from Rockall et al. 1996 [42]. Reproduced with permission from BMJ Publishing Group Ltd.

<table>
<thead>
<tr>
<th>Admission risk marker</th>
<th>Score component value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea (mmol/L)</td>
<td>≥6.5 to &lt;8</td>
</tr>
<tr>
<td></td>
<td>8 to &lt;10</td>
</tr>
<tr>
<td></td>
<td>≥10 to &lt;25</td>
</tr>
<tr>
<td></td>
<td>≥25</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>≥10 to &lt;12</td>
</tr>
<tr>
<td></td>
<td>12 to &lt;13</td>
</tr>
<tr>
<td>Hemoglobin (g/dL) for women</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>≥10 to &lt;12</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>&lt;90</td>
</tr>
<tr>
<td></td>
<td>90 to 99</td>
</tr>
<tr>
<td></td>
<td>100 to 109</td>
</tr>
<tr>
<td>Other risk markers</td>
<td>Pulse ≥ 100 beats/min</td>
</tr>
<tr>
<td></td>
<td>Melena</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
</tr>
<tr>
<td></td>
<td>Hepatic disease</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
</tr>
</tbody>
</table>

Source: Adapted from Blatchford et al. 2000 [43]. Reproduced by permission of Elsevier.

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low-risk patients after endoscopy [44]. However, in the preendoscopic setting, the GBS has proven to be the more sensitive test in predicting mortality and need for intervention [44,46]. In the preendoscopic setting, the clinician must rely on patient history, vital signs, and one’s physical exam to determine the need for hospitalization and further therapy. Although experienced clinicians may perform appropriate triage confidently, often times there are patients that fall in the uncertain category, with equivocal clinical scores.

Endoscopy remains the gold standard for the diagnostic evaluation of an UGIB. Endoscopy usually offers a direct visualization of the source, immediate implementation of appropriate therapies, and assessment of further management needs. Minimal requirements for readiness of an endoscopy will vary among physicians and institutions. Most physicians will agree that hemodynamic stability and procedural consent either from the patient or surrogate, or in the emergency setting, two physicians involved in the patient’s care, are the two criteria that need to be met prior to endoscopy. There are incidences in which endoscopic evaluation may be inappropriate. In cases of suspected gastrointestinal perforation, uncooperative or difficult to sedate patient without general anesthesia support, or when diagnosis obtained by endoscopy will not change the outcome. Under such circumstances the clinician should not proceed with endoscopic evaluation.

Endoscopy driven triage has been demonstrated to be beneficial in reducing hospitalization rates and costs [47–49]. In a study examining outcomes of patients discharged early based on endoscopic findings and clinical characteristics, only one out of the 176 patients identified had recurrent bleeding [48]. This study suggests that outpatient care can be safe and cost effective in the appropriate population.

Lee and colleagues [47] randomized 110 patients to receive endoscopy in less than 48 hours (the control group, or while in the emergency room. Endoscopic findings from the early endoscopy group allowed 46% (26 of 56 patients) to be discharged directly from the emergency department. Discharged patients did not have adverse outcomes and there was a statistically significant reduction in hospitalization rates and cost of care. Similar findings have been obtained by other groups who have evaluated endoscopy driven triage [49].

In contrary to the above findings, Bjorkman et al. did not find urgent endoscopy, defined as endoscopy prehospitalization, to be helpful in reducing resource utilization or hospitalization costs [50]. Despite 40% of the patients receiving urgent endoscopy followed by recommendation for early discharge, only four out of the 19 patients were actually discharged, underscoring that admission decisions may be affected by other factors.

Endoscopy can reduce mortality in high-risk patients [6,51,52]. The appropriate timing of endoscopy remains controversial. The definition for urgent endoscopy has some variability. In general, urgent endoscopy refers to an endoscopy performed within 12 hours of presentation. Early endoscopy refers to the timing of <24 hours from presentation. Although urgent endoscopy has been shown by some to decrease hospital stay and costs as discussed above, the actual impact on mortality is debated. A majority of patients admitted for UGIB do not have actively bleeding lesions on endoscopic exam [53].

Targownik and colleagues examined whether performing endoscopy within the 24 hour window actually made a difference in clinically high-risk patients, with signs of hemodynamic instability such as tachycardia (heart rate >100) or systolic hypotension (blood pressure <100mmHg) [54]. Adverse outcomes were defined as rebleeding, need for surgical hemostasis, mortality during hospitalization, and 30-day readmission for a nonvariceal UGIB. There was no difference in adverse bleeding outcome rates between patients who received an endoscopic exam within 6 hours to patients who underwent an endoscopy between 6–24 hours. Twenty-five percent of the patients in the 6 hour group had an adverse outcome versus 23% in the 6–24 hour group [54].

Sarin and colleagues studied the effects of endoscopy timing on patient mortality, need for surgery and blood transfusions [55]. This retrospective study involved upper endoscopies performed for suspected or overt UGIB. They, too, found no difference in mortality, surgery requirement, or blood transfusions between patients endoscoped within 6 hours compared to patients who received endoscopy within 24 hours. Similar results were also obtained in a much larger study involving 4478 patients from 212 UK hospitals, comparing patients who underwent endoscopy in less than 12 hours with those who underwent endoscopy >24 hours later [56]. However there was a trend towards increase in rebleeding rates among patients who underwent later endoscopy.

The American Society for Gastrointestinal Endoscopy 2012 guidelines, International Consensus Recommendations published in 2010, and the Scottish Intercollegiate Guidelines Network, all recommend an endoscopy to be performed within 24 hours of presentation [6,57,58].

**Peptic ulcer disease**

UGI bleeding makes up more than 75% of all admissions for acute GI bleed. While the differential diagnosis and cause for an UGIB remains broad, peptic ulcer disease (PUD) is by far the most common cause of UGIB (Figure 139.1). PUD constitutes 30% to 50% of all UGIB, with an incidence in the United States of 5.27 per 1000 adults [7,59,60]. By histological definition, PUD occurs when inflammation causes the loss of the mucosa and muscularis mucosa, often with extension into the submucosa and the muscularis propria [61]. The most common causes of PUD are nonsteroidal antiinflammatory agents (NSAID) use and H. pylori infection. However, both benign and malignant tumors can often present as a gastric or duodenal ulcer. In immunocompromised patients, atypical infectious causes include cytomegalovirus, herpes simplex virus (HSV), and fungal infections. Other less common causes include other...
gastroenterologists commonly use the specific descriptions for each stigmata [25]. High-risk stigmata for rebleed include active spurting or oozing lesion, and nonbleeding visible vessel. Adherent clots without an underlying visible vessel, flat pigmented spots, and clean-based ulcers are considered low-risk. Patients with endoscopic evidence of active bleeding, defined as spurting or oozing, or evidence of nonbleeding visible vessel, should be treated [6,25]. These high-risk stigmata carry a mortality risk of 11%, a rate for further bleeding of greater than 40%, and an increased need for surgical intervention [53,64] (Tables 139.3 and 139.4).

The decision to treat an adherent clot varies among endoscopists. This is in part due to differing definitions of what constitutes an adherent clot, varying response to medical treatment among populations, and the known risks of exacerbation or precipitation (re-initiation) of the ulcer rebleeding. Recent published studies suggest a benefit in attempting removal of the adherent clot to evaluate for underlying high-risk stigmata [65–68].

A prospective study performed by Laine et al. served to highlight the benefit of removal of an adherent clot [65]. In this study medications, chemotherapy, illicit drugs (crack cocaine, methamphetamine), systemic mastocytosis, Zollinger-Ellison, and postsurgical ulcerations. Most ulcers are uncomplicated and do not cause significant GI bleed, perforation, or obstruction. Endoscopy allows the clinician to visualize, diagnose, and take biopsies of the lesion as necessary. In the setting of overt GI bleeding, endoscopic management allows patient risk assessment and effective control of the bleeding.

During endoscopy, clear documentation of the location, size, number of ulcers, characteristics of ulcer edges, and associations with nodules or masses, is recommended. It is especially important to look for stigmata of recent hemorrhage, as it will predict further risks of rebleeding; therefore, dictate further management required. A metaanalysis identified risk factors for PUD rebleeding after endoscopic therapy to include ulcer location involving the posterior wall of the duodenum or high lesser curvature, hemodynamic instability (tachycardia >100, systolic blood pressure <100), large ulcer size >1 cm, need for blood transfusions, and an actively bleeding ulcer [62].

The Forrest classification was first introduced in 1974 and is used mainly in Europe and Asia [63]. In the United States gastroenterologists commonly use the specific descriptions for each stigmata [25]. High-risk stigmata for rebleed include active spurting or oozing lesion, and nonbleeding visible vessel. Adherent clots without an underlying visible vessel, flat pigmented spots, and clean-based ulcers are considered low-risk. Patients with endoscopic evidence of active bleeding, defined as spurting or oozing, or evidence of nonbleeding visible vessel, should be treated [6,25]. These high-risk stigmata carry a mortality risk of 11%, a rate for further bleeding of greater than 40%, and an increased need for surgical intervention [53,64] (Tables 139.3 and 139.4).
Table 139.3 Forrest classification of peptic ulcer disease: Description and prevalence of findings.

<table>
<thead>
<tr>
<th>Forrest stage of ulcer</th>
<th>Endoscopic description</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Active arterial spurting</td>
<td>9.3%</td>
</tr>
<tr>
<td>Ib</td>
<td>Active oozing</td>
<td>6.5%</td>
</tr>
<tr>
<td>Ila</td>
<td>Visible nonbleeding vessel</td>
<td>6.1%</td>
</tr>
<tr>
<td>IIb</td>
<td>Adherent clot</td>
<td>13.1%</td>
</tr>
<tr>
<td>IIc</td>
<td>Pigmented spot at ulcer base</td>
<td>52.6%</td>
</tr>
<tr>
<td>III</td>
<td>Clean based ulcer, no bleeding</td>
<td>5%</td>
</tr>
</tbody>
</table>

Source: Adapted from Enestvedt et al. 2008 [60]. Reproduced by permission of Elsevier.

Table 139.4 Rate of rebleeding and mortality in multiple studies.

<table>
<thead>
<tr>
<th>Endoscopic finding</th>
<th>Risk of rebleeding (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Flat spot</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Clean base</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: Data from Laine and Peterson [53].

46 patients with an adherent clot underwent vigorous high power water irrigation with a 3.2 mm bipolar probe for a maximum of 5 minutes. After irrigation, 57% of the clots remained adherent, 1% had active spurting, 13% with oozing, 13% had a nonbleeding visible vessel, 11% had a flat pigmented spot, and 2% had a clean based ulcer. This equates to 27% of ulcers with an adherent clot had underlying high-risk stigmata. Furthermore, 8% of the patients with persistent adherent clot rebled and required repeat endoscopy with therapy.

Another prospective trial carried out in Taiwan, also found high-risk stigmata were frequent under the adherent clot, conferring high rates of rebleeding if not treated endoscopically [66]. In this study 25% of patients had recurrent bleeding within 1 month, and 60% of those patients rebled within 72 hours. They found that those with other comorbidities, anemia with hemoglobin <10 gm/dL, or hypovolemic shock, were more likely to have rebleeding in the setting of an adherent clot.

Results from a randomized control trial support the use of endoscopic combination therapy in cases of nonbleeding adherent clots to achieve lower rebleeding rates [67]. This multicenter trial included patients with a nonbleeding adherent clot on a peptic ulcer, defined as a clot that is resistant to suction or direct irrigation with a jet, and requirement for admission to monitored bed, or intensive care unit due to significant blood loss (hemoglobin loss of 8% or the need for at least two units of packed red blood cells transfusion). A total of 32 patients met criteria for rebleeding. The adherent clot was then treated by first injecting dilute epinephrine in four quadrants at the clot pedicle, followed by gently shaving off the clot starting with the top using a cold snare (cold snare guillotine) until 4 mm of the clot was left. The remnant clot was then irrigated again, followed by coaptive coagulation. Among the 32 patients, 17 were treated medically and 15 patients received endoscopic treatment. The medically treated group required more blood transfusions, and had a 35% rate of rebleeding and 23% rate of requiring further endoscopic therapy. A metaanalysis of six randomized control trials from Asia, Europe, and the United States, also support the benefit of endoscopic therapy in treating adherent clots in terms of decreasing rebleeding rates [68].

Attempts to remove an adherent clot should go beyond irrigation through a small syringe and should include irrigation through a water pik or jet, especially in high-risk patients (older age, comorbidities, hemodynamic and/or biochemical evidence of a severe bleed). Clinical judgment, taking into account location and size of the ulcer, stability of patient, and the clinician’s comfort level, must also factor into formulation of a management plan.

Modalities of endoscopic treatment

Epinephrine injection

Epinephrine monotherapy is no longer recommended in the treatment of nonvariceal upper GI hemorrhage [6,25]. With epinephrine injection 3%–36% of patients will have recurrent bleeding [69]. Lin et al. aimed to find the optimal dose of epinephrine injection [69]. They randomized patients to high volume (16.5 mL of 1:10000 concentration) and low volume group (8 mL). The large volume injection resulted in less episodes of recurrent bleeding (15.4% vs. 30.8% low volume), but there was no difference in mortality, or need for surgery. The total volume of epinephrine injected may make a difference in initial hemostasis.

A metaanalysis of randomized controlled trials on endoscopic therapy for ulcer bleeding compared different modalities of endoscopic hemostasis with the primary end point of preventing further bleeding. Results from the study found that epinephrine therapy was effective in initial hemostasis, but was less effective than other forms of monotherapy. In addition, epinephrine monotherapy was inferior to epinephrine injection with a second therapy (hemoclips, sclerosant agent, or thermal coagulation) in preventing further bleeding and escalation to surgery (RR, 0.34; NNT, 5) [70]. Other monotherapy modalities (fibrin glue, thrombin, hemoclips, sclerosant agent, or thermal coagulation) were all superior to epinephrine injection monotherapy.

In 2010, the Cochrane Collaboration Review also demonstrated results that supported combination therapy [71]. In
comparison to epinephrine monotherapy, combination therapy consisting of epinephrine injection and a second endoscopic method, was significantly more effective in preventing recurrent bleed (18.5% epinephrine vs. 10.7% combination therapy), decreasing mortality (4.7% vs. 2.5% combination therapy), and the need for emergency surgery (10.7% epinephrine vs. 6.7% combination therapy).

Sclerosants and absolute ethanol injection
Sclerosants include agents such as sodium morrhuate, ethanamine oleate, polidocanol, and sodium tetradecyl sulfate. Sclerosants and absolute ethanol cause necrosis of the injected tissue, with subsequent vessel thrombosis and ulceration of the injected tissue. Sclerosants and ethanol are not recommended for nonvariceal bleeding, with the exception of hemostasis in the palliation of a large gastrointestinal tumor. Ethanol causes tissue dehydration with subsequent necrosis and ulceration. Due to the risk of extensive ulceration leading to perforation, the amount of ethanol injected should be limited to a total volume of 2 mL for peptic ulcer bleeding. The injection of absolute (greater than 95%) ethanol is useful in initial hemostasis and decreasing rebleeding rate compared to conservative medical management [72]. Subsequent studies comparing ethanol injection to thermal therapy, epinephrine topical spray, epinephrine injection plus or minus polidocanol, and mechanical therapy with endoclips, have found efficacy similar to other modalities; one study showed ethanol to be inferior to thermal therapy [73–77]. Absolute ethanol injection in the duodenum carries an even higher risk of perforation due to the thin duodenal wall, and therefore should not be used there.

There have been multiple studies that compare sclerosant injection therapy alone, in combination with epinephrine, and to epinephrine alone, in the treatment of bleeding peptic ulcer [78–82]. Studies fail to provide evidence that sclerosant therapy alone, or in combination with epinephrine, is superior. It does not provide any additional benefit to hemostasis, mortality, rate of surgery, transfusions, or length of hospitalization [81,83,84]. Sclerosants have been shown to cause extensive necrosis, carrying a risk of perforation and death [81,85–87].

Tissue adhesive therapy
The three main agents in this class include fibrin glue, thrombin, and cyanoacrylates. They are considered thrombogenic agents and do not cause direct tissue damage. The use of these agents is more common in Europe and in Asia than the United States, where fibrin glue and cyanoacrylates have not been approved for endoscopic use. Access to human-derived thrombin in the acute setting may be limited.

Cyanoacrylate liquid glue undergoes almost immediate polymerization creating a solid cast of the injected vessel within 20 seconds [88,89]. Most of the data suggesting use of cyanoacrylates has been obtained in trials of patients with variceal bleeding [90,91]. In the one randomized control trial involving 126 patients with both actively bleeding ulcers and ulcers with visible vessel. Lee and colleagues compared N-butyl-2-cyanoacrylate injection to hypertonic saline-epinephrine (HSE) and found that 9 N-butyl-2-cyanoacrylate led to initial 95.2% hemostasis versus 92.1% in the HSE group [92]. There was a significant decrease in rebleeding rate in the N-butyl-2-cyanoacrylate group. However, need for emergent surgery and hospital mortality were unchanged. More significantly, two patients who received N-butyl-2-cyanoacrylate, developed an arterial embolization with infarction, one of which proved to be fatal. In addition, its use requires tedious preparation before delivery due to its quick polymerization rate and potential damage to the endoscope. In general experts do not recommend N-butyl-2-cyanoacrylate for ulcer related hemostasis.

Fibrin glue is comprised of high concentration fibrinogen and thrombin, which directly affects the clotting cascade. Endoscopic use of fibrin glue is considered an “off-label” use, but nonetheless has been shown to produce effective hemostasis. Initial hemostasis rates range from 92% to 100% [89]. Fibrin glue was found to be more effective than epinephrine and polidocanol injections in prevention of rebleeding [93,94]. However, fibrin glue failed to make a difference in outcome measures such as transfusion requirements, surgery rates, hospital stay length, and mortality [93,95,96].

Proponents for the use of fibrin glue in ulcer treatment believe that fibrin glue accelerates ulcer healing. This effect is achieved through repeat injections of fibrin glue. Rutgeerts and colleagues performed a large randomized trial of repeat daily endoscopic injection of fibrin glue with single fibrin glue injection, and single injection of polidocanol [95]. All study patients were also pretreated with dilute epinephrine injection. Repeated injections of fibrin glue was found to be more effective in prevention of recurrent bleeding than single dose fibrin glue and polidocanol.

Thrombin comes in two forms: human derived and bovine thrombin. The use of bovine thrombin carries a risk of anaphylaxis, Factor V antibody formation, and possibly bovine spongiform encephalopathy and Creutzfeld Jakob disease [88]. Thrombin injection is associated with an initial hemostasis rate of 86.6% [97]. When combined with epinephrine injection, the addition of bovine derived thrombin injection did not confer a benefit to permanent hemostasis (81.3% epinephrine alone vs. 84.4% epinephrine and thrombin), mortality, volume of transfusions, or rate of surgery [98]. When compared with heater probe monotherapy, combination therapy with heater probe and thrombin injection did not change outcomes of rebleeding or emergent surgery [99]. On the contrary, when Kubba and colleagues used human thrombin injections with or without epinephrine, combination injection therapy resulted in a decrease in rebleeding rates (4.5% compared to 20% in epinephrine injection), and mortality [100].

Mechanical therapy
Endoscopic mechanical therapy consists of endoscopic hemostasis clips (hemoclips) and ligation banding. Endoscopic
ligation banding is typically reserved for variceal ligation. However, studies have demonstrated successful endoscopic band ligation of Dieulafoy’s and Dieulafoy-like lesions of the upper GI tract [101–103]. Dieulafoy’s lesions are large tortuous arterioles arising from the submucosa with a small visible mucosa defect but without any associated surrounding inflammation. In one study of 23 patients with Dieulafoy-like lesions located in the stomach, Billroth II anastomosis sites, duodenum, and jejunum, endoscopic band ligation achieved sustained hemostasis in 22/23 patients [102]. The one patient with recurrent bleed within 5 days was a patient with a jejunal lesion. A prospective trial published in 2009, compared epinephrine injection therapy to endoscopic band ligation in all patients presenting with a Dieulafoy’s lesion (18/588 Patients) [101]. Dilute Epinephrine (1:10000) therapy was administered in eight of these patients by injection in four quadrants with 2.5 mL initially and repeated injections until cessation of bleeding (mean injection of 12 mL, range 8 mL to 24 mL). There was no rebleeding in the band ligation treated group (N = 10). The epinephrine group had a 75% recurrent bleeding rate.

Hemostasis clips can be applied to Dieulafoy’s lesions, visible vessels in peptic ulcers, and defects such as Mallory Weiss tears and small perforations. There are many types of endoscopic hemostasis clips on the market that differ in deployment style, maneuverability, size, and material. A randomized study comparing two commonly used disposable clip devices in a simulator model for bleeding, did not find a difference in efficacy between the hemostasis clips [104]. As expected, application of the hemoclips and successful hemostasis were found to be dependent on the endoscopist’s experience and skill level. In the treatment of peptic ulcer disease with a visible vessel, hemoclip application as monotherapy yields high hemostasis rates that are comparable to dual therapy, and is superior to epinephrine injection alone [105]. With Dieulafoy’s lesions, hemoclips have also been shown to be more effective than epinephrine injection alone, and equally effective to endoscopic band ligation [106–108]. Mallory-Weiss tears may be treated successfully with hemoclips [109–111]. Iatrogenic duodenal perforations, depending on size and location, can sometimes be successfully closed with hemoclips [112–114]. The use of hemoclips requires more precise application than the use of endoscopic band ligation. The operation expertise and comfort level with hemoclips, the location of the lesion, and the ease of accessibility should all be considered in the decision to use hemoclip for treatment of UGIB.

**Thermal coagulation devices** (Figure 139.2a–d) Although CO₂ laser was the first laser to be used in endoscopic hemostasis [115], this has been largely supplanted by Nd:YAG laser and argon plasma coagulation. Thermal coagulation can be applied with heater probes, electrocautery probes, Argon plasma coagulation, and neodymium-yttrium aluminum garnet (Nd:YAG) lasers. Coagulation can be achieved with Nd:YAG lasers and Argon plasma coagulation without direct contact with the lesion. Kiehhaber and colleagues first reported that it was possible to transmit argon and Nd:YAG through a fiberoptic system [116]. Since then, multiple randomized control trials have been performed on the effectiveness of hemostasis by Argon Gas and Nd:YAG laser [117]. In terms of endoscopic hemostasis of visible vessels and peptic ulcers, the Nd:YAG laser has more robust results. The Nd:YAG has been shown to be effective in initial hemostasis 80% to 96% of the time, with a rebleeding rate of 10% in ulcer disease, and 30% for esophageal varices [117–119]. Not only were perforation

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**Figure 139.2** (a) A quartz laser fiber with covering plastic sheath. Fibers may also have a sheath that provides coaxial gas flow. The quartz fiber conducts the laser light but is flexible enough to be passed through an endoscope channel. Similar fibers are used for argon, Nd:YAG, and KTP lasers. (b) Bipolar electrocoagulation catheter. Electrodes circle the end of the catheter, and a central channel provides vigorous water irrigation. Some electrodes have a retractable central injection needle to allow combined electrocoagulation and injection therapy. (c) Heater probe. A flexible catheter tipped with a heating element that is placed directly on the tissue for coagulation. No electrical current passes through the patient. Vigorous water irrigation is possible through the central channel of the catheter. (d) Argon plasma coagulation catheter. This hollow catheter produces a flow of electrically charged argon gas when activated. The catheter should not come in contact with the tissue. It allows rapid electrocoagulation of larger areas of tissue, or areas that are difficult to reach with a contact probe.
rates of laser therapy low (between 1%–3%), the Nd:YAG laser made an impact in reducing the need for surgery and decreasing mortality rates [117,120,121]. Use of Nd:YAG laser therapy has declined over the years, especially with the advent of heater and electrocautery probes. The decline is due to a few factors. For one, the equipment, training of staff, and a probe for each individual patient, make it expensive compared to other coagulation modalities. Technically, the Nd:YAG laser is difficult to use for precise delivery. Ulcers are often located at an awkward angle from the direction of the fiberoptic bundle. Also the Nd:YAG laser works for hemostasis only when short direct bursts are delivered; short bursts of energy cause thermal contraction of the bleeding tissue/vessel wall. When longer shots of energy are delivered, vaporization of tissue occurs to cause burn into deep layers and possibly perforation. These same qualities make it possible to use Nd:YAG laser in palliative debulking and coagulation of gastrointestinal cancers, especially of the upper GI tract [122].

Argon plasma coagulation (APC) involves the use of a monopolar electrosurgical generator to send current to the APC probe tip, which ionizes the argon gas into plasma that delivers the thermal energy to the targeted tissue. The current and argon gas flow rate are both adjustable. The APC thermal energy can be delivered linearly (straight fire probe), or tangentially (circumferential probe). The depth of APC thermal transmission in the stomach is only 1 mm to 1.55 mm [123]. Although there have been a few studies demonstrating the effectiveness of APC on ulcer related hemostasis, APC has generally been used for the treatment of superficial lesions such as gastric antral vascular ectasias, arteriovenous malformations [124–126]. Experts do not recommend APC for hemostasis of bleeding ulcers [58,127,128].

The effectiveness of the heater probe in endoscopic hemostasis of bleeding ulcers was first reported in the 1980s and has since been validated in clinical practice [129,130]. Both the heater probe and electrocautery (monopolar or bipolar/multipolar) probe utilize a combination of direct pressure and heat or electric current, respectively, to coagulate blood vessels, a process called coaptation. Coaptation with both probes has been shown to achieve successful hemostasis in vessels up to 2.5 mm in diameter in the canine model [131]. This diameter is important as the mean diameter of arteries feeding gastric ulcers is 0.7 mm (range 0.3 mm to 1.8 mm) and the mean diameter of arteries diameter under duodenal ulcers is 1 mm (range 0.1 mm to 3.54 mm) [132–134] (Figures 139.3, 139.4 and 139.5).

**Novel endoscopic hemostasis devices**

The Hemospray has shown promise in the treatment of GI bleeds [135–140]. Hemospray is approved in Canada for endoscopic use in nonvariceal UGIB and is currently being studied for this indication in a multicenter clinical trial in Europe. However, it is not available in the United States commercially.

The hemospray consists of a mineral blend powder, TC-325, that has been used for external injury related bleeding. The proprietary powder interacts with blood to form a strong cohesive bond, creating a stable mechanical barrier. By binding to the fluid blood, it inherently causes a focal concentration of clotting factors. This in turn activates the coagulation cascade, forming a stable fibrin plug [141]. The hemospray is appealing due to its ease of use, and the fact that it is nonabsorbable. In a porcine gastrointestinal bleeding model, Giday et al. found evidence supporting the effectiveness of hemospray in UGIB. In the porcine models with spurring arterial bleeds, initial hemostasis with TC-325 was achieved 100% of the time, and rate of rebleeding was 20%. On necropsy there was no evidence of foreign body granuloma formation or embolization to the lung or brain [141].

Sung and colleagues performed a single arm pilot clinical study of 20 patients with peptic ulcer and a Forrest score of Ia or Ib [136]. All patients were treated with the hemospray within 24 hours of presentation and received up to two applications with the stipulation of a maximum of 150 g TC-325 delivered. These patients were then monitored at 72 hours with a second endoscopy and at 30-days by telephone follow-up. Initial hemostasis was 95%. One patient was found to have a pseudoaneurysm and underwent arterial embolization. Two patients had evidence of hemoglobin drop, but were not found to have active bleeding at the 72 hour endoscopy. There were no adverse events or mortality in the treated patient.

Holster and colleagues tested the use of the hemospray in patients receiving antithrombotic therapy (aspirin, clopidogrel, warfarin) in a series of eight patients on therapy and eight patients without antithrombotic therapy [137]. The causes of bleed were diverse, consisting of one Dieulafoy’s lesion, nine ulcers (Forrest Ia or Ib), one duodenal diverticular bleed, one variceal bleed, two arterial bleeds, and two tumor related bleeds. In all cases a maximum of 20 gm of powder was used. Initial hemostasis was achieved in 63% of patients on therapy, and 100% of control patients. Patients with failed initial hemostasis
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Figure 139.5 Contact therapy diagram. Treatment with contact probes focuses on coaptive coagulation of the bleeding site. Considerable pressure is applied with the probe to tamponade the bleeding vessel. Multiple bursts of energy are then delivered to coagulate the lesion and seal the bleeding vessel. Care must be taken to avoid dislodging coagulated tissue, which can adhere to the catheter tip. Source: Johnston et al. 1987 [131]. Reproduced by permission of Elsevier.

Figure 139.4 Noncontact therapy diagram. Coagulation of tissue with noncontact methods, such as laser therapy or argon plasma coagulation. The area surrounding the bleeding site is treated with the aim of coagulating the submucosal vessel. Even when the vessel is not coagulated, the resulting circumferential edema results in enough tamponade to control bleeding.
included two with spurting vessel requiring hemoclips, and one with duodenal diverticulum who required angiographic embolization. In the control group, rebleeding was seen in two patients with ulcer related arterial bleeding, which subsequently required angiographic embolization. This study suggests that hemospray may not be the treatment of choice for spurting arterial bleeds.

Endoscopic suturing devices have been used for closure of iatrogenic upper GI defects from endoscopic mucosal resections, and it is commonly used in laparoscopic surgeries. An endoscopic suturing device was first described to be effective in stopping major gastric bleeding in a porcine model [142,143]. The authors used two different prototypes of an endoscopic suturing system called the Eagle Claw; Eagle Claw II (which required endoscopists to remove the scope, tie suture knots extracorporally), and Eagle Claw V (with intracorporal knotting device). Both systems encountered technical difficulties or malfunctions, and as expected the Eagle II required more time for suture completion (13.8 minutes Eagle Claw II vs. 3.5 minutes for Eagle Claw V). Apollo Endosurgery developed a similar endoscopic suturing system called the Overstitch (Apollo Endosurgery, Austin, TX, USA). The Overstitch is a single use device that delivers full thickness suturing with either a 2.0 or 3.0 polypropylene. The needle is curved, which allows the endoscopist to control the depth of suturing. There are no published data of the application of the Overstitch to gastrointestinal hemorrhage.

There have been reports on the usefulness of endoscopic ultrasound (EUS) in determining the cause for UGIB and delivering targeted sclerotherapy precisely to the site [144–147]. In a porcine model for peptic ulcer bleeding, Elmunzer et al. demonstrated that more accurate targeted vessel injection was possible with EUS [147]. A single use Doppler ultrasound probe (20-MHz DopUS system, Vascular Technology Inc., Nashua, NH, USA) has been proposed as a novel technique for increasing the diagnosis of active arterial bleeding by examining subsurface blood flow [148].

**Other nonulcer upper gastrointestinal bleeding**

**Esophagitis** (Figure 139.6a)

Esophagitis rarely causes acute GI hemorrhage. When it does, it is typically manifest as melena, coffee-ground emesis, or iron deficiency anemia from slow chronic blood loss. In immunocompetent individuals, the development of esophagitis is associated with gastroesophageal reflux disease, medication or...
chemical toxicity, eosinophilic esophagitis. In immunosuppressed patients, infectious causes of esophagitis such as candida, HSV, or cytomegalovirus (CMV) may be responsible. Generally, esophagitis does not require endoscopic hemostasis. Therapy involves treating the underlying infection, removal of offending agent, antireflux measures, and PPI therapy.

**Dieulafoy's lesion** (Figure 139.6b)
Dieulafoy's lesions, also known as caliber persistent artery, are bleeding lesions of large tortuous arterioles from the muscularis mucosa that erode through into the mucosa [61]. It was first described by Gallard in 1884 as “miliary aneurysms of the stomach” and further characterized in 1898 by George Dieulafoy’s [150,151]. Dieulafoy's lesions most commonly occur in the stomach, but may be seen in the small bowel, esophagus, and the colon. There are no surrounding ulcers or inflammation associated with the aberrant vessel. These defects are often only a few millimeters in diameter, but the amount and rate of hemorrhage generated by the large caliber vessel is often significant enough to cause hemodynamic instability and even death. The incidence has been reported to be between 0.3% and 6.7% [103]. Clinical presentation is typically acute without inciting factors or prior symptoms. Endoscopic management of Dieulafoy's lesions has decreased the necessity for surgery. Hemostasis can usually be successfully achieved with the combination of epinephrine and heater probe coagulation, or monotherapy with mechanical therapy using the hemoclip, or endoscopic band ligation [103].

**Mallory Weiss tear** (Figure 139.6c)
Mallory Weiss tears were first described in 1929. They are longitudinal mucosal lacerations of the distal esophagus and proximal stomach that extend intramurally and may cause severe bleeding. They are thought to result from increased abdominal pressure causing the upward movement of the proximal stomach [61]. Rarely, it may progress to spontaneous esophageal perforation also known as Boerhaave's syndrome. Forceful coughing, lifting, pregnancy, trauma, retching/vomiting can all be underlying causes of the increased abdominal pressure leading to a Mallory Weiss tear. Often, the patient will offer a history of nausea following by a period of nonbloody vomiting or retching. The incidence has been reported to be between 3% to 15% of all patients with UGIB [152–154]. Over 90% of patients will respond to conservative management with PPI treatment and avoidance of nonsteroidal antiinflammatory agents (NSAIDS) [155]. A small subset will have severe hemorrhage and require endoscopic hemostasis. Epinephrine monotherapy (amount injected from 8 mL to 18 mL), multipolar coagulation, mechanical therapy with band ligation or hemoclips, or a combination of epinephrine and another modality, can be effective in achieving hemostasis in actively bleeding Mallory Weiss lesions [110,153,156]. Endoscopic band ligation has been shown to be as effective as injection of dilute epinephrine [156,157]. Endoscopic band ligation and endoscopic hemoclips are equal in effectiveness and safety regardless of the presence of other comorbidities or hemodynamic shock [110].

**Gastric antral vascular ectasia (GAVE)**
(Figure 139.6d)
Gastric antral vascular ectasia, also known as watermelon stomach, has a distinct pattern of concentric linear mucosal hyperemia that converges at the pylorus. Gastric dysmotility causes the dilated capillaries, which often contain microthrombi, that is the diagnostic characteristic of GAVE [61]. There is mild inflammation; it can be distinguished from portal hypertensive gastropathy by the absence of mosaic mucosal pattern and its antral location. GAVE represents approximately 4% of nonvariceal causes of upper GI bleed and is most common in women (4 : 1 ratio) [61,158]. GAVE is associated with portal hypertension due to cirrhosis in 30% to 40% of cases [61,159]. Associations with autoimmune connective tissue disorders, chronic kidney disease, atrophic gastritis, and achlorhydria have been reported [61,160,161]. Up to 60% of patients with GAVE will have coexisting Raynaud's syndrome and sclerodactyly, or CREST syndrome [159].

The most common method for treatment of GAVE is thermal coagulation therapy with APC, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, or heater probe [158,159,162,163]. Treatment with APC is effective and safe in patients with portal hypertension [158,164]. Most patients will need multiple sessions of thermal coagulation before improvement and ideally obliteration of GAVE is achieved.

Endoscopic mucosal ablative therapy using the HALO [90] system is a novel method that has been reported in a prospective case series involving six patients [165]. The mean number of treatments was 1.7, ranging from 1 to 3 treatment sessions. Five of the six patients were no longer transfusion dependent after therapy. The Halo system is promising given the ease of applicability, the increased surface area covered per application by the rectangular applicator, and the decreased procedural time.

Wells and colleagues have proposed the use of endoscopic band ligation as an alternative to coagulation therapy [163]. Their retrospective study included a total of 22 patients, 13 treated with thermal coagulation, and nine treated with endoscopic band ligation. The endoscopic bands were deployed from the pylorus, working backwards into the antrum. The goal was to deploy as many bands as needed to cover the abnormal tissue. The patients who underwent band ligation had a much higher rate of bleeding cessation (67% vs. 23%; P = 0.04), improvement in hemoglobin, decrease in blood transfusions requirements, and decrease need for repeat endoscopy for retreatment (1.9 vs. 4.7; P = 0.05). Complete mucosal healing was seen after band ligation.

In patients refractory to endoscopic therapy, the administration of daily estrogen-progesterone supplementation, octreotide, thalidomide have been described in case reports to be effective in preventing further significant bleed, resolving transfusion dependency, and preventing antrectomy [162,166,167].
Angiodysplasias, arterial venous malformation (AVM)

The term angiodysplasia has been used synonymously with vascular ectasias and AVMs. They present either as chronic occult bleeding or an acute GI hemorrhage. Although from a pure endoscopy therapeutic standpoint, differentiating them may not be as helpful. Histologically these lesions have different characteristics. Angiodysplasias are aberrant dilated vessels located mainly in the submucosa and is acquired with aging [61]. They have been associated with end stage kidney disease, radiation injury, both primary and secondary von Willebrand deficiency, and aortic valve stenosis [168–173]. They rarely cause significant bleeding, and are usually in the lower GI tract [61]. They can occur in the small intestines, esophagus, and stomach too. AVMs have an abnormal connection between arterial and venous beds, bypassing the capillary beds, and resulting in a high pressure flow. The high pressure flow through the AVM can potentially cause a life threatening hemorrhage if uncontrolled. Arterial venous malformations also differ from angiodysplasias in that they are believed to be genetic defects that develop during embryologic and fetal life [61]. AVMs can present in any age group, but is most common in the elderly population. Associated disease processes include genetic vascular collagen syndromes such as Ehlers-Danlos syndrome type IV, and hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).

Coagulation therapy with APC, Nd:YAG laser, or heater probe, with or without epinephrine injection, achieves hemostasis in most patients with either angiodysplasia or AVMs. The heater probe carries increased risk of perforation if used distal to duodenum because of the depth of energy penetration in the relatively thin walled intestine. If endoscopic hemostasis fails, angiographic embolization by interventional radiology should be attempted before surgery in a hemodynamically stable patient.

Gastrointestinal tumors (Figure 139.6e)

Both benign and malignant tumors of the esophagus, stomach, and duodenum can cause UGIB. They often present as chronic intermittent melena or occult bleeding with iron deficiency anemia. A subset of patients will present with hematemesis and severe GI hemorrhage. In a large retrospective study of 935 patients presenting with UGIB, 5% of the patients were found to have a tumor; a large majority of these tumors were late stage malignancies [174]. Acute upper GI hemorrhage was the initial presenting symptom in 52% of the patients found to have tumors. This presentation is an ominous sign and conveys a 30-day mortality rate of 10%, and a 1-year mortality rate of 89%. Endoscopic hemostasis can be achieved with laser coagulation, epinephrine injections, heater probe coagulation, or injection of a sclerosant such as sodium tetradecyl sulfate (STS), or ethanol [175]. As ethanol induces tumor necrosis, it has been demonstrated to be effective in the palliation of severe dysphagia due to gastroesophageal tumor obstruction [176]. Rebleeding rates are high, ranging from 33% to 80% in patients in whom initial hemostasis was achieved [174,175]. Therefore, endoscopic hemostasis should be viewed as a bridge towards a more definitive surgical treatment in suitable patients.

Second look endoscopy

A routine second look endoscopy, defined as a repeat endoscopy performed after 24 hours from initial endoscopy, is not recommended [6,25,177]. The majority of supporting evidence for the performance of a second look endoscopy is based on multiple trials carried out prior to current practice that includes avoidance of single epinephrine injection therapy for high-risk stigmata bleeds, and the use of high dose PPI therapy after endoscopic hemostasis. A recent metaanalysis with the primary outcome of rebleeding rates and secondary outcomes of mortality and surgical intervention, found that rebleeding rates with a second endoscopy were only statistically decreased in patients that did not receive high dose PPI therapy [178]. When the data was further analyzed by excluding two studies involving patients with very high-risk for rebleeding (active bleeding with coagulopathy), there was no significant benefit to performing a second look endoscopy (odds ratio [OR], 0.65).

There are select circumstances in which a second endoscopy may be indicated and helpful. This subset of patients includes those with high-risk stigmata at time of initial endoscopy, in which high dose PPI therapy is not available, or implemented [178–180].

The benefit of second look endoscopy with intervention succeeds in its primary goal of decreasing the rate of rebleeding. In a metaanalysis involving four randomized controlled trials, with patients treated for bleeding ulcers between 1990 to 2000, the pooled data showed an absolute risk reduction of 6.2%, and significant reduction of rebleeding risk with OR 0.64, with NNT of 16 [181]. Tsoi and colleagues studied the efficacy of second look endoscopy with therapy, either thermal coagulation versus epinephrine or fibrin glue injection [182]. The analysis included a total of five randomized control trials involving 998 patients; 505 patients underwent single endoscopy, 119 underwent thermal coagulation with second endoscopy, and 374 received injection therapy with the second endoscopy. There was a significant decline in recurrent bleeding only in the group that received thermal coagulation when compared to the single endoscopy group (4.2% vs. 15.7%). A randomized control trial based on a single center experience reported benefit in reducing the rate of rebleeding and subsequent need for surgery in patients with high-risk stigmata, who received second endoscopy with appropriate therapy within 16–24 hours after initial successful hemostasis [179]. Based on these initial findings, the authors identified patients who were at risk for developing recurrent bleeding after the second endoscopy [183]. Associated risk factors include large ulcer size >1 cm, persistent high-risk stigmata at second endoscopy, and an American Society of Anesthesiologists (ASA) grade of greater than II [183]. Despite demonstrating a benefit in reducing recurrent bleeding rates...
with a second endoscopy, none of the studies above proved to significantly decrease overall mortality rates, alter hospitalization duration, need for blood transfusions, or reduce the need for surgery [179–181,183].

**Post endoscopic management**

The main goal after hemostasis should be prevention of recurrent bleed. After successful hemostasis of severe UGIB, gastric acid secretion should be controlled. Patients should remain on intravenous PPI for 72 hours, followed by daily PPI therapy for at least 8 weeks in cases of peptic ulcer disease [184]. Other nonulcer related etiology of upper GI bleed would benefit from PPI therapy, due to the decrease in intraluminal gastric acid and subsequent stabilization of fibrin clot formation [185]. Avoidance and confirmed treatment of other risk factors such as *H. pylori* infection, NSAIDS, other gastrotoxic medications, and physiological stress, should be a priority. In patients with history of nonvariceal upper GI bleed who require chronic anticoagulation or NSAID use, long term PPI therapy may be warranted [186,187].

Patients with a history of acute coronary syndrome, unstable angina, atrial fibrillation, are often on antithrombotic therapy to prevent the increased risk of stroke, repeat myocardial infarction, and mortality. These anticoagulated patients are at increased risk of severe GI bleed, especially if they are older and have other comorbidities. A retrospective study from Danish national registries, found that the risk with a number needed to harm (NNH) of 12.5 for triple therapy with Aspirin, clopidogrel, and Vitamin K antagonist, 15.2 for clopidogrel plus vitamin K antagonist, 45.4 for aspirin plus vitamin K antagonist, 81.2 for aspirin plus clopidogrel. The hospitalizations for bleeds included cerebral, gastrointestinal, urogenital, femoral pseudoaneurysms; the highest incidence of bleeds was of gastrointestinal sources [188]. The new oral anticoagulants, direct thrombin inhibitors (Dabigatran) and direct factor Xa inhibitors (rivaroxaban), are given at fixed doses without the need for monitoring of coagulation factors. They are convenient for both the patient and cardiologists and increase patient compliance. However, these new anticoagulants in combination with clopidogrel and/or aspirin, are associated with a high-risk of major bleeding event [189]. Most cardiologists prescribe daily PPI therapy to patients with antithrombotic therapy. The timing of reinitiation of antithrombotic therapy after a significant upper GI bleed is dependent on the clinical scenario and should include close cooperation between both the cardiologist and gastroenterologist. At this time there are no interdisciplinary studies published to clarify best practice guidelines in the management of patients on anticoagulation therapy, who present with UGIB.

**Summary**

In patients presenting with acute UGIB, the first priority is the assessment of the hemodynamic states of the patient and under-taking measures to achieve stability in those with impairment states. Endoscopy remains the gold standard for diagnosis of acute UGI bleeding. Endoscopy aids the clinician in appropriately triaging the patient, provides a means of direct hemostatic therapy, and therefore decreases the need for surgery. Intravenous proton pump therapy in the setting of confirmed or suspected peptic ulcer disease should be administered prior to endoscopy. In select patients, outpatient triage may be appropriate. In all other patients, endoscopy should be performed within 24 hours from presentation. In the management of nonvariceal acute UGIB, epinephrine monotherapy is strongly discouraged. When epinephrine is used, it should be used in conjunction with either cautery, or endoclips. Monotherapy with mechanical therapy with hemoclips, or thermal therapy with heater probe and multipolar electrocautery, may be used for hemostasis. There is no role for routine second look endoscopy. In cases of recurrent bleeding after initial hemostasis, repeat endoscopy is indicated. In cases of failed endoscopic hemostasis, further management by angiographic embolization or emergent surgery, may be appropriate.

References are available at [www.yamadagastro.com/textbook](http://www.yamadagastro.com/textbook)

**Further reading**


Endoscopic resection of gastrointestinal polyps and tumors has become an important alternative to traditional surgical therapy. Endoscopic lesion removal often has multiple advantages over open and laparoscopic surgery: (1) endoscopic lesion resection preserves the affected organ and is less traumatic and usually involves less risk than surgery; (2) endoscopic resection is usually done as an outpatient procedure under sedation, obviating the need for general anesthesia and hospital admission with significant cost saving; and (3) endoscopic procedures provide faster patient recovery and early return to work and normal physical activity compared with traditional open and laparoscopic surgery.

This chapter reviews currently available methods and tools for endoscopic therapy of polyps and tumors, complications of endoscopic therapy, and endoscopic treatment of specific lesions in the esophagus, stomach, duodenum, and colon. Endoscopic therapy for tumors in the pancreas and biliary tree is covered in a separate chapter.

**Methods of endoscopic therapy**

**Polypectomy**

Polypectomy is the most commonly used method of endoscopic removal of lesions that are confined to the mucosal layer of the gastrointestinal tract. Other endoscopic techniques (endoscopic mucosal resection, endoscopic submucosal dissection) should be used for removal of lesions with a broad base or those originating from or expanding into the submucosal layer. Tumors extending into the muscularis propria or originating from it are usually not amenable to curative endoscopic resection, although recent advances in submucosal endoscopy have allowed endoscopic resection of small lesions originating from the muscularis propria [1].

Polypectomy can be done without use of electrical current (“cold” snare/forceps) or with electrical current (“hot” forceps/diathermic snare). Effective polypectomy technique is essential to prevent interval cancers.

**Cold snare/forceps polypectomy**

Small or diminutive (≤5 mm) polyps can be removed endoscopically without electrocautery using cold biopsy forceps [2]. Minor immediate bleeding is common, but it usually does not require any treatment and stops spontaneously within 1–2 min of observation. Delayed bleeding is uncommon in patients who are not anticoagulated and who do not have a bleeding tendency. However, despite apparently complete polypectomy, residual polypoid tissue was still detected on subsequent endoscopy in 29% of patients treated with cold biopsy [2]. Recent data
suggest that biopsy forceps is inadequate even for resection of diminutive polyps [3].

Cold snare polypectomy (without electrocautery) is usually possible for polyps 5 mm or less in size [4]. The polypectomy snare is placed around the base of a polyp, which is then guillotined by mechanical closure of the snare. Minor immediate bleeding may occur, but usually stops spontaneously without any therapy within 1–2 min of observation. The major advantage of both cold forceps and cold snare polypectomy is a reduction in the risk of delayed bleeding seen more commonly when electrocautery is used (delayed hemorrhage is usually caused by sloughing off of coagulated tissue or extension of coagulation-induced necrosis into larger-diameter submucosal vessels) [4]. Although cold snare polypectomy is usually not recommended for polyps larger than 7 mm in size, recent data suggested efficacy and safety of cold snare polypectomy for management of polyps up to 10 mm in size [5].

Hot forceps polypectomy

Polyps 1–3 mm in size can also be removed with hot biopsy forceps [6]. Proper use of the hot biopsy forceps involves grasping the top of the polyp with the forceps and stretching or tenting the polyp to produce a stalk and then applying electrocautery (Figure 140.1). Application of electrical current causes endoscopically visible whitening (coagulation) of the polypoid tissue starting at the tip of the forceps. After destruction of the polyp the forceps are withdrawn and the part of the polyp preserved in the forceps is sent for histological assessment. Unfortunately, the extent of tissue coagulation by hot forceps is difficult to control and it may cause deep ulcers with subsequent delayed bleeding and even perforation [7]. The right colon is particularly susceptible to transmural injury and perforation [8]. Accordingly, the use of hot biopsies in the right colon is discouraged. The American Society for Gastrointestinal Endoscopy (ASGE) recommends that hot forceps should be used only for diminutive polyps ≤5 mm. Even so, the use of hot forceps is generally discouraged given safer alternative methods and the use of minisnares is advocated instead of hot forceps for diminutive colorectal polyps, especially in the right colon.

**Polypectomy with diathermic snare**

Diathermic snares, comprising a wire loop contained inside an electrically isolating catheter, are usually used for polyps larger than 7 mm in size [6]. A variety of sizes (jumbo, standard, mini) and shapes (oval, round, crescent) of diathermic monopolar snares are available for endoscopic polypectomy. The diathermic snare is placed around the base or stalk of a polyp with subsequent application of electrocautery followed by mechanical transection of the polypoid tissue. Electrocautery heats the tissues to 45–100°C, which results in tissue coagulation and endoscopically visible coagulation necrosis (tissue whitening), reflecting denaturation of proteins and cell death. Heat generated by the snare also causes desiccation and shrinkage of coagulated tissues with blood vessel constriction and thrombosis. This prevents postpolypectomy hemorrhage and facilitates subsequent mechanical tissue transection.

Three modes of electrosurgical current are available: pure cut, pure coagulation, and a mixture (blend) [9]. In pure-cut mode, the electrical current waveform continuously oscillates between peak positive and negative voltage producing a local heating effect [9]. In pure-coagulation mode, the current wave is turned on in powerful bursts for short intervals of time [9]. For the blend mode, the periods of time when the duty cycle is off are attenuated compared with the cutting mode [9]. At the same power setting, the peak power in coagulation mode is five times higher than in blend mode and 10 times higher than in pure-cut mode, causing a wide coagulation zone [9]. Some cautery units (e.g., ERBE GmbH, Tuebingen Germany) adjust the delivered

![Figure 140.1](https://example.com/figure140.1.png)

*Figure 140.1* Use of hot biopsy forceps for removal of a diminutive polyp. (a) Diminutive polyp. (b) Correct use of hot biopsy forceps: the polyp is grasped with the forceps and pulled away from the bowel wall while cautery is applied. Notice how proper positioning of the forceps prevents coagulation injury to the colonic wall. (c) Wrong use of hot biopsy forceps: grasping too much tissue (i.e., too close to the colonic wall) or failure to “tent” the polyp by pulling it away from the wall may allow coagulation damage to the normal colonic wall.
electrocautery energy based on tissue resistance during the resection process (less energy is needed for less tissue), which may potentially reduce the risk of thermal injury.

Monopolar electrocautery should be used with caution in patients with implanted electrical devices (pacemakers, defibrillators) due to the risk of inactivation or electrical damage to these devices by the electrical current traveling from the monopolar snare to a grounding pad placed on the patient’s skin. Short (<5s) bursts of electrocautery is recommended in these instances.

Special diathermic snares with barbs (e.g., Olympus Optical Ltd, Tokyo, Japan), spikes, or needle at the tip of the snare (e.g., Cook Medical Inc., Winston-Salem, NC) are designed to prevent snare slippage during polypectomy and are particularly useful for removal of large flat lesions.

When a pedunculated polyp is removed using a diathermic snare, most endoscopists recommend leaving a short portion (approximately half or one-third) of the stalk not involved with polypoid tissue. This remnant of the stalk, in case of postprocedure bleeding, can be injected, cauterized, or enable mechanical hemostasis with application of clips or detachable loops.

Most polypectomy complications are electrocautery related. Electrocautery is not needed in the resection of many small polyps. Most sessile polyps <8 mm in size can be effectively treated with cold snaring. A hot snare should be used for resection of pedunculated polyps that are >5 mm in size because their stalk may enclose large blood vessels. Electrocautery coagulates blood vessels and helps avoid bleeding complications.

Endoscopic mucosal resection
Endoscopic mucosal resection (EMR) refers to removal of sessile or flat neoplasms confined to the mucosa or penetrating but not extending beyond the submucosa [11]. There are multiple techniques of EMR: injection-assisted EMR, suction-assisted EMR, and ligation-assisted EMR.

Injection-assisted endoscopic mucosal resection
Injection-assisted EMR (also sometimes called saline-assisted polypectomy) starts with injection of a solution into the submucosal space under the lesion to create a cushion. This cushion lifts the lesion, facilitating its removal and preventing damage to the deep layers of the gastrointestinal tract wall during EMR. Nonlifting of the tumor after submucosal injection is the best predictor of deep invasion and has an 83% positive predictive value for invasive carcinoma. Prior failed attempts at polyp resection with snaring produce a false nonlifting sign due to submucosal fibrosis. Lesions that manifest nonlifting sign should be biopsied and endoscopic resection should not be attempted until carcinoma is excluded [12].

Various endoscopic needles are used for injection, for example 25G Carr–Locke injection needle (US Endoscopy), 23G Interject needle (Boston Scientific, Natick, MA), and VIN23 (Cook Medical Inc., Winston-Salem, NC). Various solutions can be used for injection including normal saline, hypertonic solution of sodium chloride, glycerol, dextrose, albumin at various concentrations, hydroxypropylmethylcellulose, fibrinogen mixture, and hyaluronic acid [13,14].

The ideal agent for submucosal cushion creation should be cheap, readily available, easy to inject, and should provide a long-lasting submucosal cushion without damaging the tissues at the site of injection. A cushion created with normal saline, even with addition of epinephrine (adrenaline), lasts only a short time and is not optimal for removal of large lesions. Several studies have shown that hyaluronic acid, hydroxypropylmethylcellulose, and glycerol provide a long-lasting submucosal cushion [15,16]. Unfortunately, these agents are expensive, not readily available in most endoscopy units, and difficult to store and inject [13,17]. Other studies have demonstrated tissue damage and local inflammatory reactions at the site of injections of hydroxypropylmethylcellulose and hypertonic solutions of sodium chloride (3.75%) and dextrose (20%) [17].

The volume of injected fluid needed varies with the size of the lesion. Usually between 5 and 50 mL of injected solution is required to create an adequate submucosal mound. After creation of the submucosal cushion, two different techniques can be used.

1. Inject-and-cut technique (Figure 140.2) is used with a single-channel endoscope: the lesion is lifted and the endoscopic diathermic snare is then placed around the lesion and electrical current is used to cut it off [18].
2. Inject-lift-and-cut technique (Figure 140.3) requires a double-channel endoscope: submucosal fluid injection is performed and then the lesion grasped and lifted with endoscopic forceps through one channel of the endoscope [19]. Then a diathermic snare is passed through the second channel and placed around the lesion to cut it off with electrical current.

Suction-assisted endoscopic mucosal resection
This procedure requires several steps [20]:

1. A specially designed crescent-shaped snare is placed around the margin of the cap (Figure 140.4). The open snare is positioned at the tip of the cap. The lesion and surrounding normal mucosa are suctioned into the cap.
2. The snare is tightened around the lesion.
3. The suction is stopped to release the lesion from the cap (but still captured by the snare).
4. The snare is pulled up several times to ensure that only the lesion, not the entire wall, is moving; this prevents full-thickness resection of the gastrointestinal wall.
5. The EMR is completed with the snare, using electrical current.
6. The resected lesion can then be aspirated into the cap to facilitate its removal for pathological examination.

Ligation-assisted endoscopic mucosal resection
A variceal ligation band can be placed around the mucosal lesion using commercially available variceal band ligators
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(Chapter 140) [21]. The lesion is then removed with electrical current using a diathermic snare above or below the band. The Duette Multi-Band Mucosectomy device (Cook Medical Inc., Winston Salem, NC) is a combination of a specially designed six-band ligator with a large channel. This device allows banding and passage of a diathermic snare for subsequent resection of the banded lesion without the need to remove the banding device from the endoscope [21].

**Endoscopic submucosal dissection**

Endoscopic submucosal dissection (ESD) has been a significant advance in therapeutic endoscopy. It is an accepted therapy for early gastrointestinal neoplasia, especially in East Asia where the incidence of early gastric cancer is high, accounting for 50% of cases worldwide [22–26]. ESD of early gastric lesions is becoming widely used because it is less invasive and is associated with shorter recovery periods and lower procedural costs in comparison to surgical resection [27]. Although EMR is widely utilized for treatment of early gastrointestinal neoplasia as well, a major advantage of ESD over EMR is that it allows en bloc resection and thus decreases the risk of neoplastic recurrence [28]. ESD is usually performed in several steps [29]:

1. The margins of the lesion are marked by electrocautery (to facilitate its visualization when the submucosal injection changes the local anatomy).
2. A submucosal injection is made to lift the lesion.
3. A circumferential incision is made around the lesion to divide it from surrounding normal tissues.
4. The lesion is separated from underlying deep layers of the gastrointestinal tract wall by submucosal dissection, removed en bloc, and sent for pathological examination.

Endoscopic mucosal resection and ESD have dramatically expanded the spectrum of potentially endoscopically removable lesions. Large sessile, very flat, and even depressed lesions can now be removed endoscopically. Despite the significant benefits of ESD, it is infrequently performed in the West. This is the
result of a multitude of reasons, including procedural complexity, lengthy procedural times, low procedural volume, and likely poor reimbursement [30,31]. Furthermore, ESD is associated with higher complication rates compared to EMR [32–35].

**Submucosal endoscopy**

If the lumen was historically the first, and the peritoneal cavity the second (with the advent of natural orifice transluminal surgery or NOTES [36,37]), then the intramural space has come to represent the “third space” for use of endoscopy [38]. Unlike the others, this space remains virtual and has to be created by dissecting and expanding the tissue layer between the mucosa and the muscularis propria, allowing the endoscope to gain access. Submucosal tunneling in this fashion was initially described by Sumiyama and colleagues [39] and was adopted for esophageal myotomy by Pasricha et al. [40] in 2007, culminating in its application in patients with achalasia by Inoue [41], in what has now become known as the POEM (per oral endoscopic myotomy) procedure. More than 2000 clinical POEM cases have been performed in centers across the world. Initial clinical data from Asia, Europe, and the USA have demonstrated the effectiveness and safety of this procedure when performed by experienced endoscopists [41–47].

Figure 140.3 Endoscopic mucosal resection: inject-lift-and-cut technique. (a) Flat mucosal lesion (indicated by blue color). (b) Submucosal injection of fluid has lifted the mucosal lesion, separating it from the deep muscularis layer. (c) The lesion is grasped and lifted with a biopsy forceps, and a snare is advanced through the second channel of a dual-channel endoscope and placed around the lesion. (d) The lesion is resected and retrieved for pathological examination.

Figure 140.4 Suction-assisted endoscopic mucosal resection. (a) Submucosal injection of fluid to create a cushion under the mucosal lesion (indicated by blue color). (b) The mucosal lesion is aspirated into a cap mounted on the tip of the endoscope and grasped with a snare (arrows). (c) Suction is stopped so that the lesion is released from the cap. The lesion will be removed by application of electrical current and further tightening of the snare.
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Intestinal bleeding. Furthermore, indications have expanded to include closure of iatrogenic perforations and anastomotic leaks, marking of tumors prior to surgery or radiotherapy, and anchoring stents and feedings tubes [50–54]. For the majority of these indications, it is critical to know how long the clip will remain in situ (clip retention time) to perform its intended function. Prior studies have demonstrated long retention rates of the Resolution clip (Boston Scientific, Natick, MA) compared to the Triclip (Cook Medical Inc., Winston-Salem, NC), HX-5L clip (Olympus America, Inc., Center Valley, PA), and QuickClip (Olympus America) in gastric ulcer and bleeding animal models [55–57]. Endoscopic clips have continued to evolve and the Triclip and HX-5L clips are no longer available. Currently, commercially available clips include the Instinct clip with 16-mm jaw width (Cook Medical Inc.), Resolution clip with 11-mm jaw width (Boston Scientific), and QuickClip2 with 11-mm jaw width (Olympus) [58]. A recent study compared mechanical strength, rotational capabilities, and endoscope retroflexion capabilities with the currently available endoscopic clips [59].

All three clips have the ability to rotate [60]. The Instinct and Resolution clips are magnetic resonance imaging compatible and can be reopened several times prior to final deployment [61,62].

In patients with endoscopically resected polyps and lesions of the gastrointestinal tract, endoscopic clips have been highly successful when used for prevention and control of complications [63–65]. Cipoletta and colleagues reported on prophylactic clipping of stalks of large pedunculated polyps, preventing bleeding after polypectomy [66,67]. Liaquat et al. evaluated the effect of prophylactic clip closure of polypectomy sites after resection of 524 large (>2 cm) sessile and flat colorectal lesions and showed that there was significantly increased risk of delayed postpolypectomy bleeding in the nonclipped group (adjusted odds ratio [OR] 1.3; 95% confidence interval [CI] 1.1–1.7). Other authors have reported successful use of endoscopic clips for closure of perforations after endoscopic resection [68].

Recently, a new clip, the over-the-scope clip (OTSC) (Ovesco Endoscopy AG, Tubingen, Germany), has become commercially available. The OTSC provides more durable closure than standard clips because of its wider mouth and ability to grasp larger amounts of tissue [69]. In addition, full-thickness closure is achievable due to greater compressive force [70]. However, outcomes of OTSC closure of gastrointestinal defects are only available from case reports and small case series [47,71].

Detachable loops

Endoscopic detachable loops are also very useful during endoscopic removal of polyps and lesions of the gastrointestinal tract. The loop can be applied to the base of the lesion or stalk of a polyp to prevent bleeding (Figure 140.6) [72]. In a large randomized controlled trial of 488 consecutive patients with pedunculated colorectal polyps, application of a detachable loop prior to polypectomy helped to decrease the risk of bleeding by four times (from 7.9% to 1.8%) [73].
Argon plasma coagulation

Argon plasma coagulation (APC) is a method for noncontact thermal tissue coagulation. APC is based on the conduction of high-frequency electric current to the treated tissue through the argon gas emitted from the tip of the APC probe. The depth of injury is determined by power settings and the duration of application. Inadvertent transmural injury with application of APC has been reported [74].

To decrease the risk of transmural injury in the cecum and right colon, power settings of 40–45 W and short bursts are usually used. In the rectum and stomach, settings of 60–75 W and more prolonged applications are appropriate for benign tumor ablation [74]. For palliation of cancers, power settings of 90–100 W and repeated applications are usually necessary.

APC is widely used to treat actively bleeding diffuse mucosal lesions (arteriovenous malformations, radiation proctitis), eradicate gastrointestinal tumors and Barrett esophagus, restore stent patency in cases of tumor in-growth or overgrowth, and treat residual flat neoplasia after snare resection of the main lesion [75–77].

APC is also used as an adjunct therapy in management of large sessile and flat colon polyps (Figure 140.7a–c). The use of APC to ablate the edges of a polypectomy site and any visible residual adenomatous tissue has been shown in a randomized controlled trial to decrease the incidence of polyp recurrence [78].

Endoscopic tissue tattooing

Tattooing refers to the local labeling of a lesion or site where a lesion was endoscopically resected by intramural injection of a pigment for future identification during subsequent surgery or repeat endoscopy. India ink and suspension of pure carbon particles (Spot, GI Supply, Camp Hill, PA) are the most commonly used solutions, producing a blue-black submucosal stain visible from serosal and lumenal surfaces [79,80].

The tattoo mark is made by direct injection of 1–2 mL of India ink or Spot into each site through a sclerotherapy needle inserted tangentially to make a submucosal bleb. Injections into three or four quadrants are usually sufficient and ensure subsequent intraoperative or endoscopic identification of the lesion. Many endoscopists prefer Spot over India ink for marking of colonic polyps because transmural (intraperitoneal) injection of India ink can cause significant patient discomfort or pain and can result in colonic abscess and focal peritonitis [79,81]. This can be minimized by the creation of a submucosal bleb with injection of normal saline followed by injection of a tattooing agent (through the same needle without its withdrawal from the bleb) into this submucosal bleb [82]. This ensures injection of the tattooing agent into the correct layer of the gastrointestinal wall, decreases the amount of agent needed, and prevents transmural puncture with subsequent injection of the tattooing agent into the peritoneal cavity.

The advent of a prepackaged sterile carbon particle suspension (Spot) has greatly enhanced the accessibility and ease of

Figure 140.6 Use of a detachable loop for endoscopic resection of a pedunculated polyp. (a) A detachable loop is placed around the stalk of the polyp, tightened, and then released from its delivery device. (b) A cautery snare is placed above the loop (closer to the head of the polyp) to transect the stalk of the polyp.

Figure 140.7 Use of argon plasma coagulation (APC) as adjunct therapy during piecemeal polypectomy of large sessile colon polyps. (a) A 50-mm Paris-IIa granular polyp is seen in the ascending colon. (b) Polyp was lifted with saline/methylene blue and was then successfully resected in piecemeal fashion. (c) APC was then applied to the resection margin to decrease the incidence of residual/recurrent neoplasia during follow-up.
use of endoscopic tattooing. Concomitantly, the indications for colonic tattooing expanded beyond marking of carcinomas to also include endoscopic localization of difficult-to-detect polyps, polypectomy sites, or dysplastic areas for future colonoscopic surveillance or therapy [80].

Complications of endoscopic therapy

The most serious immediate complications of endoscopic lesion removal are perforation and bleeding. Perforations occur in 0.3% of patients after polypectomy [83]. Small perforations can be closed with application of endoscopic clips and treated conservatively, but larger perforations require immediate surgery [84]. The recently available over-the-scope clip (OTSC) has increased the ability to close larger colonic perforations [85]. However, access to right colonic defects is technically challenging due to the size and the stiffness of the OTSC cap.

The reported frequency of postpolypectomy bleeding ranges from 0.2% to 1.0% but occurs in about 10% of patient after piecemeal removal of large sessile or flat polyps [86,87]. In one large prospective study involving 5152 patients with 9336 polyps immediate after postpolypectomy, bleeding was documented after removal of 262 polyps (2.8%) in 215 patients [88]. This study revealed nine factors associated with immediate post-polypectomy bleeding: age older than 65 years, comorbid cardiovascular or chronic renal disease, anticoagulant use, polyp size greater than 1 cm, gross morphology of polyps such as pedunculated polyp or laterally spreading tumor, poorer bowel preparation, cutting mode of electrosurgical current, and inadvertent cutting of a polyp before current application [88]. Most cases of active bleeding during endoscopic procedures can be successfully controlled by injection, local application of coagulation (bipolar, thermal, or APC), or mechanical hemostasis (band ligation, endoscopic clips, and detachable loops).

Delayed postpolypectomy bleeding can occur up to 3 weeks after the procedure. Approximately 70% of delayed hemorrhage cases stop bleeding spontaneously and can be managed conservatively. Colonoscopy should be performed urgently in patients with active hemorrhage. Since the location(s) of polypectomy site(s) are known a priori, colonoscopy may be performed without bowel purging. Bleeding is best treated with epinephrine injection and clip placement, because additional thermal therapy can potentially extend tissue injury.

The most common delayed complications of endoscopic therapy for gastrointestinal tumors are formation of strictures, delayed bleeding, and postpolypectomy syndrome [89,90]. In general, the risk of stricture formation is higher when the lesion occupies more than half of the lumen circumference [91,92].

Aspirin and other nonsteroidal antiinflammatory drugs in standard doses do not increase the risk of significant immediate or delayed bleeding after colonoscopy with biopsy and polypectomy [93]. However, the risk of bleeding is definitely higher in patients who have bleeding disorders, low platelet count, or who are therapeutically anticoagulated [93,94]. Friedland and Soetikno have demonstrated that in therapeutically anticoagulated patients with polyps less than 10 mm in diameter, prophylactic application of endoscopic clips after removal of the polyp can prevent postpolypectomy bleeding [11,95,96].

Electrocoagulation injury to the bowel wall during polypectomy causes transmural burn in approximately 0.5%–3.7% of patients, which may result in the postpolypectomy (postcoagulation) syndrome [97]. Patients with this syndrome usually present 1–5 days after colonoscopy with symptoms of localized abdominal pain, fever, peritoneal signs, and leukocytosis [98]. Abdominal radiography and computed tomography are not suggestive of perforation (no free air or extravasation of contrast into a free peritoneal cavity) and conservative therapy (bowel rest, antibiotics) is usually sufficient for resolution of the symptoms [98].

Esophageal lesions

Lesions in the esophagus that are amenable to endoscopic treatment include Barrett esophagus and squamous cell neoplasias. The choice of therapy depends on the morphology of the lesion, depth of invasion, and the therapeutic intent.

Ablation for high-grade dysplasia

Endoscopic treatment is considered the primary treatment for Barrett esophagus with high-grade dysplasia (HGD) [99–101] (see Chapter 52). If HGD is detected within flat mucosa it can be treated with ablative methods. Of these radiofrequency ablation (RFA) has shown to be the most effective and safe option. In a randomized sham-controlled study, RFA eradicated HGD in 81% of patients [102]. After HGD resection, metachronous neoplasia has been reported in 11%–30% of patients [103,104]. Therefore, the remaining Barrett segment should also be completely removed. Complete Barrett eradication can be achieved by RFA in 70%–80% of patients [105]. After eradication, dysplasia may recur in 10%–15% of patients within 3 years, and recurrent intestinal metaplasia is observed at an annual rate of 5% [105,106]. RFA is safe and has a low stricture rate of 1%–8%. However, transient chest discomfort or pain may frequently occur following the procedure [102,107]. Other ablative methods including photodynamic therapy (PDT) and APC have been less effective and associated with risk of submucosal neoplasia [108,109]. Furthermore, PDT is associated with a high stricture rate of 35% [108].

Endoscopic resection for high-grade dysplasia

Nodular lesions should be removed by EMR [99–101] (Figure 140.8a,b). The large EMR resection specimen allows for a more accurate diagnosis of prevalent cancer than a smaller biopsy specimen [91,110]. If cancer is present, EMR can further provide information on depth of tumor infiltration to decide if subsequent surgery is needed.
Squamous cell carcinomas with invasion into the upper third (m1) of the mucosa are considered to have no risk of nodal metastasis and invasion into the middle third mucosal layer (m2) confers a minimal risk of node metastasis (Figure 140.10). In contrast, mucosal esophageal adenocarcinomas have a minimal risk of lymph node metastasis (<1% for m3 cancers). While nodal involvement is low for sm1 cancers (<10%), the risk increases exponentially with further submucosal invasion. More than 50% of tumors with invasion into the deep submucosa (sm3) have positive lymph nodes [113–115] (Figure 140.9).

Following focal EMR, the remaining Barrett segment should be eradicated with ablative therapies (e.g., RFA or cryotherapy) [99–101]. Prior to the availability of RFA, stepwise EMR of the entire Barrett segment proved to be effective, at the expense of a high stricture rate of 50% and need for repeated dilatations [111]. To minimize the risk of stricture formation, EMR should be limited to an area of less than half of the circumference.

HGD in squamous cell epithelium may be approached similarly to HGD in Barrett esophagus. RFA can be applied for flat lesions and EMR for nodular lesions. However, studies investigating RFA in this setting are limited [112].

**Endoscopic resection for early esophageal cancer**

Curative endoscopic resection of early esophageal cancer is possible if there is no risk of lymph node metastasis. The risk of lymph node metastasis depends primarily on the depth of tumor invasion (Figure 140.9). Unfortunately, the majority of early esophageal cancers do not show these characteristics.
studies suggested that cryotherapy provides safe and efficient tumor debulking either as a palliative measure or as a bridge to surgery [119,120]. Stents can be easily deployed and restore luminal patency to allow commencement of a soft diet [119]. Some patients will require endoscopic reintervention with possible stent removal because of severe chest pain, reflux symptoms, or stent migration.

Gastric lesions

The most common gastric lesions found during endoscopy are gastric polyps (fundic gland, hyperplastic, and adenomatous), malignant neoplasms, and submucosal tumors (gastrointestinal stromal cell tumor, lipomas). Prevalences of the various gastric polyps differ between countries, perhaps reflecting frequency of proton pump inhibitor (PPI) use and prevalence of Helicobacter pylori [121]. Fundic gland polyps are typically small, multiple, have negligible malignant potential, and do not need to be removed [122,123].

Hyperplastic and adenomatous polyps

Hyperplastic polyps are believed to be associated with 

Endoscopic therapy can be used to restore esophageal passage of obstructing tumors, or to close malignant fistulas. Ablative methods include yttrium–aluminum–garnet (YAG) laser, APC, PDT, bipolar thermocoagulation, and cryotherapy. Repeated treatments are typically required to treat tumor regrowth. Some studies suggested that cryotherapy provides safe and efficient tumor debulking either as a palliative measure or as a bridge to surgery [119,120].

Stents can be easily deployed and restore luminal patency to allow commencement of a soft diet [119]. Some patients will require endoscopic reintervention with possible stent removal because of severe chest pain, reflux symptoms, or stent migration.

Critical to carefully prepare the EMR (or ESD) specimen before fixation to allow adequate pathological examination (e.g., pinned on a cork board).

Selected patients with relatively low risk of node metastasis (e.g., sm1 esophageal adenocarcinoma) and a higher surgical risk may be also considered for endoscopic resection after carefully weighing the risk of node invasion, as well as the risks and potential benefits of surgery [101,117].

Endoscopic resection may be performed either using EMR or ESD. ESD is more commonly performed in Asian countries where endoscopists have a greater experience with this technique. EMR is established as the primary approach in western countries, whether using the cap- or ligation-assisted EMR. Although some argue that cap-assisted EMR may yield larger resection specimens and allow for a cleaner margin-to-margin piecemeal resection as compared to ligation-assisted EMR, perforations are more common with the cap assisted technique [118].

Palliation of advanced esophageal cancer

Endoscopic therapy can be used to restore esophageal passage of obstructing tumors, or to close malignant fistulas. Ablative methods include yttrium–aluminum–garnet (YAG) laser, APC, PDT, bipolar thermocoagulation, and cryotherapy. Repeated treatments are typically required to treat tumor regrowth. Some studies suggested that cryotherapy provides safe and efficient tumor debulking either as a palliative measure or as a bridge to surgery [119,120].

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Hyperplastic and adenomatous polyps

Hyperplastic polyps are believed to be associated with H. pylori infection and atrophic gastritis [124]. They are typically located...
in the antrum and can be solitary or multiple. They are more common in elderly patients. If a hyperplastic polyp reaches significant size, it may result in chronic gastrointestinal blood loss and iron deficiency anemia. Occasionally, large hyperplastic polyps undergo malignant transformation [125–127]. Gastric adenomas are considered premalignant lesions. The risk of malignancy increases with size. Approximately 24% of gastric adenomas larger than 2 cm are malignant as compared to only 4% of adenomatous polyps smaller than 2 cm [127,128].

Endoscopic appearance cannot reliably distinguish variants of gastric polyps [122]. Although fundic gland polyps have a distinct bland appearance, a biopsy should be obtained from the largest polyps to establish the diagnosis. Forceps biopsy sampling of large gastric polyps has limited accuracy. Therefore, all gastric polyps larger than 1 cm in size should be adequately sampled or completely removed [121,129]. If only sampled, decision on whether to subsequently perform a complete endoscopic resection needs to be based on the histology results and the possibility of false-negative sampling with the understanding that biopsies may miss advanced histology in 3% of nonfundic gland polyps [130].

In general, lesions that harbor HGD are at increased risk to transition to cancer and should be resected. Reported progression rates vary broadly. Furthermore, Japanese and European/North American pathologists differ in their definition of neoplastic lesions. For example, the same lesion may be categorized as “noninvasive intramucosal cancer” in Japan, but may be diagnosed as HGD by Western pathologists [131]. To resolve this discrepancy, the WHO definition of dysplasia and intramucosal cancer has been updated and should be universally applied [132].

Indications for endoscopic resection of early gastric cancer (EGC) according to the Japanese classification include well-differentiated mucosal cancers (T1a) that are ≤20 mm in size (≤10 mm for depressed lesions) without ulcerative changes [133]. The reported risk of lymph node invasion in these mucosal cancers is <1% [134,135]. Surgical resection is the treatment of choice for tumors with submucosal invasion (T1b) because of an increased risk of lymph node involvement [136,137]. In selected patients, endoscopic resection may be considered for cancers with minimal invasion into the submucosal layer [134,138].

The techniques of gastric and colonic polypectomy, EMR, and ESD are similar. However, endoscopic resection of gastric lesions is associated with a higher risk of bleeding and a lower risk of perforation than that of colonic lesions [139–141]. Special caution should be exercised during retrieval of resected gastric specimens and patients’ airways need to be protected to prevent aspiration.

The largest experience in endoscopic resection of early gastric cancer has been accumulated in Japan, where screening for early gastric cancer has been active since 1957, and approximately 50% of gastric cancers (10000 cases yearly) are discovered at an early stage [142,143]. EMR and ESD are accepted as minimally invasive treatment options of early gastric. A Cochrane review from 2009 showed a high complete endoscopic resection rate of more than 70% with EMR/ESD of early gastric cancer [144]. Similar to esophageal and colonic cancers, rate of lymph node invasion increases with tumor depth (Figure 140.9) [134]. In the absence of lymphovascular invasion, ulcers and poor differentiation, mucosal gastric cancers can be resected endoscopically with curative intent. Bleeding is the most common complication and occurs in 1%–20% of resections. The bleeding risk increases with size of the lesion and occurs more commonly when the lesion is removed by EMR as opposed to ESD [144]. PPIs started prior to endoscopic resection may prevent bleeding and promote healing [145]. Perforation rates with ESD vary between 0.4% and 5% [144]. Recurrence of cancer after endoscopic resection of EGC occurs in up to 4% of patients; however, these cancers are typically early and amenable to either endoscopic retreatment or surgical resection [144]. Reported 5- and 10-year survival rates after endoscopic resection for EGC approach 100% and are comparable to surgical resection with a likely benefit of better quality of life after endoscopic resection [144]. In the absence of surveillance guidelines, patients are typically followed with at least annual upper endoscopies to assess for recurrence or metachronous lesions.

Duodenal lesions

Adenomas are the most common indicator for possible endoscopic resection in the duodenum. They can be sporadic or part of a genetic syndrome (familial adenomatous polyposis, Peutz–Jeghers syndrome) [146]. Sporadic duodenal adenomas probably follow a similar adenoma–carcinoma sequence as colonic adenomas [147]. As dysplastic lesions, they have potential for malignant transformation and should be removed.

Duodenal adenomas are typically found in the posterior and lateral wall of the second portion of the duodenum at or below the level of the major papilla. The location appears to be influenced by bile flow and its growth promoting properties [148].

Although resection should follow the same principles of colonic polypectomy, endoscopic removal of duodenal adenomas is more challenging. The duodenal wall is thinner and adenoma location may compromise access. With resection of comparable lesions, complications occur more frequently than in the colon. Therefore the decision to proceed with endoscopic resection should be carefully weighed against the patient’s age and comorbidities. Endoscopic resection of large duodenal adenomas should be performed by a highly experienced endoscopist.

Duodenal adenomas can be categorized as either ampullary lesions or lesions elsewhere in the duodenum. Ampullary lesions are usually removed with standard polypectomy technique without submucosal injection unless the polyp extends beyond the ampullary area [146]. There is no consensus in the literature regarding what type of electrical current should be
used during ampullary polyp removal [146]. Some authors advocate pure cutting current to prevent coagulation damage to the pancreatic duct, whereas others recommend blended current to decrease the risk of bleeding [149,150]. Prophylactic pancreatic stent placement is recommended after endoscopic ampullectomy to reduce the risk of pancreatitis [151]. APC may be used after ampullectomy to destroy residual adenomatous tissue and to control postprocedure bleeding [145]. Very large and ulcerated ampullary lesions may harbor malignancy [146]. Endoscopic removal of malignant ampullary tumors is usually inadequate and these patients should be referred for surgical resection [146,147].

Duodenal adenomas located outside the major duodenal papilla are typically flat and should be treated similarly to flat colonic polyps [148]. Difficulty in positioning the endoscope may render endoscopic resection challenging. A transparent cap at the tip of the endoscope stabilizes the endoscope and facilitates access to the polyp. Lesions located in the second or third portion of the duodenum are frequently better evaluated with a side-viewing duodenoscope.

Various polypectomy and EMR techniques can be used to remove duodenal polyps [148]. Cap-assisted EMR has been used but is associated with increased perforation risk. Similarly, ESD in the duodenum has been reported but is associated with a 20%–35% perforation rate [152,153].

Colorectal polyps and tumors

Most colon polyps are diagnosed in asymptomatic patients during routine screening colonoscopy. The benefit of colorectal cancer screening relies primarily on the detection and resection of colorectal polyps to halt the adenoma–cancer progression and prevent incident cancers [148]. Colonoscopy has been shown to reduce colorectal mortality by approximately 30% in population-based studies [154,155] and by 53% in the National Polyp Study [156].

Polyps can be categorized by size and by morphology to provide some guidance for their resection. The Paris Classification categorizes polyps by morphology into protruded lesions and flat lesions [157]. Protruded lesions include pedunculated polyps (Paris Ip), subpedunculated polyps (small polyp base, Paris Isp), and sessile polyps (height >2.5 mm, Paris Is). Flat lesions include those with a slight elevation (height <2.5 mm, Paris IIa), without elevation (Paris IIb), and excavated lesions (Paris III). A combination of these characteristics is also possible (e.g., slight elevation with central depression, Paris IIa+c).

Diminutive polyps

About 70%–80% of all colorectal polyps are diminutive polyps measuring 5 mm or less in diameter [158,159]. Diminutive polyps are more likely to be adenomatous in the right colon and transverse colon but are mostly hyperplastic in the left colon [8,159]. Digital chromoendoscopy as narrow band imaging (NBI), Fujinon Intelligence Chromoendoscopy (FICE), or iScan combined with high definition imaging has allowed recognition of minute mucosal details, prompting studies of real-time polyp diagnosis. In a metaanalysis of 18 studies, high-definition NBI imaging accurately distinguished diminutive adenomatous from hyperplastic polyps and enabled correct prediction of surveillance interval in more than 90% of patients [160]. Furthermore, the negative predictive value for rectosigmoid adenomatous polyps was ≥90%. These results reached benchmarks to suggest a change in diminutive polyp resection practice [161]: (1) diminutive polyps can be resected and discarded if a diagnosis of hyperplastic or adenomatous polyp can be made with high confidence; and (2) diminutive rectosigmoid polyps do not have to be resected if they are diagnosed with high confidence as nonadenomatous polyps. However, the above results must be reproduced in nonexpert community setting before implementing changes in resection practice [162].

Diminutive polyps can be removed with a forceps or a snare. Hot forceps polypectomy has a high rate of bleeding complications especially in the right colon and should not be routinely used [9]. Although cold forceps polypectomy appears safe, adenoma resection may be incomplete in up to 38% of patients [2,163]. Considering that the typical forceps diameter is less than 2.5 mm, only polyps 2 mm or smaller would be amenable to complete removal with one bite and, thus, polyp resection using a forceps should be restricted to 1–2 mm polyps. Many experts advocate use of small snare without electrocautery for resection of diminutive polyps [11,12].

Small and large polyps

Most small (6–9 mm) and large polyps ≥10 mm are sessile (Paris Is) or flat (Paris IIa). As the risk of prevalent cancer and transition to cancer increases with polyp size [158,164], complete resection of larger polyps is particularly important. En bloc snare resection should be attempted and appears to be safe for polyps up to 20 mm. However, hot snare resection does not guarantee complete polyp removal. A study on 346 neoplastic polyp resections found that 10% of polyps between 5 and 20 mm were incompletely removed [165]. Incomplete resection occurred more often with larger polyp size and with resection of sessile serrated adenomas/polyps (31%). The incomplete resection rate also varied broadly among endoscopists and highlights the importance of a detailed inspection of the resection margin. Complete resection appears to be particularly important, as incomplete resection may be responsible for 10%–27% of interval colorectal cancers following a colonoscopy [166–168].

Nonpedunculated large polyps ≥20 mm

Polyps larger than 20 mm in diameter can present a significant challenge for endoscopic therapy. Feasibility of endoscopic resection depends on location of the polyp, ease of positioning the endoscope, polyp size, and underlying histology of the
polyp. In addition to the Paris classification, large lesions have been categorized by lateral spread into a granular (or carpeted) type, a nongranular type, and a mixed type [169].

Typically, large colon polyps are resected using inject-and-cut EMR technique. While en bloc resection can be attempted, most large polyps will require piecemeal resection [170]. The submucosal injectate typically contains a contrast agent (indigo carmine or methylene blue) to stain the submucosal layer and to better delineate neoplastic polyp from surrounding nonneoplastic mucosa. After submucosal injection, the snare is placed around the polyp and gently pressed against the mucosa. Excess air is aspirated to decrease colonic distention and facilitate grasping of the polyp. A stiffer snare may ease engagement of polyp tissue and prevent slippage. Residual polypoid tissue is removed in similar fashion until all polypoid tissue is resected and the muscularis propria visualized [170].

Several techniques have been used to aid resection of difficult polyps. Attaching a transparent cap to the tip of the endoscope may allow for a more stable endoscope and improve exposure of the proximal polyp margin [171]. If the polyp is located in an unfavorable position (behind a fold or colonic turn), retroflexion, the use of a side-viewing endoscope, or of a gastroscope may facilitate access [170,172].

Resection of large colonic polyps is associated with increased incidence of complications. These occur in 5%–15% of patients and include abdominal pain in 5%, delayed bleeding in 2%–10%, perforation, and postpolypectomy syndrome each in approximately 1% of patients [170,173–175]. Closure of the mucosal defect after resection reduced the rate of delayed bleeding complication in a large retrospective study from 10% to 2% (Figure 140.11); however, prospective data are lacking [176].

The best prospective data on outcomes of resection of large colon polyps come from an Australian colonic endoscopic resection study that included 479 patients with large polyps [174]. Complete large polyp resection was achieved in 89% of patients. Adenoma recurrence was observed in 20% of these patients within 4 to 12 months. Predictors of adenoma recurrence included previous failed attempts at resection, involvement of the ileocecal valve, larger adenoma size, and adjunctive use of APC for complete polyp eradication.

Resection of a large polyp should be completed in a single session if technically feasible. Complete resection should be assured by detailed inspection of the resection margin and removal or destruction of all minute visible polyp tissue (Figure 140.12). As noted, one small randomized study found a reduced adenoma recurrence (10% vs 64%, \( P = 0.02 \)) when the resection margins were cauterized with APC [78]. However, the study included only 21 patients and was performed before the introduction of high-definition imaging.

ESD is also used for removal of large colon polyps, predominantly in Asia. ESD is associated with a lower risk of adenoma recurrence than EMR, albeit at the expense of a higher perforation rate of about 4% [177]. A hybrid technique between EMR
and ESD has been applied in a few studies [178,179]. It involves a circumferential mucosal incision around the polyp using ESD knives, followed by en bloc snare resection of the “freed” polyp. Outcome of this hybrid technique have been inconsistent and larger studies are needed to better study its efficacy and safety.

Special retrieval devices have been designed to allow retrieval of polyps that cannot be suctioned through the working channel into the trap [180,181]. Larger polyps can be grasped for removal by endoscopic snare, graspers with multiple prongs, or specially designed retrieval nets and instruments combining a snare and a removal basket.

**Pedunculated polyps**

Pedunculated polyps are attached to the colonic wall by stalks of various sizes (morphologically classified as Paris Ip). Histologically, the head of a pedunculated polyp usually represents colonic adenoma, sometimes with high-grade dysplasia or cancer. Adenomatous changes rarely involve the stalk of pedunculated polyps.

Most pedunculated polyps are removed with hot snare resection. It is advisable to avoid resection of the bottom third of the stalk close to the colonic wall. This prevents extension of coagulation necrosis to the colonic wall. In addition, the remnant stalk can be targeted endoscopically in cases of postpolypectomy bleeding. The stalk can be injected, cauterized, or grasped with endoscopic snares, clips, or detachable loops for mechanical hemostasis. If malignant transformation of the polyp is suspected, the snare should be positioned as far from the polyp head as possible to avoid residual neoplastic tissue within the resection margins. To prevent electrical damage to the colonic wall during polypectomy, special attention should be paid to avoid touching the intact colonic wall with any part of the snare or polyp (Figure 140.13).

Endoscopic polypectomy of large pedunculated polyps, especially those in the tortuous and narrow sigmoid colon, can be technically difficult [182,183]. Changing the patient’s position or retroflexion may improve view and ease placement of the snare [172]. A double-channel endoscope may facilitate polypectomy [182]. Piecemeal reduction of the polyp can be performed if the head of the polyp is too large to fit into a large polypectomy snare or into a detachable loop. Finally, clip application to the stalk with subsequent needle-knife transection of the stalk can be performed if placement of a snare around the stalk is not possible [66].

The risk of perforation during removal of pedunculated polyps is lower than that for large sessile lesions [97]. Epinephrine injection into the stalk or application of a detachable endoloop has been recommended to prevent postpolypectomy bleeding, particularly for polyps with a large stalk (≥1 cm) [184].

**Endoscopic treatment of colorectal cancers**

Small rectal carcinoids, adenomas with high-grade dysplasia, and superficially invasive colon cancers can be successfully removed by endoscopic resection [185,186]. Invasive carcinoma is found in 2%–4% of colonic polyps removed endoscopically [185]. The risk of cancer is increased in flat lesions (Paris IIb) or ulcerated lesions (Paris III), particularly with a nongranular appearance. Nongranular depressed lesions (Paris IIc) have a very high cancer risk of 67%, while flat elevated polyps (Paris IIa) with a granular carpeted morphology have a low risk of prevalent cancer of 1%–2% [170,174,187]. Because of the higher risk of cancer in the nongranular region, this area should be resected first in an effort to capture all potential cancer in the first larger resection specimen. Special attention should be given to retrieval and preparation of these specimens to allow adequate pathological evaluation.

Characteristic features of vasculature and mucosal architecture of a lesion provide additional clues of prevalent cancer and possible submucosal invasion. The Kudo classification uses high-magnification chromoendoscopy to associate mucosal pit pattern with underlying histology [188]. An irregular arrangement and shape (class V) suggests carcinoma. More applicable to clinical practice is the modified Sano classification, which describes lesions based on microvascular changes seen with high-definition NBI imaging [189]. For example, irregular capillaries with branching and blind endings or nearly avascular areas (Sano class IIIb and IIb) suggest invasive carcinoma (Figure 140.14). Such findings, especially when seen in conjunction with nonlifting submucosal injection or nongranular (or even ulcerated) morphology, suggest submucosal invasion. These lesions are usually not amenable to endoscopic resection.

In general, endoscopic resection should only be attempted if complete resection of neoplastic lesion is anticipated [190]. Endoscopic resection of mucosal carcinomas may be considered curative if histological features associated with lymph node
After endoscopic resection of large premalignant or early malignant colorectal tumors, patients should have close endoscopic surveillance. Surveillance after piecemeal resection is recommended within 2–6 months to rule out residual neoplastic tissue at the polypectomy site [185]. If residual tissue is found and removed during repeat colonoscopy, then a follow-up examination should be performed again within another 3–6 months to verify complete resection of the lesion [185]. If the polyps cannot be removed completely after two to three attempts, surgery should be recommended [192].

If curative endoscopic or surgical resection is not possible, tumor palliation with ablative techniques (laser, APC, photodynamic therapy) or restoration of lumenal patency with endoscopic stents should be considered [190].

References are available at www.yamadagastro.com/textbook

**Further reading**


CHAPTER 141

Laparoscopy and laparotomy

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Introduction

The development of modern laparoscopy, more than 20 years ago, represented a huge paradigm shift, and in the intervening years has replaced laparotomy for most diagnostic purposes and many therapeutic interventions. Laparotomy has been mostly replaced as a diagnostic tool, except in cases where there is a high possibility of a need for open surgical therapy. For high-risk or very ill intensive care patients, minilaparoscopy is now available in many centers. This chapter on laparoscopy and laparotomy covers diagnostic indications, technique, and complications, as well as new procedures that might have a place in surgical diagnosis and therapy in the near future.

Evolution of modern laparoscopy

At the beginning of the last century, a few physicians established the foundations of the laparoscopic revolution. Georg Kelling (1866–1945) pioneered intragastric and intraabdominal insufflation. During the 1890s, he constructed a semiflexible endoscope, despite the skepticism of his colleagues [1]. In 1901, he performed the first abdominal laparoscopy (which he termed “celioscopy”) in dogs using intraabdominal pressures as high as 100 mmHg, with the assurance that, “After an examination, a dog is as cheerful as it was before” [2]. He is assumed to have also performed celioscopy in human, but never published this work. Working independently, Hans Christian Jacobaeus (1879–1937), a Swedish internist from Stockholm, was responsible for the first publication of a human laparoscopy (“laparothoracoscopy”) in 1910 [3]. A Russian gynecologist from St. Petersburg also claimed to have performed the first laparoscopy in humans, using a transvaginal approach, and apparently also carried out laparoscopy through the abdominal wall [4]. In 1911, Bertram Bernheim performed diagnostic laparoscopy in humans, using a transvaginal approach, and apparently also carried out laparoscopy through the abdominal wall [5].

Kurt Semm is recognized as the father of modern laparoscopy and conceptualized a number of techniques that ultimately resulted in the first laparoscopic appendectomy in 1982 [6]. Semm developed the basic instrumentation and added important refinements to the existing insufflators, which led to the modern electronic insufflator capable of automatic feedback and variable flow. He also pioneered the early surgical skills for laparoscopic dissection, ligation, and suturing, despite the resistance of many colleagues to these innovations. Not even the first laparoscopic cholecystectomy, carried out by Mühe in 1985 using an instrument called a “Galloskope,” was sufficient to initially convince other surgeons of the value of these approaches [1]. However, broader acceptance eventually followed when, in
1987, Mouret performed the first laparoscopic cholecystectomy using modern videoendoscopic equipment. Currently, most complex procedures of abdominal surgery can be performed laparoscopically, including cholecystectomy, appendectomy, colectomy, diagnosis in acute abdomen and intensive care, adrenalectomy, and splenectomy.

The desire to diminish the trauma and pain resulting from conventional abdominal incisions has been the driving force for the development of minimally invasive surgery in recent decades. Evolution from large surgical incisions to the multiple small incisions used in laparoscopic surgery has improved recovery times and better cosmesis with similar outcomes. Natural orifice translumenal endoscopic surgery (NOTES) represents the next stage in this overall paradigm shift, as first conceptualized in 1998 [7]. NOTES is discussed in Chapter 143.

Further refinement in minimally invasive surgery through efforts to reduce the size and/or number of ports has led to minilaparoscopy (multiple needle-size trocars), reported by Gagner [8] and single-port surgery (laparoscopy through a single incision) [9,10]. Minilaparoscopy allows for less access injury than conventional laparoscopy, and new technology has made available instruments 2 and 3 mm in diameter. These techniques have yielded good clinical and cosmetic results [11]. There are two access options for single-port surgery in the abdomen. One is the multitrocar in one incision, in which a port is introduced transumbilical with the insertion of the instruments occurring inside this port, a technique designated OPUS (one-port umbilical surgery) [12]. Curved instruments correct the perceived loss of triangulation using one entry site. In contrast, single-port access (SPA) surgery [12] uses multiple trocars through separate fascial incisions within one skin incision. SPA surgery has found wider usage, perhaps reflecting the greater familiarity of most surgeons with techniques of laparoscopic surgery than with NOTES. The cost of the procedure and the rates of incisional hernia and conversions are still being evaluated in randomized studies. At present, the choice of approach should be guided by patient safety; regardless of the initial plan, additional ports should be used if needed during the procedure to obtain clear delineation of the anatomy and effective dissection.

**Indications for diagnostic laparoscopy and laparotomy**

**Staging laparoscopy for intraabdominal malignancies**

Laparoscopy has become the standard for preoperative diagnostic staging of selected gastrointestinal cancers. The value of gastrointestinal (gastric, pancreatic) staging and laparoscopic evaluation of pelvic masses is now well established given the low sensitivity of computed tomography (CT) for the detection of small (<5 mm) peritoneal and superficial liver metastases. Thus laparoscopy may save patients with disease, otherwise thought to be resectable on the basis of CT findings, from undergoing laparotomy that in fact yields no therapeutic benefit. Laparoscopic ultrasound is a useful tool for detecting deep hepatic lesions. It is indicated for patients with preoperative T3 and T4 tumors without evident distant metastases in high-quality CT staging. It can recognize local advanced disease and small metastases (Figure 141.1), sparing the potential complications of a nontherapeutic laparotomy and allowing chemotherapy to be initiated sooner. Laparoscopy is not appropriate when it is clear palliation is needed for perforation, obstruction, or bleeding.

Lowy et al. and Burke et al. evaluated the role of laparoscopic staging after CT staging for gastric cancer. Laparoscopy enabled identification of CT-occult metastatic disease in 23%–37% of the patients [13,14]. Less than 2% of the patients in whom CT-occult metastases were identified by laparoscopy required subsequent laparotomy for palliation. In a systematic review of the value of diagnostic laparoscopy for staging, Chang et al. found that diagnostic laparoscopy identified unsuspected metastatic disease in 13%–57% when preoperative imaging studies were negative, and laparotomy was avoided in 17%–40% of patients [15]. Many centers have integrated laparoscopy into recommended routine staging algorithms for patients with locoregional gastric cancer and for selected patients with advanced gastric cancer [16,17]. Patients with early-stage gastric cancer (T1 and T2) do not benefit from diagnostic laparoscopy and should be treated directly by surgical resection. Flexible diagnostic laparoscopy is a recent innovation, which can be performed via either umbilical or transvaginal NOTES [18], but current clinical evidence is still anecdotal and it is not yet clear if it is superior overall to established methods.

Laparoscopy before laparotomy (during a single anesthesia induction) is a reasonable approach in patients with biopsy-proven or suspected, potentially resectable pancreatic cancer in whom a decision has been made to proceed with pancreaticoduodenectomy [19,20]. However, despite reports in which the
management was changed in more than 40% of patients on the basis of diagnostic laparoscopy, the use of this method has decreased as preoperative imaging techniques have improved, and it is currently used only for patients with large tumors or patients with highly elevated CA19-9. Peritoneal washing cytology and ultrasound laparoscopy are reported to increase the yield of the procedure. A nontherapeutic laparoscopic exploration was avoided in 4%–36% using this technique [15]. However, this procedure can be unreliable for evaluation of local unresectable disease found at laparotomy in 6% of patients. Staging laparoscopy is not used as a preoperative method, but rather before a planned laparotomy. It can be performed with a single trocar in cases where only peritoneal surface and liver will be evaluated (usually a 10-min procedure), or with three trocars in case of retroperitoneal exploration with opening of the bursa omentalis and the aid of laparoscopic ultrasound. When a locally advanced tumor is found with evidence of irresectability, laparoscopic palliation can be achieved with laparoscopic gastroenteroanastomosis or biliary derivation when indicated.

**Port site metastasis after diagnostic laparoscopy**

In the early days of laparoscopy for oncological indications, a higher incidence of trocar site metastasis was reported leading to poor outcome. The occurrence of this complication is now reduced to acceptable levels, allowing similar results for laparoscopic and open surgery for many indications. Studies report 0%–2% incidence of port site metastasis after staging laparoscopy, and in one comparative study with exploratory laparotomy, diagnostic laparoscopy was not related to increased incision recurrences or peritoneal dissemination [21].

**Acute abdomen**

Abdominal pain is a common problem encountered by the gastroenterologist and gastrointestinal surgeon. It may be mild, but it may also represent a life-threatening condition. It accounts for 5%–10% of all emergency visits. Elderly patients (>65 years) who suffer from acute abdominal pain have around six to eight times greater risk for mortality, especially if the final diagnosis cannot be established at the time of initial evaluation [22]. In general, abdominal pain is categorized as acute or chronic pain. Sudden onset of abdominal pain that lasts for less than 24 h is considered as acute abdominal pain. Patients presenting with acute abdomen typically are not relieved by usual analgesic medications and have distinct clinical findings at examination. Diagnostic laparoscopy is helpful in evaluation of some patients with acute abdomen, allowing for both accurate diagnosis and less invasive treatment.

Acute abdominal pain may have various etiologies. Common causes of acute abdomen are appendicitis, biliary colic, choledocholithiasis, abdominal wall obstruction, visceral perforation, pancreatitis, peritonitis, salpingitis, mesenteric adenitis, and renal colic. One study found that the most common causes of acute abdominal pain in patients presenting in the Emergency Unit are nonspecific abdominal pain (35%), appendicitis (17%), bowel obstruction (15%), urology causes (6%), biliary disorder (5%), diverticular disease (4%), and pancreatitis (2%) [23]. Less common causes of acute abdomen include hepatoma necrosis, splenic infarction, myocardial infarction, diabetic ketoacidosis, inflammatory aneurysm, sigmoid, cecum or stomach volvulus, and a manifestation of herpes zoster. Occasionally, the etiology of abdominal pain can be predicted based on its location and the character of the pain, which may be useful clues in establishing the diagnosis.

Although many patients with acute abdominal pain can benefit from therapeutic laparoscopy, major contraindications are suspected intestinal obstruction, where the procedure is technically difficult due to excessive bowel distension and inadequate visualization, and in cases of intestinal ischemia. Other contraindications for diagnostic laparoscopy are similar to those for exploratory laparotomy. Unique contraindications for laparoscopy are patients unable to tolerate pneumoperitoneum, those with clinically suspected abdominal compartment syndrome (when laparoscopic decompression is also desired), hypercapnia, coagulopathy, and recent (30 days) laparotomy [24].

**Diagnostic laparoscopy in the intensive care unit**

Early diagnosis of catastrophic, acute, life-threatening intraabdominal conditions, such as mesenteric ischaemia, acute intestinal perforation, cholecystitis, and sepsis, among critically ill patients remains a diagnostic challenge. Evaluation of acute surgical conditions in the intensive care unit is often unreliable because of patient's sedation, the effects of analgesics, and inability to communicate. A high positive fluid balance usually leads to a rigid and edematous abdominal wall, making clinical palpation unreliable. Hemodynamically unstable patients are sometimes unable to be transported for radiological testing because of the risk of complications such as sudden arrhythmias, hypotension, and respiratory insufficiency [25]. However, delay in diagnosing acute surgical conditions is a major contributor to the morbidity and mortality of intensive care unit patients. In a metaanalysis assessing the use of laparoscopy in detecting acute abdomen in critically ill patients, the sensitivity, specificity, and diagnostic accuracy of diagnostic laparoscopy to predict the need for laparotomy was high (75% to 100%) [24]. Overall effectiveness was affected by several factors, including patient's habitus, the experience of the surgeon, abdominal bowel distension, and previous abdominal surgery with adherences. Evaluation of retroperitoneal organs is a limitation of this method. It has high accuracy to detect the most frequent diagnoses in intensive care patients (i.e., acalculous cholecystitis and mesenteric ischemia) and is effective in preventing nontherapeutic laparotomy for 36%–95% in this setting [26–30].

Bed-side laparoscopy performed in the intensive care unit may improve outcomes, as patients' medication and treatment are not interrupted, and the risks for transporting a critically ill patient and the morbidity of an open exploration can be avoided.
Acute mesenteric ischemia
In the acute setting of ischemic bowel disease in a critically ill patient, radiological imaging plays a major role in directing the therapeutic management. Mesenteric ischemia represents about 1% of the acute abdomen cases overall, but is much more frequent in the critically ill patient. In half of the cases, acute arterial occlusion is responsible. The remainder reflects nonocclusive arterial ischemia (20%–30%) and venous occlusion (5%–15%). All of these forms of ischemic bowel disease can be diagnosed by conventional angiography, abdominal CT scan, or duplex sonography [31]. Laparoscopy is highly sensitive in the detection of intestinal ischemia, but less effective for therapy. Traditional surgical therapy remains laparotomy with bowel segment resection or embolectomy, depending on the timing and extent of the episode. Laparoscopy can avoid unnecessary laparotomy, especially if there are negative findings or conversely massive (over 90% of ischemic small bowel) infarction where the possibility of salvage is very low.

Acute acalculous cholecystitis
This entity is easily diagnosed by radiological imaging techniques. However, in intensive care patients, laboratory and clinical findings can obscure the onset of sepsis and instability. Such patients often have an edematous, thick-walled gallbladder due to positive fluid balance and free peritoneal fluid. In obese and distended patients, transabdominal ultrasound may not be helpful. In patients with suspected acalculous cholecystitis, or those with unexplained leukocytosis and rising C-reactive protein, a diagnostic laparoscopy may be indicated. If there are positive intraoperative findings, laparoscopic cholecystectomy is the procedure of choice, with the possibility of conversion to laparotomy. The timing of the surgical therapy, more than the method of choice, is of critical importance in avoiding complications. Many studies demonstrate that conversion rates, complication rates, recovery times, and hospital costs increase directly with increasing delay between admission and operation [31,32]. In the presence of gangrenous or hemorrhagic cholecystitis, immediate surgery is indicated. Although technically demanding, laparoscopic cholecystectomy is the procedure of choice, especially if an experienced surgeon is available.

Perforation of hollow viscus
Acute bowel perforation in a previously healthy patient usually can be recognized by deteriorating clinical condition, peritoneal findings and sepsis. In intensive care patients the diagnosis may be delayed and has to be based on high suspicion in the setting of sudden worsening in the clinical condition, unexplained sepsis, and rising signs of infection. Intestinal perforation may be caused by acute appendicitis, diverticulitis, and peptic ulcer, or secondary to intestinal obstruction, strangled inguinal and incisional hernias, and mesenteric infarction. Many of these conditions are successfully managed by laparoscopy, thus reducing local complications such as wound infection and incisional hernias. Perforated gastroduodenal ulcers are well managed by laparoscopic omental patch, or by laparoscopic sutures (Figure 141.2). Conversion to open surgery is necessary in approximately 10%–20% of patients, usually because of large, posterior or multiple perforations, or advanced peritonitis [33,34].

Colorectal perforation
Many endoscopic closure devices are currently available for closure of perforations of the upper and lower gastrointestinal tract, the most effective being the Over-The-Scope-Clip (OTSC) Ovesco System and the Overstitch (Apollo Endosurgery). If the perforation was unsuspected and took longer to identify with septic signs, laparoscopy with peritoneal irrigation is indicated. Therapeutic laparoscopy is the procedure of choice after colonic perforation during colonoscopy when endoscopic intraluminal closure is not possible or not available. Laparoscopic closure of the defect by suturing or stapling, sometimes along with temporary protective laparoscopic colostomy, is effective in controlling sepsis.

Percutaneous endoscopic gastrostomy tube complications
Dislodged percutaneous endoscopic gastrostomy (PEG) tubes occur in between 2% and 28% of patients, but only a small percentage of these will require surgical intervention [35,36]. A leak-proof gastrocutaneous tract usually develops several days after placement, thereafter avoiding dislodgement and intraabdominal leak and peritonitis. In healthy individuals, a gastrostomy tract is typically mature within 2–4 weeks [37]. For PEG tubes displaced in the early period, when the gastrocutaneous fistula tract is incompletely formed, there is risk for gastric intraabdominal leakage. This is rare in surgically performed gastrocutaneous gastromotomies because of surgical fixation to the abdominal wall [38]. Traditional management of a dislodged
PEG tube in the early postoperative period involves careful attempts to blindly establish the gastrotomy tract with a new tube followed by confirmatory contrast radiography to verify intragastric positioning. Findings consistent with contrast extravasation, peritonitis, or sepsis typically merit expeditious surgical exploration with irrigation of the peritoneal cavity, closure of the gastrotomy, and replacement of a gastrotomy tube through a new site. Without evidence of peritonitis and clinical stability, early PEG tube dislodgement can be successfully treated conservatively with nasogastric decompression and intravenous antibiotics [37]. Repeat endoscopy with immediate intraluminal PEG replacement adjacent to the internal gastrotomy site has been described for premature PEG dislodgement. NOTES PEG rescue was first performed by Marks et al. [39] and involves transmural passage of flexible endoscopes introduced per os, allowing access to the peritoneal cavity without abdominal wall invasion. In the setting of early dislodged PEG tubes, the NOTES approach offers several advantages (see Chapter 143).

**Diagnostic and therapeutic laparoscopy for trauma**

The evaluation of patients suffering from penetrating and blunt abdominal trauma is undergoing a critical reappraisal from both a technical and conceptual standpoint. Stable patients with blunt abdominal trauma may undergo diagnostic laparoscopy to exclude significant injury. With penetrating trauma, diagnostic laparoscopy is effective in detecting peritoneal penetration and treating organ injuries. It is clear that some patients who in the past underwent routine laparotomy may be effectively managed through conservative monitoring with selective intervention as dictated by physical examination [40]. Indeed, though considered in the past to be low risk, nontherapeutic laparotomy has been recognized to be a cause of significant morbidity and mortality [41,42], and in most patients suffering from blunt trauma, management should be guided by serial computed tomography rather than diagnostic laparotomy. However, in penetrating trauma, serial computed tomography imaging may fail to identify at-risk patients. Penetrating stab wounds in stable patients who have negative peritoneal lavage may be treated conservatively. In contrast, patients with penetrating injuries from firearms need mandatory laparotomy because of the high rate of injury (over 90%) [43]. This algorithm leads to a rate of nontherapeutic laparotomy of 5%–20%, reducing the considerable morbidity for patients undergoing negative laparotomy [41–45].

Currently, there are doubts about whether laparoscopy is able to detect all abdominal injuries safely. The modern approach to abdominal trauma requires use of the physical examination and the judicious use of available diagnostic methods. As preconditions for laparoscopy in trauma, patients should fulfill the following criteria: (1) hemodynamic stability upon arrival or after initial resuscitation, (2) normal Glasgow scale, (3) minimal comorbidity, and (4) technical and staff availability.

Laparotomy for abdominal trauma used to be negative or nontherapeutic in approximately one-third of patients, but with the advent of modern imaging techniques, this rate is reduced to less than 10% [46]. The literature contains approximately 40 prospective or retrospective cohort studies on the diagnostic role of laparoscopy in trauma [31,47]. Based on these studies, laparoscopic evaluation is able to avoid unnecessary laparotomy in around 60% of patients. Undetected injuries may occur in diagnostic laparoscopy in approximately 1% of patients, usually in the setting of blunt trauma. Laparoscopy is contraindicated in hemodynamically unstable patients, because rapid control of the bleeding is needed and hypotension may be aggravated by pneumoperitoneum. In patients with altered Glasgow scale at admission and suspected cranial trauma, laparoscopy is contraindicated due to the deleterious effects of hypercapnia on the central nervous system. Laparoscopy is able to avoid unnecessary laparotomy and reduce hospital stay compared to laparotomy, but prolongs hospital stay compared to conservative management [48].

Laparoscopy is useful to diagnose diaphragmatic injury, penetration into the cavity, and injury to organs of the upper abdomen in patients with thoracoabdominal trauma [45]. Despite the theoretical danger of pneumothorax with diaphragmatic injury, this complication has not been documented. In our experience with over 150 cases of diagnostic and therapeutic laparoscopy for blunt and penetrating abdominal trauma, the procedure was high yielding, avoiding laparotomy in 79% of patients [49]. Therapeutic interventions included diaphragmatic and bladder suturing, small bowel and gastric suturing, resection from colon and small bowel, and bleeding control for liver and spleen lesions. The presence of multiple visceral perforations or injury of retroperitoneal organ (such as ureter, pancreas, and duodenum) usually required conversion to open laparotomy. In a series of 121 patients with penetrating gunshot abdominal injuries, there were reportedly no false-negative evaluations for abdominal penetration [50]. Laparoscopy was able to identify organ lesions for abdominal penetration with 100% sensitivity and 98.7% specificity. In a multicenter study involving 510 patients, Zantut et al. evaluated the role of diagnostic and therapeutic laparoscopy [51]. Laparotomy was avoided in 277 patients (54.3%), in whom there were no significant injuries. In another 26 patients (5.1%), the procedure had therapeutic interventions. Of patients undergoing laparotomy (203), therapeutic interventions were performed in 155, still leaving in 52 patients undergoing laparotomy that was unnecessary in retrospect (25%). In contrast, Chol et al. achieved therapeutic interventions with laparoscopy in 100% of their series of 78 patients [52].

Diagnostic laparoscopy is the key to reducing nontherapeutic laparotomies, and is effective in selecting patients for laparotomy [52]. It has little, if any, significant morbidity or missed injuries. Further, conversion to laparotomy can be undertaken if complete assessment of the peritoneum is not possible laparoscopically. It is important to avoid unnecessary laparotomy in
patients with penetrating stab and gunshot wounds because of its associated morbidity and mortality.

**Technique for diagnostic laparoscopy**

For diagnostic laparoscopy, especially for bedside laparoscopy, fewer trocar insertion sites are generally needed than for therapeutic procedures. Generally, two will suffice, though occasionally three may be required. However, in patients in which there is a high likelihood of laparotomy (large bowel distension, free high density peritoneal fluid, or intestinal obstruction), the best strategy is to go directly to explorative laparotomy.

Bedside laparoscopy can be performed for diagnostic purposes in the intensive care unit. For bedside laparoscopy, patients should be monitored with continuous pulse oximetry, electrocardiogram, and blood pressure monitoring. Patients not requiring mechanical ventilation prior to laparoscopy usually do not require airway intubation. A monitor, insufflator, light source, camera, and appropriate instruments must be available. The patient is positioned supine on an ICU bed. The abdomen is prepped with Betadine solution and then sterile drapes arranged as in the operating room. Local anesthesia (mix of 1% lidocaine with 1% ropivacaine, 50%–50%) is used to anesthetize the trocar sites. An incision is made infraumbilical or supraumbilical and a 5 or 10-mm trocar and camera are inserted using an open Hasson technique. After insufflation with CO₂ to a pressure of 10–14 mmHg, additional trocars are placed under direct laparoscopic view as needed to manipulate the bowel and complete the exploration. The presence and character of intra-peritoneal fluid is noted, and fluid collected for microbiological exams. The viability and integrity of the bowel can be assessed, and the condition of the liver and gallbladder evaluated. For formal diagnostic laparoscopy, the procedure is always under general anesthesia since the resultant relaxation of abdominal wall makes more complex procedures possible.

**Technique for explorative laparotomy**

Under general anesthesia, the patient is positioned in the supine position, unless there is a likely need for a rectal anastomosis, a Lloyd-Davies position is desirable. Full abdominal wall relaxation is required. Clinical history and preoperative imaging information may guide the incision site as either infraumbilical (diseases of colon and rectum, appendix, gynecological) or supraumbilical (stomach, pancreas, and gallbladder). A median incision may be chosen for explorative laparotomy to allow for easy access of all abdominal and retroperitoneal organs when there is insufficient basis to localize the source of symptoms. After skin, subcutaneous, and fascial incision the next step is complete dissection of adhesions in previously operated patients. Lysis of very dense adhesions sometimes results in small bowel injury, which can be repaired with suturing. Exploration includes visualization and palpation of the liver, stomach, spleen, major omentum, and pelvic organs. Hernias of the abdominal wall are investigated and if present should be treated in the same procedure. Intestinal exploration starts with the appendix through ascending, transverse, descending, sigmoid colon, and rectum. Small bowel evaluation starts from the Treitz ligament in the direction of the terminal ileum. Retroperitoneal masses, lymph nodes, and peritoneal lesions can be examined and biopsied. Intraoperative ultrasound enhances the identification and staging of deep hepatic and pancreas lesions.

Abdominal closure is preferentially performed using a strong, absorbable or nonabsorbable running suture as a one-layer closure for the aponeurosis. Some transverse incisions may require a double-layer suture, and many surgeons prefer single sutures instead of running ones. The closure of subcutaneous tissue is not always performed, and skin closure is accomplished with intradermal running suture, skin staplers, or biological glue. Subcutaneous drainage may be needed to reduce hematoma in patients where there is a large dissection surface, in contaminated operations, or in obese patients. After laparotomy, the patient should avoid abdominal exercises or lifting more than 10 kg for at least 2 months to optimize the strength of the incision and avoid incisional hernias.

**Complications of laparoscopy and laparotomy**

In the early stages of the development of laparoscopic surgery, reports of higher than expected complications led to public criticism, but these problems were soon corrected by adequate training in well-organized courses and credentialing was required under the control of surgical organizations. With growing experience in laparoscopic surgery, it is now possible to perform most complex surgical procedures laparoscopically. However, less frequently performed procedures (such as those with rare indications or rarely performed) maybe problematic because of lack of adequate training and proctoring.

Intraoperative complications of diagnostic laparoscopy include bowel perforation, laceration of solid organs, subcutaneous or retroperitoneal emphysema caused by dissection by the insufflating gas, and vascular injury. This latter is frequently from a laceration of epigastric vessels in the abdominal wall or omental vessels caused by trocar or needle insertion. Major vessel injury is rare, but may be catastrophic and potentially fatal. It should be suspected in patients with growing retroperitoneal hematoma. This complication can be minimized by routine use of initial open access, which avoids the blind insertion of the Veress needle [53]. Tension pneumothorax is rare but may occur if there is an occult diaphragmatic perforation (for example diagnostic laparoscopy after recent cardiac surgery or for blunt or penetrating trauma).
Complications of the laparoscopic access
The insertion of a laparoscopic camera and working ports into the peritoneal cavity is required to start any laparoscopic procedure. The trocars must be carefully placed in positions that minimize the risk of injury and allow visibility and instrument access to the operative site. Despite significant advances in laparoscopic instrumentation and techniques, injury to intraabdominal structures remains a potentially serious complication. The estimated complication rate associated with laparoscopic access is 0.01%–1.00% [54]. Complications described in several publications include intraabdominal visceral injury, blood vessel damage, gas embolism, and postoperative hernias. Although these complications are uncommon, they are a significant cause of the morbidity associated with laparoscopic surgery.

Various techniques to achieve peritoneal access and capnoperitoneum have been described. These include the Veress needle followed by the blind insertion of a trocar, open access with direct visualization (Hasson technique) [53], direct trocar insertion without prior capnoperitoneum [55], optical Veress needle [56], optical trocars, and a reusable, peritoneal entry technique without camera visualization using water [54] visual access cannula with and without prior insufflation [57,58]. Although the Veress needle technique with blind insertion of needle and trocar are still largely used, open technique and direct visualization of trocar insertion should be preferred to avoid major, life-threatening complications.

Effects of CO$_2$ pneumoperitoneum
Insufflation of the abdomen with CO$_2$ is a requirement for most laparoscopic procedures, except when a gasless technique with retractors is chosen. Hemodynamic and respiratory changes, along with temporary alterations in many organs, result from this insufflation. Using pressures limited to 12–14 mmHg, hemodynamic changes in a previously healthy patient are well tolerated and not maintained after deflation. However, in a patient with underlying medical conditions there can be hemodynamic complications. The augmented intraabdominal pressure leads to relative hypovolemia due to compression of the inferior vena cava and perinephric veins, reduction in the cardiac output, increases in mean arterial pressure, and peripheral resistance. Administration of intravenous fluids (saline solution) prior to the insufflation may minimize these effects. Placing the patient in a Trendelenburg position may improve the adverse hemodynamic effects whereas the reverse Trendelenburg positioning (head up) usually accentuates them. Pneumoperitoneum may adversely affect patients with cardiovascular disease. Table 141.1 lists the most common effects of pneumoperitoneum with CO$_2$.

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Parameter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system$^a$</td>
<td>Venous return</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Preload</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Cardiac output (CO)</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Heart rate (HR)</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Mean arterial pressure</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Systemic vascular resistance</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Pulmonary vascular resistance</td>
<td>Increase</td>
</tr>
<tr>
<td>Abdominal pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase</td>
</tr>
<tr>
<td>Lung physiology$^b$</td>
<td>Gas exchange</td>
<td>Hypercapnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory acidosis</td>
</tr>
<tr>
<td></td>
<td>Airway resistance</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Pulmonary compliance</td>
<td>Reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous blood return$^c$</td>
<td>Lower extremities venous return</td>
<td>Reduction</td>
</tr>
<tr>
<td></td>
<td>Femoral venous pressure</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Risk for deep venous thrombosis (DVT)</td>
<td>Increase</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal blood flow</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Glomerular filtration rate</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Urine output</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Renine plasma activity</td>
<td>Increase</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hepatoportal circulation</td>
<td>Reduction</td>
</tr>
<tr>
<td></td>
<td>Liver enzymes</td>
<td>Elevation</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>Splanchnic microcirculation</td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td>Oxygen delivery</td>
<td>Impaired</td>
</tr>
<tr>
<td>Immunological stress response</td>
<td>Better immune function</td>
<td>No conclusive data</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Risk of bacteremia (animal experimental)</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Risk of bacteremia (clinical)</td>
<td>No difference</td>
</tr>
<tr>
<td>Tumor spreading</td>
<td>Risk of port-site metastasis (animal experimental)</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Risk of port-site metastasis (clinical)</td>
<td>No difference</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Maternal respiratory compliance</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>Uterine blood flow</td>
<td>Reduced</td>
</tr>
<tr>
<td></td>
<td>Preterm labor</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Risk of fetal loss</td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>Fetal acidosis</td>
<td>Increase</td>
</tr>
<tr>
<td>Neurological$^b$</td>
<td>Intracranial pressure</td>
<td>Increase</td>
</tr>
</tbody>
</table>

$^a$Effects intensified by the head-up (anti-Trendelenburg) positioning of the patient in the operating table.

$^b$Effects intensified by the head-down (Trendelenburg) positioning of the patient in the operating table.
Vascular injury
Life-threatening complications can occur from injury of large abdominal vessels, by insertion of the Veress needle or trocar. Around 80% of these lesions occur during the initial access. Using the open technique for the first access, serious vascular injuries may be avoided [59,60]. Injuries from insertion of the Veress needle are usually less harmful and self-limited, but may remain unsuspected until a retroperitoneal hematoma develops in the postoperative recovery. If there is serious vascular damage, best results are achieved with formal vascular repair through conversion to laparotomy. Even with immediate recognition and therapy, mortality ranges from 9% to 36% [61]. The vessels most affected are the distal aorta, common iliac artery and vein, and inferior vena cava, due to the vessel size and relatively fixed location. Injury to epigastric and abdominal wall vessels are easily repaired by percutaneous suturing or bipolar coagulation. This complication can be avoided by placing the secondary trocar under direct laparoscopic visualization.

Visceral damage
Small bowel or colon lesions may occur during insertion of the trocars or, less often, by thermal injury when dissecting using monopolar, bipolar, or ultrasonic energy. Unrecognized lesions may result in fatal complications. Bowel injury occurs in 0.05%–0.4% of all laparoscopic procedures, with a mortality of 5% [59]. Patients may present with fever, abdominal distension, sepsis, and peritonitis between the second and eight postoperative days. Aggressive diagnosis with early repeat laparoscopy in suspected cases may improve outcomes and reduce mortality.

Gas embolism
This rare condition may occur during accidental intravascular insufflation with CO₂, specifically by the Veress needle technique. Potential embolism may also be encountered with laparoscopic liver resections and kidney surgery, where greater-sized veins are able to conduct larger amount of gas, when higher insufflation pressures are used. The estimate incidence is around 0.003% [61]. Intraabdominal pressures for pneumoperitoneum should be limited to 12–14 mmHg of CO₂, thus also reducing cardiovascular and hemodynamic changes.

Laparoscopy in the pregnant patient
Special care has to be taken in the setting of pregnancy, due to the altered anatomy of intraabdominal organs, a voluminous uterus that may be injured by accessing trocars, a higher rate for postoperative deep vein thrombosis, and by the potential adverse effects of pneumoperitoneum on the fetus. Even with the best care, premature birth and abortion may occur after open or laparoscopic surgery. Accordingly, in the pregnant patient, laparoscopy should be reserved, for emergency indications such as acute appendicitis or other acute abdominal conditions.

However, if necessary, laparoscopy can be performed safely during any trimester of the pregnancy with minimal morbidity for mother or fetus [62–64]. Intraoperative fetal heart monitoring is effective for detection of fetal distress during laparoscopy. Cumulative experience in laparoscopy during pregnancy has shown no intraoperative fetal heart rate abnormalities and no increased fetal morbidity have been reported, although some still recommend routine monitoring before and after the procedure. In the past, laparoscopy was avoided in the first (due to potential CO₂ toxicity) and third trimester (because of uterine volume) of pregnancy, but nowadays may be performed in any gestational period. Although there is growing experience with laparoscopy in pregnancy, the published literature is mostly limited to small case series. Current guidelines recommend preoperative and perioperative fetal monitoring in the case of urgent laparoscopy during pregnancy.

Future of emerging diagnostic methods
The technique of minimally invasive surgery continues to evolve. Refinements in modern laparoscopy in the search for even less invasive procedures have resulted in the development of robotic surgery, NOTES, single-port surgery, and minilaparoscopy (needlescopes). Many of these advances are still at the stage of identification of indications and are undergoing clinical trials.

Single-port surgery
Rao et al. from India, in their preliminary experience of single-port surgery in 2008, noted that there were issues that need to be solved by developments in technology [12,65]. One concern is that the instruments entering through a single port lead to clashing of instruments and the loss of triangulation (Figure 141.3). Curcillo et al. introduced the concept of single-access surgery using different trocars inserted in different fascial orifices, but through the same umbilical skin incision, allowing
better triangulation with the available laparoscopic instruments [10,66,67]. When the anatomy is unclear it is necessary to add more trocars in order to operate safely. Using separate trocars instead of an umbilical single-access device allows for each instrument to have independence of movement. As a result, movement of one instrument does not affect movement of others. The surrounding fascia allows this unique property not found in multiport trocars.

Advantages of the single-port technique include: (1) technical similarity to traditional laparoscopic surgery, (2) reduced pain due to overall less skin incisions, (3) superior cosmetic results by using an intraumbilical incision, (4) easy conversion to multi-порт laparoscopy, and (5) the use of conventional laparoscopic instruments and clips [68,69]. It is also simpler and possibly safer than NOTES.

Disadvantages of single-port surgery include: (1) the smaller degree of instrument triangulation compared to conventional laparoscopy, (2) the parallel and close positioning of the instrument shafts resulting in “crowding” of the instruments, (3) clashing of instruments and the laparoscope, and (4) dissection through a single port is more difficult than in conventional multiport laparoscopy. Additional concerns include hernia formation and wound hematoma and infection, as well as the possibility of procedure complications due to limited visualization and restrained freedom of movements. As the fascial incisions required for some ports are 2.5–4.0 cm, it could be considered a minilaparotomy, with increased risk of incisional hernia, adhesions, and intestinal obstruction. As the technique is relatively new, there are no data to document the actual frequency of these potential disadvantages, as many complications (incisional hernia, intestinal obstruction) may occur many years after the procedure [70]. An increased risk of early wound complications, such as infection, is expected, as the skin incision and subcutaneous dissection are wider than in multiple trocar laparoscopies. Regarding the fascial incision, large ports are ideal when a larger specimen extraction is needed (spleen, kidney, colon), as the minilaparotomy is inappropriate for these specimens. Conversely, the incision needed for a large port may be excessive for smaller organs such as the gallbladder, or when no extraction is needed (Nissen procedure), with the possibility of increased postoperative pain.

**Minilaparoscopy**

The advent of NOTES and subsequently single-port surgery has raised interest in developing even less invasive modalities for surgical access [65,71,72]. Minilaparoscopy (MINI) is a natural advancement of laparoscopy, which proposes to diminish surgical trauma by reducing the diameter of the standard laparoscopic instruments, without losing range of motion for triangulation, important aspects that can be a major challenge in NOTES and single-port surgery (Figure 141.4). Minilaparoscopy was first described more than 15 years ago [8,11,73–75]. Although interest in the past has been limited [8,73], the technique warrants recommendation because of a number of developments. First, newer instruments have been developed with much better design and with more durable materials [76]. In procedures where enhanced visualization in a restricted space is necessary, MINI offers advantages over regular laparoscopic surgery, for example inguinal hernia repair, lumbar or thoracic sympathectomies, common bile duct exploration/reconstructions, and transanal endoscopic operation [77]. When it is necessary to suture or even simply to tie a knot, the enhanced precision of the new low-friction MINI instruments have advantages in their handling over the conventional 5-mm equipment that uses rubber sealing and valves that can affect range of movement. Because MINI instruments require less space to move, they are especially useful when pneumoperitoneum is limited, like bedside laparoscopy, or when low CO₂ pressures must be employed.

The enhanced view is another advantage of the MINI approach, though it has sometimes been overlooked in favor of the cosmetic benefit of alternate approaches. MINI allows the surgeon to work much closer to the subject and functionally gain up to 2.7 times in magnification when using MINI instruments, as the thinner instruments occupy less of the visual field. The smaller instruments are also highly suited for transanal endoscopic operation because of the enhanced view and freedom of movements. Other more intricate surgeries may also be preferably performed using minilaparoscopy for the same reasons.

Current technical limitations of MINI are being addressed by the development of more resistant and higher performing instruments. Longer trocars without sealing (low friction) help to stabilize miniforceps and increase the strength and durability of the MINI equipment without limiting surgical movements. Current low-friction MINI trocars (unlike their predecessors from the 1990s) do not have a sealing membrane (as the basis for the designation “no rubber or low-friction trocars”). As a
result, almost no force is needed to move the instruments inside the trocars. This prevents undesirable movement including displacement of the trocars, which may injure the skin and worsen cosmesis. The new trocars also have a ball-shaped dilating tip, allowing for a minimal skin incision by radially dilating the skin, muscle layers, and fascia.

Advantages of MINI extend beyond improved cosmesis (the only proven gain so far of single-port surgery), and include less abdominal wall trauma [78–80], more precise surgical movements, enhanced view, and better dexterity, without significantly increasing the operative time, surgical effort or costs, or compromising the standards of surgical safety.

Conclusion
Continued efforts are being made to reduce surgical trauma and to produce safer, faster, and more cost-effective surgery, improving quality standards ultimately to advance all aspects of patient care. Judicious use of a growing number of options that permit diagnostic evaluation and management of most patients through less morbid approaches than was necessary in the past allows the surgeon to provide even better care of patients.

References are available at www.yamadagastro.com/textbook

Further reading
Pasricha P.J., Krummel T.M. NOTES and other emerging trends in gastrointestinal endoscopy and surgery: the chance that we need and the change that is real. Am J Gastroenterol 2009;104:2384.
Prelude to submucosal endoscopy

In 1998 an intensive effort began in the Mayo Clinic Developmental Endoscopy Unit (DEU) to develop approaches for safe and easy *en bloc* resection. At that time endoscopic submucosal dissection (ESD) was being developed in Japan but had obvious drawbacks, which persist today (risk, training, limited expertise, primitive free hand technique) despite increasing use of this procedure. Cap-based EMR provided *en bloc* resection of targeted areas up to 20 mm in diameter, but less than satisfactory results with piecemeal resection were obtained for larger mucosal lesions [1]. The initial efforts to accomplish large sample *en bloc* resection in the Mayo DEU involved two-handed dissection using a fixed or mounted endoscope, a grasper and needle knife, including the earliest versions of the insulated tip needle knife (Olympus Corporation, Japan). Although this method had appeal within the broader expansion of flexible endoscopic technology, the lack of triangulation frustrated this intended application which was subsequently recognized to be more suited to robotics. An important observation made during this effort was the ready delamination of the mucosa from the submucosa, as evidenced by the ability to create giant submucosal fluid cushions (SFC) (Figure 142.1). Work within the Apollo group, directed at the esophagus, demonstrated that large strips of mucosa could be peeled off from an SFC at any length desired. This animal-based research led to the concept of widespread endoscopic mucosal resection (WEMR) which was applied chiefly for excision of a Barrett segment. Specialized cutting caps enabled WEMR in the esophagus. The caps had cutting wires permitting longitudinal and horizontal cutting to be performed while the edge of the cap skidded between the mucosa and SFC taking advantage of the delamination effect [2]. However, WEMR using this tool permitted only piecemeal stripping.

Endoscopic interventions in the gastrointestinal tract are based on mechanical activities directed from the lumen towards the serosa. The deeper the intervention, the greater is the risk for serious complications such as bleeding and perforation with contamination of sterile spaces. Recognizing the mechanical effects of an SFC, in particular delamination, efforts were undertaken to convert the submucosa into a protective barrier. These efforts led to the discovery that hydroxypropyl methylcellulose was both less expensive and more readily available than hyaluronic acid for use as an SFC [3]. If an impenetrable SFC could be created, then excising any mucosal disease could be made safer and perhaps easier. Submucosal dissection can also be achieved by gas. Clinicians were already familiar with incidental submucosal gas dissection with argon gas when using an argon plasma coagulator. Initial animal studies revealed that CO₂ gas dissection could create areas of gas-filled submucosa, far larger than could be attained with any SFC. Use of gas for submucosal dissection was the basis for the submucosal inside out project (SIOP) program and expanding the field of submucosal endoscopy.
the submucosa into a free space facilitated an off-set access to the peritoneal cavity, allowing the overlying mucosal “flap” to serve as a protective barrier and sealant against soiling and contamination. This theoretical approach to viscerotomy was proposed during the inaugural Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) meeting in 2005 and incorporated in the first white paper [7]. This procedure was successfully performed in the stomach to direct an endoscope to the gallbladder and utilized to perform cholecystectomy [8].

The esophagus from an anatomic standpoint is ideal to use this off-set tunneling technique to gain access to the mediastinum, including the external esophagus, esophagogastric junction, heart, great vessels, and lymph nodes [9]. In order to accomplish this, a myotomy is necessary. Our initial experience with the technique was published and reported as the submucosal endoscopy with safety valve mucosal flap (SEMF) method.
submucosal endoscopy

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Sufficiently enough (longitudinally) to place the tip of the endoscope into this new space. Repeating the steps of advancing the deflated balloon catheter a few centimeters distally, inflating the balloon and pulling the balloon back towards the endoscope tip allows rapid advancement of the submucosal space, or a tunnel down to the esophagogastric junction. Blunt dissection has historically been a valued atraumatic surgical technique. Within the micro-environment of the submucosa, blunt balloon dissection is consistently protective of the overlying mucosal flap (Figure 142.3). The SEMF technique combined with myotomy of the circular muscle layer only was demonstrated to be an effective option in the treatment of achalasia [13].

The SEMF method

The first step of the SEMF method is gaining access to the submucosa, which is accomplished by the creation of an SFC, followed by opening the mucosa sufficiently to allow balloon catheter insertion, followed by endoscope insertion. SEMF in the animal lab (and currently in the author’s clinical practice) is based upon blunt dissection using small endoscopic retrograde cholangiopancreatography (ERCP) stone retrieval balloons to create a submucosal space or tunnel (Figure 142.4). Once a several centimeter length of submucosal space is initiated by inflation of the 11.5 mm balloon, the fully inflated balloon is pulled through the mucosal insertion site to fracture it open sufficiently enough (longitudinally) to place the tip of the endoscope into this new space. Repeating the steps of advancing the deflated balloon catheter a few centimeters distally, inflating the balloon and pulling the balloon back towards the endoscope tip allows rapid advancement of the submucosal space, or a tunnel down to the esophagogastric junction. Blunt dissection has historically been a valued atraumatic surgical technique. Within the micro-environment of the submucosa, blunt balloon dissection is consistently protective of the overlying mucosal flap, expediting access to the esophagogastric junction, without associated significant bleeding; it requires minimal endoscopic skills. Entry into the cardia proved more challenging in the porcine model (Figure 142.5). The tunneling process at this point became noticeably slower; there was greater resistance to dissection, requiring a more meticulous balloon dissection. Regardless of method, gastric mucosal perforation is the most
notable risk during this aspect of the dissection. The prominence of large vessels crossing the submucosal space within the cardia, and more so, the presence of the sling muscle fibers intertwined with the circular muscles provide reliable landmarks to confirm passage into the cardia, critical for a successful therapeutic myotomy (Figure 142.5). In the left lateral decubitus position, whether in the porcine model, or in the human, the path of the endoscope falls naturally in a posterior five to six o’clock positional direction.

In 2008, NOSCAR funded a study comparing partial and full thickness needle knife myotomy, the later a true NOTES procedure [14]. This study, performed in pigs incorporated deep tattooing to mark the cardia and serve as an endpoint for dissection. The tattooing proved unnecessary because of the predictable wandering of the tunnel, regardless of whatever tunneling method used, the better reliability of the sling muscle fibers to identify the cardia, and the practice of measuring the distance within the tunnel from the animal snout, correlating it with the intraluminal measurement. All of the author’s studies (and clinical practice) were carried out using a posterior approach. The posterior approach was advocated because of the more natural movement of the endoscope with left lateral decubitus positioning, maintaining the anterior esophagus clean if eventual traditional myotomy were needed, and if there were complications due to leakage, better containment and management. Both partial and full thickness myotomy, distal to proximal, could be performed without injury to the aorta or the posterior trunk of the vagus nerve which is covered by a protective mobile sheath. The longitudinal muscle layer proved vulnerable to incidental injury during the partial myotomy of the circular muscle. The pig proved vulnerable to this with the development of fatal pneumothorax, due to the pleural anatomy of their mediastinum (Table 142.1). The use of CO₂ insufflation, positive ventilation, and a small prophylactic chest tube eliminated this problem, and became standard protocol for subsequent live animal training. The tunnel distance between the end of the myotomy and the mucosal entry point was maintained at 4 cm to 5 cm for safe sealing of the tunnel by the overlying mucosa.

Interestingly, partial and complete myotomy demonstrated similar results. Complete myotomy using an insulated tip needle knife (Olympus America, Center Valley, PA, USA) was technically easier to perform and more expedient, requiring only seconds to accomplish.

Other investigators have duplicated the original efforts at access and most importantly confirmed safety, feasibility, and benefit of endoscopic myotomy [15–17]. A study by Perretta et al., used the novel technique of EndoFLIP imaging (Crospon, Galway, Ireland) which provides dynamic imaging of lumenal geometric changes using impedance planimetry [17]. The study is notable for demonstrating that the most critical aspect of the peroral endoscopic myotomy (POEM) is the cardia component. Specifically, the length of the esophageal myotomy did not impact improvement in distensibility over that established by division of the circular muscle layer within the cardia. This observation not only emphasized the value of the cardia myotomy, but also suggested a possible solution to the problem of reflux after myotomy.

In 2012 NOSCAR conducted an international survey of POEM [18]. There were 16 locations internationally reporting experience with the procedure in 841 cases. The first case performed was in Japan in 2008 using an ESD method to create the submucosal space [19]. The first case in the United States was performed in 2009 using blunt balloon dissection to create the submucosal tunnel [20]. The highest volumes had been performed in Japan and Shanghai, China. Since POEM is relatively new, clinical success can only be measured in the short-term and has been described in centers with case experiences in excess of 45 patients and is greater than 95%, accompanied by significant lower esophageal sphincter (LES) reductions of 55% from pre-procedure baselines and improvement in Eckardt scores of 80% over baseline at median follow-up periods of 1 year.

**SEMF for diagnosis**

The SEMF tunnel can be used for diagnostic sampling of the deep layers of the esophagus, stomach, and rectum. Refinements in the diagnosis and management of motility disorders can benefit from study of the neuroenteric system, largely located within the muscle layer of the gut. Until recently, obtaining specimens for study has required surgical intervention. It is possible to use submucosal endoscopy for direct large specimen sampling of the muscularis propria and also for in vivo imaging of neurons by means of confocal microscopy and fluorescence, using DNA probes [6,21,22].

SEMF access to the mediastinum can be used to biopsy of lymph nodes, pericardium, and epicardium [9,11]. The use of small caliber endoscopes adds to maneuverability within the mediastinum and around structures such as the esophagus and major vessels. While these capabilities have been demonstrated in the animal and cadaver laboratories, they have not yet been translated into any reported clinical experiences.

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**Table 142.1 Limitations of the porcine animal model for studying and training in peroral endoscopic myotomy (POEM).**

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<thead>
<tr>
<th>Limitation</th>
<th>Explanation</th>
<th>Solution</th>
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<tr>
<td>Pneumothorax</td>
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<td>CO₂ insufflation</td>
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<td>Gastric mucosal perforation</td>
<td>Esophagus/cardia transition</td>
<td>Slower catheter and balloon</td>
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<td>blunt dissection</td>
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<td>Cardia entry</td>
<td>Resistance to dissection</td>
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<td>Cardia identification</td>
<td>Resistance to dissection</td>
<td>Visualization of sling fibers</td>
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<td>Crossing vessels</td>
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Staging laparoscopy is one of the few NOTES procedures that can be performed with standard endoscopes and endoscopic devices. Experience with transgastric and transcolonic approaches compared to laparoscopy has been mixed [23–29]. The greatest problem encountered is the restricted ability to manipulate organs and structures to permit both navigation of the endoscope and visualization. Despite these limitations, translumenal peritoneoscopy appears safe [23–29]. SEMF has successfully been applied to humans for staging transgastric peritoneoscopy using a protective tunnel length of 4 cm created by traditional ESD dissection of the submucosa, balloon seromyotomy, and hemoclip closure of the mucosal entry site [30,31]. Importantly, this method has been used successfully under propofol sedation in a standard endoscopy procedure room. Submucosal endoscopy with transcolonic peritoneoscopy has appeal for easier and more direct staging of gastric cancer and other upper abdominal neoplasms such as pancreatic cancer. The transcolonic approach eliminates the mechanical restrictions of a retroflexed endoscope used via a transgastric approach and the potential interference with en bloc resection of a nearby gastric neoplasm. The safety of the transcolonic SEMF method, using either blunt balloon dissection or traditional ESD to create the tunnel has been established in animal survival studies [32]. The SEMF transcolonic approach has also been demonstrated to provide accurate staging capability by testing access to implanted beads (pseudo-metastases) in typical locations for metastases derived from gastric cancer [33].

**Submucosal endoscopy with mucosal resection (SEMR)**

If a large SFC can effectively isolate a sessile polyp there is no reason that the same fluid filled area beneath a polyp cannot be transformed into a space. Doing so further isolates the lesion ensuring an en bloc resection. This can be extended to any form of mucosal disease (e.g. early gastric cancer and Barrett esophagus). Once a lesion has been isolated and freed up from the deeper layers of the gut wall, it can be removed, without the meticulous and tedious dissection required of ESD and the frustrations of slipping, and less than optimally positioned snares. This concept has been successfully tested in the porcine rectum and distal colon (Figure 142.6) and the esophagus [4,34]. In the author’s laboratory, the technique has also been directly compared to traditional ESD in the porcine esophagus and stomach with more favorable outcomes in efficiency, expediency, and safety. It has not been possible to completely free up an area of mucosa through balloon dissection alone; it requires supplemental needle knife cutting of residual strands of connective tissue. Overall the latter activity requires dramatically less skill and experience than traditional ESD for removing similar sized areas of mucosa. Mesna, sodium sulfanylethanesulfonate, has the ability to weaken the connective tissue within the submucosa when added to an SFC [35,36]. The adjunctive use of this agent in the SFC may facilitate SEMR.

**Figure 142.6** SEMR (submucosal endoscopy with mucosal resection), a hybrid endoscopic submucosal dissection (ESD) technique which uses an isolating circumferential mucosal excision to create a disease free margin around a mucosal lesion, robust submucosal fluid cushions (SFC) to further isolate the targeted lesion, balloon dissection and supplemental conventional needle knife excision of residual strands of submucosal connective tissue. Source: Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.
Other uses for submucosal endoscopy

Submucosal endoscopy has been used to diagnose and excise subepithelial tumors (SET) such as gastrointestinal stromal tumors (GISTs) and leiomyomas within the esophagus and stomach [37–39]. SETs located in the proximal gastric cardia, especially posterior, are very challenging to remove either by a minimally invasive surgical approach, or traditional ESD. Current clinical experiences have used traditional ESD needle knife dissection to create the tunnel approaching the neoplasm and dissect the neoplasm within the submucosal space with more control over the positioning of the endoscope. The protective overlying mucosal flap allows full thickness resection, either intentional or incidental to occur without serious sequelae. Neoplasms up to 4 cm have been excised by this method [37]. Table 142.2 lists the existing and potential applications of submucosal endoscopy. Other applications include loop anchoring of tubes or devices using open-ended tunnels, depo-drug therapy intramurally, or on the outer surface of the gut, device implantation, and electromechanical device lead placement. Cardiac applications include left atrial appendage excision, intracardiac stem cell therapy, and monitoring of electrophysiological (EP) ablation therapy to avoid incidental full thickness esophageal coagulation injury [40].

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Further reading

CHAPTER 143
Natural orifice translumenal endoscopic surgery (NOTES)

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The field of gastrointestinal endoscopy has evolved from flexible endoscopy in the 1950s to endoscopic retrograde cholangiopancreatography in the 1970s and endoscopic ultrasound (EUS) in the 1980s. Endoscopy has been transformed from a purely diagnostic method to one with significant therapeutic applications. A major advance is the notion of using the flexible endoscope beyond the confines of the gastrointestinal tract into the peritoneal and thoracic cavities. Natural orifice translumenal endoscopic surgery (NOTES) involves translumenal resection of an abdominal viscus using a flexible endoscope through a natural orifice (mouth, vagina, anus, and urethra). NOTES offers the potential to be less invasive, safer, and possibly more cost-effective than either laparoscopy or traditional open surgery. The principles, history, current status, and future applications are outlined in this chapter.

Since the first report by Gauderer and colleagues describing a tube-feeding gastrostomy without a laparotomy in 1980 [1], other endoscopic procedures using a transgastric approach have been described [2,3]. However, these procedures have targeted only organs that were in close anatomical relation to the gastric wall. NOTES provides a paradigm shift in minimally invasive surgery, challenging the traditional view that endoscopists should not cause a breach in the integrity of the gastrointestinal wall.

Kalloo and colleagues from the Johns Hopkins Hospital first reported NOTES in 2000 [4]. After standard upper endoscopy, the gastric wall was punctured using a needle-knife, the incision extended by balloon dilatation or a pull-type sphincterotome, and a standard gastroscope advanced into the peritoneal cavity in a live porcine model. In addition to examination of the peritoneal cavity, biopsy of the liver was accomplished. On completion of the procedure, closure of the gastric wall incision was performed using standard commercially available clips, enabling long-term survival of the animal without significant morbidity or mortality.

The initial report attracted widespread interest from both surgeons and gastroenterologists. In 2004, human transgastric appendicectomy was reported by Reddy and Rao [5]. Subsequently, numerous investigators used NOTES in animal models to perform a variety of intraperitoneal procedures including cholecystectomy, colectomy, distal pancreatectomy, etc. [6–9]. The first human transvaginal cholecystectomy was reported in 2007 [10], and the first successful human transgastric cholecystectomy [11] also in 2007.

There are two current major surgical approaches to NOTES. The approach initially described is the "pure" NOTES approach, which refers to procedures performed only with transluminally inserted flexible or rigid tools without laparoscopic assistance.
The term “hybrid” NOTES is used to describe procedures that involve any laparoscopic transcutaneous assistance, usually referring to procedures performed using transcutaneous rigid laparoscopes in combination with a flexible endoscope passed through a visceral incision.

**Potential benefits of NOTES over current surgical techniques**

NOTES enables intraperitoneal surgical interventions with the elimination of abdominal wall incisions, resulting in no remnant scars and obviating the possibility of abdominal wall infection and incisional hernia formation. Theoretically, it also allows surgery that results in minimal pain and less potential for adhesion formation compared with currently available surgical approaches. It also may be associated with less impact on the immune system and the subsequent reduced neuroendocrine, immune, inflammatory, and delayed-type allergic responses compared to conventional laparoscopic surgery [12].

Laparoscopic techniques were readily accepted by patients because it resulted in minimal scarring, rapid recovery time, and less cost [13,14]. Applying the same inference, the absence of abdominal wall incisions with subsequent reduced pain, less morbidity, faster rehabilitation, shorter hospital stay, and the economic benefit of returning to work earlier may also make NOTES more attractive to patients. Additionally, because advanced endoscopic procedures can be performed using deep sedation, it may be possible for NOTES to be performed without general anesthesia and endotracheal intubation, unlike laparoscopic and open surgery. Furthermore, NOTES may be applicable for patients unsuited to laparotomy or even laparoscopic surgery such as morbidly obese patients.

In addition to the above-mentioned factors, the location of many peritoneal organs allows better access via the transluminal route and will thus make NOTES advantageous. Since the first description of transgastric peritoneoscopy, several investigators have confirmed the ease of attaining good intraabdominal visibility and manipulation of organs using currently available endoscopic accessories [8]. NOTES might also be beneficial in environments where performing abdominal wall incisions is less desirable, for example in underdeveloped countries, situations of acute abdominal trauma, and locations remote from healthcare facilities. In these situations, NOTES can theoretically provide a safe approach to triage and allow immediate life-saving procedures, if adequate sterility can be maintained.

**Closure of the gastrointestinal wall after NOTES**

Obtaining reliable closure of visceral transluminal defects is one of the major challenges for NOTES. A variety of devices have been tested in preclinical and clinical studies. Interestingly, Jagannath and colleagues showed that gastrotomies opened with balloon dilatation were able to spontaneously close in a porcine model [15]. These results have stimulated debate amongst NOTES investigators regarding the importance of luminal closure and suitability of the use of a porcine model to assess closure devices. Contemporary closure techniques are being improved and updated constantly and include endoclips, endoscopic suturing, flexible stapling devices, and occluding devices. Submucosal tunneling may represent the optimal visceral closure technique in the upper gastrointestinal tract.

There are two endoscopically deployed clip platforms currently available. Endoclips have been extensively used in humans for over a decade. These through-the-scope clips have the ability to be placed with precision, are rotatable, and can be removed at the discretion of the endoscopist [16]. Endoclips have traditionally been used to approximate two mucosal surfaces. The premise of healing without the need for seromuscular apposition is the basis for the success of this method, though the integrity of closure in the acute setting is a concern. Hashiba and colleagues describe endoscopic repair of gastric perforations with an omental patch and endoclips [17]. In a survival porcine study, the omentum was pulled into the gastric lumen and fixed endoscopically to the muscularis propria layer with endoclips. Histological examination revealed complete healing between the omentum and the stomach wall without microabscess formation or perforation. Closure of a posterior gastric wall viscerotomy is more difficult with this technique and may be one limitation of its application.

Recently, an over-the-scope clip (OTSC; Ovesco Endoscopy AG, Tubingen, Germany) has been studied for the purposes of closing perforations. The compressive forces generated are substantially greater than that of the endoclip. The OTSC consists of a Nitinol alloy and is installed on a cap that is mounted on the tip of the gastroscope (Figure 143.1a–c). Veormans and colleagues, in a prospective international multicenter study of acute iatrogenic perforations, report an 89% closure rate [18]. However, it is single use, difficult to remove, and multiple clips may be required for defects >2 cm. Additionally, the cap narrows the field of vision and enlarges the gastroscope tip dimension increasing the risk of esophageal trauma [19].

Full-thickness gastrointestinal closure devices are generally superior in achieving accurate tissue approximation to enhance the process of healing. Endoscopic suturing devices have been developed to mimic surgical suturing within the gastrointestinal tract. Currently, two types of endoscopic suturing devices have been approved: Overstitch™ (Apollo Endosurgery Inc. Austin TX, USA) and the Tissue Apposition System (TAS, Ethicon Endosurgery, Cincinnati, OH, USA). The Overstitch™ endoscopic suturing system is a disposable, single-use device that allows placement of running or interrupted full-thickness absorbable or nonabsorbable sutures (Figure 143.2a,b). The device has been used to successfully close a refractory gastrointestinal fistula in a patient [20]. The TAS system has so far only been reported clinically to approximate partial colonic wall...
Figure 143.1 (a) Endoscopic view of an over-the-scope clip (OTSC) mounted on the endoscope about to close an acute esophageal perforation. (b) Image of the OTSC after deployment. (c) Fluoroscopic image of the OTSC after deployment.

Figure 143.2 (a) Overstitch™ suturing system mounted on the endoscope. (b) Endoscopic view of the Overstitch™ whilst being used for luminal closure.
defects at the time of laparoscopic-assisted polypectomy [21]. These suturing systems are still somewhat cumbersome, impair visualization when mounted on the endoscope, and there is no good method to avoid inadvertent entrapment of extraluminal tissue adjacent to the gastrotomy. Liu and colleagues performed a study comparing endoscopic full-thickness suturing and endoclips to surgical suturing in an ex vivo porcine stomach model [22]. Closure time was significantly longer with endoscopic suturing but the median pneumatic burst pressure was higher for endoscopic suturing than endoclips.

An endoscopic detachable loop ligating device (Endoloops, Olympus Optical Ltd, Tokyo, Japan) has also been used successfully as a method of attaining gastric closure. Pai and colleagues first used endoloops as a method of closure following transcolonic peritoneal exploration experiments [23]. Subsequently, a simple variation of gastrotomy site closure using endoloops was reported by Katsarelis and colleagues [24]. These authors used one endoloop on either side of the incision site to create a fold. The two folds were then grasped using a forceps passed through an endoloop. The endoloop was deployed securing the two sides of the incision as one.

Tags and tissue-anchoring devices are gaining popularity for NOTES. This technique uses two sutures individually deployed transmurally and then secured with an anchoring system. This system is currently being refined and can now be deployed through a 2.8-mm accessory channel of an endoscope [25,26]. As for endoscopic suturing, transmural placement of the tag is performed blindly and may lead to adjacent organ damage.

An alternative method of managing a perforation by occluding the defect has been described using the Amplatzer septal occluder (Amplatzer, St Jude Medical, Plymouth, MN, USA). This device was developed for occlusion of cardiac septal defects but has been used “off-label” for the management of gastrointestinal fistulae such as tracheoesophageal fistula and postsurgical gastric leak [27–30]. This dumbbell-shaped device consists of two self-expandable discs that are deployed adjacent to the endoscope under direct visualization (Figure 143.3). After deployment, each disc apposes the wall on each side of the defect, mechanically occluding it. The device is available in a variety of sizes together with a sizing balloon to aid appropriate selection. It is unclear whether tissue in-growth occurs with the potential for disc migration.

The development of endoscopic anastomotic devices for NOTES has evolved over the last decade. As yet, there are only a small number of reports of the surgical creation of anastomoses during NOTES procedures. Hand sewn coloanal anastomoses during transanal NOTES has been described. Additionally, a flexible, powered surgical stapler (SurgAssist™ SLC 55, Power Medical Interventions, PA, USA) has been assessed during cystgastrostomy [31]. In the cystgastrostomy series, the stapler was passed down the esophagus through an overtube alongside a flexible endoscope. Although successfully used, the authors reported difficulty passing the rigid part of the stapler and directing the stapler to the desired location in the stomach.

The creation of a submucosal tunnel, which places the access site distal to the mucosal defect, allows the mucosal defect to be closed by endoclips alone without the need for complex endoscopic suturing (Figure 143.4a,b). This closure method has been successfully employed for the management of achalasia by peroral endoscopic myotomy (POEM). Additionally, our group has used this technique in the stomach for endoscopic pyloromyotomy [32]. As experience, evolving techniques, and accessories to facilitate rapid submucosal tunneling are developed, this may be the optimal method of closing NOTES access sites in the upper gastrointestinal tract.

**Risk of infection in NOTES**

The potential for infection following full-thickness incision through a viscus is one of the greatest potential risks of NOTES. The notion of introducing instruments through nonsterile orifices into the normally sterile peritoneal cavity is counter to longstanding surgical principles.

The initial animal laboratory experiments resulted in occasional and insignificant intraperitoneal microabscesses [33]. This, however, resulted in the implementation of sterile techniques, including gastric lavage with antiseptic solution, administration of prophylactic antibiotics, and use of sterile instruments. These measures appear to have resulted in better outcomes in subsequent transluminal endoscopic surgical experimental models.

Bacterial contamination has been evaluated in patients undergoing laparoscopic roux-en-Y gastric bypass as a surrogate for NOTES. The study by Hazey and colleagues evaluated bacterial contamination of the peritoneal cavity after gastrotomy during this operation. Despite the presence of bacteria in the peritoneal cavity after the gastrotomy (from zero colony-forming units (CFU) before gastrotomy to 24,720 CFU postprocedure), none of the patients experienced clinically evident

![Figure 143.3](image-url) Septal occluding device used for luminal closure.
peritonitis. The authors concluded that the presence of peritoneal contamination after gastrotomy did not result in adverse clinical sequela [34]. Another study of patients undergoing transgastric NOTES peritoneoscopy prior to planned pancreaticoduodenectomy also found minimal peritoneal contamination (160 CFU post procedure), with no infectious complications at 30-day follow-up.

The risk of infection may depend on the site of access, type of access, and method of closure. Transesophageal and transrectal NOTES would theoretically have a higher risk of infectious complications due to the proximity of the oropharyngeal and colonic flora, respectively. As yet, no human studies have quantified the level of bacterial contamination from either of these approaches. Nonetheless, in the first reported series of 17 POEM patients who received perioperative intravenous antibiotics and antibiotic irrigation of the esophageal lumen, no infectious complications were reported [35]. Reports of mediastinitis and peritonitis have been rare despite over 2000 POEM cases being performed worldwide. With regards to the transanal approach, to date there have been 72 published cases of hybrid NOTES transanal rectosigmoid resection [36]. Of these, six patients (8.3%) experienced infectious complications (peritonitis, presacral abscess, anastomotic fistula, pneumonia). This compares favorably to the published complication rates (27%) of laparoscopic total mesorectal excision [37].

Transvaginal and transgastric NOTES may theoretically have a lower risk of infection than either the transesophageal or transanal approach. The best data to date come from the large German prospective NOTES registry of 488 patients who underwent transvaginal cholecystectomy [38]. Infectious complications reported in this registry include urinary tract infection, vaginal mycosis, and bacterial vaginitis, with a combined incidence of 1%. This is comparable to the rate of infectious complications seen with conventional laparoscopic cholecystectomy.

The transgastric route to the peritoneal cavity has potential for contamination from microorganisms in the buccal cavity, esophagus, gastric lumen, and refluxate from proximal small bowel. One study in a porcine model demonstrated that attaining maximal sterile conditions, including sterilization of equipment and accessories and use of combination systemic and local antibiotics, effectively prevented infection regardless of the closure method used during transgastric surgery [39]. Based on currently available studies, sterile preoperative conditions should be maximally attained regardless of route of peritoneal entry, with secure closure of the access site.

**NOTES: current status and human experience**

In 2005, the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) convened to form the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR). A summary of this meeting was jointly published by ASGE and SAGES in February 2006 as a “white paper” [40]. NOSCAR has made recommendations about the direction of future research and steps that need to be taken for the safe introduction of NOTES to clinical practice. Significant published studies arranged by access route are summarized below.

**Transesophageal NOTES**

Access to the mediastinal and thoracic cavities through the transesophageal route is attractive as it avoids transthoracic incisions, reducing invasiveness of thoracic procedures.
Transesophageal NOTES allows access to the posterior mediastinum with visualization of the thoracic aorta, esophagus, trachea, pleura, lung, vagus nerves, and hilar lymph nodes. Due to the presence of vital organs, safe access to the mediastinum is critical. Using EUS, Woodward and colleagues established the safety of the right side at the level of the aortic arch for forward-viewing exploration and interventions [41]. When the endoscope enters the mediastinum, it is critical that CO\(_2\) be used for insufflation instead of air, which can result in tension pneumothorax and tension pneumomediastinum.

Multiple mediastinal and thoracic interventions using NOTES in animal models have been described, including lymphadenectomy, vagotomy, pleural biopsy, and creation of a pericardial window (Figure 143.5). However, complications such as bleeding, hilar injury, pneumothorax, and perioperative death have been reported.

The preferred method of transesophageal NOTES involves the creation of a submucosal tunnel, which was initially described by Sumiyama and colleagues [42]. This tunnel creates an offset entrance and thereby minimizing the risk of mediastinal and peritoneal contamination. Pasricha and colleagues used submucosal endoscopy to perform an endoscopic myotomy of the lower esophageal sphincter in pigs [43]. Inoue and colleagues performed the first human transesophageal NOTES procedure: peroral endoscopic myotomy (POEM) [35]. In his initial report of 17 patients, POEM significantly reduced the dysphagia symptom score (from a mean of 10 to 1.3, \(P = 0.0003\)) and resting lower esophageal sphincter pressure (from a mean of 52.4 mmHg to 19.9 mmHg, \(P = 0.0001\)) without serious complications being encountered. POEM has since gained increasing acceptance and is being performed by surgeons and gastroenterologists both in the operating theatre and endoscopy unit. It is estimated that nearly 2000 POEM procedures have now been performed worldwide. POEM probably represents the first sentinel application in NOTES that may supplant a current method. The increasing experience working in the submucosal space has resulted in endoscopic resection of lesions in the muscularis propria layer: submucosal tunneling endoscopic resection (STER). Ye and colleagues report a 100% success rate in removing 85 lesions from the muscularis propria layer (mean tumor size 19.2 mm with a mean procedure time of 57.2 min) [44]. The STER approach is gaining momentum as the preferred approach over a thoracoscopic approach for removal of esophageal lesions from the muscularis propria layer. However, currently lesions greater than 3 cm are not suitable for resection as they are unable to be removed from the tunnel due to the size of the mucosal entry.

**Transgastric NOTES**

Transgastric NOTES has been the most extensively studied technique in experimental animals. Human transgastric NOTES procedures include peritoneoscopy, cholecystectomy, appendectomy, and rescue of dislodged percutaneous endoscopic gastrostomy (PEG) tubes. Nau and colleagues and Nikfarjam and colleagues reported on a total of 70 cases of transgastric peritoneoscopy [45,46]. Currently, most cases are performed as hybrid procedures with the use of a laparoscopic port for guidance and insufflation. A few cases that did not use laparoscopic assistance resulted in cautery burn at the anterior peritoneal surface during creation of the gastrotomy.

Zorron and colleagues published the results of the international multicenter trial on NOTES in 362 patients [47]. Transgastric cholecystectomy and transgastric appendicectomy were performed in 29 and 14 cases, respectively. The remainder of the patients underwent transvaginal procedures. The mean operative time for transgastric cholecystectomy was 111 min and the mean time for transgastric appendicectomy was 135 min. Operations performed via pure NOTES technique were highly technically demanding. Peritonitis occurred in one case and intraprocedural hemorrhage treated with laparoscopically placed clips was seen in another. Therefore, the complication rate was similar to that seen in laparoscopic surgery.

There are several barriers that must be overcome for transgastric NOTES to become part of routine clinical practice. Although diagnostic procedures with this approach are feasible, therapeutic procedures remain challenging due to the lack of appropriate instruments.

**Transvaginal NOTES**

One of the challenges of the transgastric NOTES approach is the safety of gastrostomy closure. Transvaginal access appeared to provide a solution to these problems as closure of the vaginal wall has been performed for over a century by gynecologists and this approach provides a straight route to the upper abdomen (Figure 143.6). Most current transvaginal surgeries are performed with the use of rigid instruments. The transvaginal approach has gained popularity as it is not only readily accessible and easy to decontaminate but it also provides safe entry and simple closure.
approach [47]. Other transvaginal procedures performed included rectosigmoidectomy (n = 12), right hemicolectomy (n = 1), gynecological surgery (n = 11), cancer staging (n = 1), sleeve gastrectomy (n = 5), nephrectomy (n = 4), and hepatic cyst resection (n = 1). For transvaginal procedures, the outcomes appear slightly better than the transgastric approach with an operative time of 96 min for cholecystectomy and 60 min for appendicectomy. Adverse events were reported, including intraoperative hemorrhage in five (four required conversion to laparoscopic to aid in hemostasis) transvaginal cholecystectomies and three (all converted to laparoscopic) transvaginal appendicectomy. One perforation and a bile leak were also reported with this approach.

Transvaginal nephrectomy has now been reported using the NOTES approach. Kaouk and colleagues reported the first pure NOTES transvaginal nephrectomy in 2009 for management of a recurrent urinary tract infections and an atrophic right kidney [48]. They accessed the right kidney through a 3-cm posterior colpotomy. Using rigid instruments, the right kidney was mobilized, renal hilum divided, and the specimen removed through the vaginal incision. The procedure was successfully completed in 420 min with an estimated blood loss of 50 mL. There were no postoperative complications. She was discharged within 24 h with a Visual Analog Pain Scale of 0/10. This report of pure NOTES suggests the potential benefits of transvaginal urological surgery, although its applicability in the management of renal cancer is still unknown.

Until recently, there was a paucity of comparative data evaluating NOTES versus traditional laparoscopic or standard approaches. A prospective quality-of-life study compared laparoscopic appendicectomy to a hybrid NOTES transvaginal appendicectomy in 20 female patients (10 in each arm) [49]. The NOTES group experienced less pain on postoperative day 1, better overall quality of life, and more rapid return to activities of daily living. There were no major complications in the NOTES arm compared to one in the laparoscopic group (postoperative abscess).

A retrospective study of 107 patients who underwent transvaginal NOTES revealed adequate healing of the vaginal access without any local complications [50]. In time, 13 patients became pregnant after the procedure and 10 had a normal vaginal delivery. As the transvaginal route has emerged as the most common approach, assessment of outcomes following transvaginal access is of important.

Despite two large registries being published, ongoing international collaboration is necessary to further refine the NOTES techniques for cholecystectomy and appendicectomy. For pure vaginal NOTES to be appropriate for routine use, new platforms that allow multiple larger accessories are necessary. The most obvious limitation of this approach is its exclusive applicability to women and hence other routes of access such as a transrectal approach are being investigated.

However, transvaginal closure is currently the most feasible closure method for NOTES as the incision is closed by direct

Greater than 4000 transvaginal NOTES procedures have been performed worldwide with many experienced operators considering transvaginal cholecystectomy and appendicectomy noninferior to laparoscopic approaches. However, most procedures have been performed with the assistance of one or more laparoscopic ports, which are used for insufflation, visualization, retraction, and/or dissection. Laparoscopy assistance is beneficial to avoid injury to the structures that lay in close proximity to the vagina such as the small bowel, rectum, urinary bladder, and ureters.

Lehmann and colleagues published results from the large German registry for NOTES. A total of 551 female patients underwent transvaginal NOTES procedures (85% were cholecystectomy) [38] (Figure 143.7). Conversion to laparoscopy or open surgery occurred in 4.9% of cases (similar to the conversion of laparoscopic to open surgery). Complications occurred in 3.1% of patients (all in those undergoing cholecystectomies). These included bleeding, infection, rectal injury, bladder injury, small bowel injury, and abscess formation. Once again, the complication rates are similar to those encountered in laparoscopic or open surgery. Zorrón and colleagues reported 240 cholecystectomies and 37 appendicectomies using the transvaginal approach [47]. Other transvaginal procedures performed included rectosigmoidectomy (n = 12), right hemicolectomy (n = 1), gynecological surgery (n = 11), cancer staging (n = 1), sleeve gastrectomy (n = 5), nephrectomy (n = 4), and hepatic cyst resection (n = 1). For transvaginal procedures, the outcomes appear slightly better than the transgastric approach with an operative time of 96 min for cholecystectomy and 60 min for appendicectomy. Adverse events were reported, including intraoperative hemorrhage in five (four required conversion to laparoscopic to aid in hemostasis) transvaginal cholecystectomies and three (all converted to laparoscopic) transvaginal appendicectomy. One perforation and a bile leak were also reported with this approach.

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However, transvaginal closure is currently the most feasible closure method for NOTES as the incision is closed by direct
suturing rather than through endoscopic tools needed to close a gastrotomy.

**Transrectal NOTES**

Transrectal NOTES allows preservation of spatial orientation, intuitive movements, and a large port for the introduction of instruments and removal of large specimens. Transrectal NOTES is a promising alternative to the transgastric route as it provides straight access to organs in the upper abdomen and has more widespread applicability than transvaginal NOTES. For colorectal procedures, visualization of the pelvic anatomy from the anal route is excellent compared to laparoscopic or even open procedures. Theoretical concerns have been raised with regards to closure of transrectal NOTES and the majority of access has so far been accomplished by incorporating the rectotomy into a hand sewn coloanal anastomosis. The technique increases the safety of transrectal NOTES because it uses currently accepted anastomotic closure techniques but is limited to closure in the rectum or left colon. Transrectal closure left in situ (not incorporated into the anastomosis) may be theoretically safe as evidenced from the transanal endoscopic microsurgery (TEM) literature, which suggests that intraperitoneal rectal closures can be performed as safely as those without peritoneal entry during full-thickness rectal tumor excision.

Several groups have proven the feasibility of rectosigmoid and mesorectal resection via transrectal NOTES in animal and cadaveric models. Sylla and colleagues reported the first clinical case of a hybrid NOTES transanal resection of a rectal cancer using TEM [51]. Velhote and colleagues utilized a pure transanal NOTES technique to successfully perform transanal endorectal pull-through surgery for Hirschsprung disease [52]. Zorron and colleagues performed total mesorectal excision and rectosigmoidectomy with lymphadenectomy using transcolonic access in two patients with rectal adenocarcinoma with a mean procedure time of 355 min and no complications [53]. Leroy and colleagues reported the first pure transanal NOTES total mesorectal excision with retroperitoneal sigmoid mobilization and coloanal side-to-end anastomosis [54]. The specimen length was >20 cm. No diverting stoma was necessary and the anastomosis was hand sewn. The patient required minimal analgesia postprocedure.

Although promising, concerns remain about the transrectal approach due to the contamination risk. One animal study by Wilhelm and colleagues evaluated the use of a rigid sterile overtube to provide a contaminant-free conduit for the endoscope and secure closure [55]. The authors instilled an antibacterial solution into the peritoneal cavity to provide a preliminary hydroperitoneum using a percutaneously placed Veress needle. EUS was used to identify a site where there was no adjacent small bowel loops. This site was secured with a purse string and used to “prolapse” the rectum. Breach of the wall was then achieved under direct visualization to attain a transcolonic route. After peritoneoscopy, closure was achieved using the preplaced purse string in addition to a surgical stapler.

**Transvesical NOTES**

A transvesical approach is sterile, easy, safe to create, and can be closed without leaving a bladder catheter. In comparison with other ports, the urinary tract appears to have distinct clinical advantages for NOTES. Gettmann and Blute performed a transvesical prostatectomy in a patient with prostatic adenocarcinoma, after placing a needle through the bladder wall, intraperitoneal positioning of a guidewire, and balloon dilation of the bladder wall using a hybrid technique [56]. No perioperative and postoperative complications were observed, and the patient was discharged from the hospital 1 day after surgery, with return of bowel function, excellent pain control, and no evidence of urine leakage from the bladder. Given its anatomic and physiological properties, beyond peritoneoscopy, a transvesical port in human beings may be useful for simple abdominal procedures, varicocelectomy, tubal ligation, and renal cyst removal. Moreover, the usefulness of the transvesical port as an accessory port could facilitate pure combined NOTES complex procedures such as cholecystectomy and nephrectomy.

The potential advantage of this method is mainly that the bladder is a sterile space and transvesical access may lead to less intraperitoneal infectious complications. Drawbacks of this technique include limited robust accessories that can perform major surgical procedures and the inability to remove any significantly sized specimens.

**Future applications of NOTES**

Endoscopic drainage of pseudocysts and pancreatic necrosectomy for the management of walled-off pancreatic necrosis has been practiced for over a decade. There is a clear rationale for these approaches as the conventional surgical approach has a higher morbidity without a higher chance of success. NOTES-based endoscopic approaches should have applications in specific patient cohorts where conventional surgical approaches can be challenging, such as in the bariatric patient [57].

**NOTES echoendoscopy**

The advent of forward-viewing echoendoscopes enables EUS to be directly used on both thoracic and abdominal organs. A study describing transgastric approach for the diagnostic and therapeutic utility of echoendoscopy using forward-viewing echoendoscopes in 10 animals has been reported [58]. EUS-guided fine-needle aspiration of the liver, spleen, and kidney was performed successfully in nine out of ten animals using a 19-g needle. EUS-guided radiofrequency ablation of the hepatic parenchyma and was successfully performed. Minor bleeding was encountered in four animals, which was successfully treated with argon plasma coagulation.

**Real-time image-guided NOTES**

Image registration systems are already used in interventional pulmonology and a computed tomography (CT)-based image
Ryou and colleagues created a gastrojejunostomy anastomosis in a porcine model with the aid of a gastrotomy and two magnets [61]. The endoscope was advanced into the peritoneal cavity through the gastrotomy, a segment of small bowel was grasped and pulled into the stomach, and an enterotomy was created. The small bowel was deeply intubated via an overtube and the magnet deployed. Then a reciprocal magnet was deployed into the stomach, and two magnets were mated under endoscopic and fluoroscopic guidance to create a gastrojejunos- tomy. No leaks were found on contrast evaluation. This proof-of-concept study is an important step in providing an alternative minimally invasive approach to the creation of a gastrojejunos- tomy in obese or potentially unwell patients.

Transoral Thyroidectomy
NOTES thyroidectomy through a transoral route would have cosmetic benefits in an area that is commonly revealed. Witzel and colleagues reported transoral access for endoscopic thyroid resection in a porcine model and subsequently in human cadavers [62,63]. Although orientation in the retroperitoneum is difficult due to the lack of real space, they were successfully able to perform a variety of procedures by developing a highly standardized technique using predetermined anatomical landmarks. They demonstrated the feasibility of lymphadenectomy, nephrectomy, adrenalectomy, and distal pancreatectomy using a pure NOTES approach and standard endoscopic accessories in both survival and nonsurvival studies.

NOTES for Retroperitoneal Disease
Laparoscopic retroperitoneal interventions are currently performed via a transabdominal approach and therefore entry into the peritoneum occurs. Ideally, management of extraperitoneal disease should avoid the peritoneum entirely to decrease the risk of damage to intraperitoneal organs and tumor seeding in case of oncological interventions. Some authors even advocate that there is an immune role of the peritoneal barrier. Allemann and colleagues developed a model of transvaginal extraperitoneal access to the retroperitoneum in both animal and human cadaver models [60]. Although orientation in the retroperitoneum is difficult due to the lack of real space, they were successfully able to perform a variety of procedures by developing a highly standardized technique using predetermined anatomical landmarks. They demonstrated the feasibility of lymphadenectomy, nephrectomy, adrenalectomy, and distal pancreatectomy using a pure NOTES approach and standard endoscopic accessories in both survival and nonsurvival studies.

Transgastric Gastrojejunostomy
Laparoscopic gastrojejunostomy is important for palliation of malignant gastric outlet obstruction and surgical obesity procedures. A transgastric NOTES technique for the formation of a gastrojejunostomy is attractive for patients with malignant gastric outlet obstruction or to aid in endoscopic obesity therapies. The first successful creation of a peroral endoscopic gastrojejunostomy was published by Kantsevoy and colleagues in 2005 [7]. An endoscopic needle-knife and pull-type sphincterotome were used to create a gastric incision. A small bowel loop was grasped, pulled into the gastric lumen, and connected to the gastric wall using a prototype endoscopic suturing device (Eagle Claw, Olympus Optical Ltd). Then, a 15-mm long incision was made on the small bowel loop using the needle-knife and the open ends of this incision were connected to the gastric wall with more sutures to complete the gastrojejunostomy. Two animals were survived for 2 weeks. Postmortem examination 2 weeks after creation of the gastrojejunostomy revealed the gastrojejunal anastomosis on the border of the anterior abdominal wall and the greater curve of the stomach and normal-appearing small and large bowel and stomach (Figure 143.8).

Figure 143.8 Endoscopic gastrojejunostomy.
partial thyroidectomy in another four patients [65]. Procedures were performed through multiple 10-mm sublingual mucosal incisions using CO₂ as insufflation. Nakajo and colleagues reported the safety and feasibility of NOTES thyroidectomy using mechanical lifting without CO₂ to avoid postoperative emphysema [66]. In their series of eight patients, all resumed oral intake by day one and could have been discharged then. There were no infectious complications, but one patient suffered a recurrent laryngeal nerve palsy. While these studies demonstrate the technical feasibility of pure NOTES thyroidectomy, the approach is limited to patients with small glands (maximum volume 40 mL) and small nodules (<2 cm). More clinical experience is necessary to demonstrate the efficacy and benefit of this approach beyond improving the cosmetic outcome.

**Transgastric splenectomy and hernia repair**

A feasibility study to assess transluminal splenectomy was published by Kantsevoy and colleagues in 2006 [67]. After a gastrotomy, the endoscope entered the peritoneal cavity, dissection of the spleen from stomach and omentum was performed with ligation of the splenic vessels using endoloops and clips. After mobilization, the spleen was pulled into the stomach via a gastric incision. It was found that not only can resection of a large organ be performed using this route but also adequate hemostasis is achievable during transluminal endoscopic procedures.

Jagannath and colleagues reported, in abstract form, acute experiments in a porcine model that evaluated the feasibility of a transgastric endoscopic approach for repair of abdominal wall hernias [15]. After gaining transgastric access to the peritoneal cavity, an anterior abdominal wall incision was made with a needle-knife to create an animal model of abdominal wall hernia. Using a prototype endoscopic suturing device (Eagle Claw, Olympus Optical Ltd), a 3-cm incision of the abdominal wall (hernia model) was closed without any difficulties. The authors concluded that transgastric endoscopic repair of abdominal wall hernias is feasible and may be technically easier than laparoscopic surgery.

**Transgastric fallopian tube ligation**

Fallopian tube ligation in a survival porcine model has been performed successfully [15]. Tubal ligation was accomplished using an endoloop applied via transgastric endoscopic access to the peritoneal cavity. Endoscopic visualization of pelvic anatomy was excellent, and orientation inside the peritoneal cavity and identification of pelvic structures was technically simple. There were no adverse effects or complications over a 2 to 3-week survival period. Postprocedure hysterosalpingograms demonstrated complete occlusion of the fallopian tube with histological evidence of obliteration of the lumen with chronic inflammation and no evidence of abscesses. Furthermore, interventions in the pelvis via a transgastric approach was noted to be technically easier than in other parts of the peritoneal cavity because of the “straight shot” from the gastric wall incision toward the pelvis that eliminates the need for endoscope retroflexion.

**Transgastric pelvic organ resection**

Wagh and colleagues explored the peritoneal cavity and resected the pelvic organs in nine pigs [9]. Endoloops were attached to the mesentry and the fallopian tube resected along with a portion of the uterine horn and ovary. There were no reported complications, and all animals tolerated the procedure well. The same group reported transgastric oophorectomy and tubectomy with an extended survival period of 2 weeks. During this 2-week period there were no adverse clinical events in any animals [68].

**Peritoneal interventions in the intensive care unit**

Patients in the intensive-care setting have multiorgan dysfunction that precludes transportation and major surgical interventions. NOTES may avoid transportation to an operating room, allowing for bedside intervention. One example that has been described in the laboratory is diaphragmatic pacing for patients who are difficult to wean from ventilators [69]. NOTES may become a more practical approach for diagnosing ischemic bowel in the intensive-care patient who has contraindications for more definitive imaging such as CT or magnetic resonance imaging (MRI) [70].

**Acute management of blunt trauma**

The use of NOTES as a method for immediate assessment of organ injury and repair is theoretically possible. Its minimally invasive nature, due to the elimination of an abdominal incision and need for general anesthesia, makes NOTES an attractive approach in the prehospital trauma/disaster setting.

In a preliminary study our group was able to demonstrate the feasibility of NOTES in the assessment of penetrating abdominal injury. We performed a controlled injury to intraabdominal organs (liver, spleen, kidney, and small bowel loops) under laparoscopic guidance using laparoscopic shears. Transgastric peritoneal access was attained using a PEG-like approach by an operator blinded to the sites of organ injury. The peritoneal cavity in all animals was systematically examined, including the anterior abdominal wall, diaphragmatic dome, liver, spleen, and both kidneys. Based on these results, we concluded that NOTES provides rapid and accurate identification of organ injury for penetrating wounds to the abdominal viscera [71].

Our group has also assessed the feasibility of achieving hemostasis after organ injury using nonthermal hemostatic mechanisms, comparing three nonthermal methods of achieving hemostasis. The first group was randomized to QuikClot (QC; Z-Medica, Wallingford, CT), a granular zeolite powder with 1% residual moisture that, when placed on a bleeding wound, adsorbs water in an exothermic reaction, thereby concentrating platelets, erythrocytes, and clotting factors at the site...
of application. It has been tried on the battlefield with excellent success in achieving hemostasis. Several studies, including a swine liver injury model, have also shown its effectiveness as a hemostatic agent in life-threatening bleeding. The second group was randomized to oxidized regenerated cellulose (ORC), which is also used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. The third group of animals was randomized to TC-325, a novel bioabsorbable hemostatic agent (Cook bioengineering prototype material; Cook Medical, Bloomington, IN).

The anterior liver surface was lacerated using a laparoscopic shear to create a grade three (>3 cm) liver laceration and modified endoscopic delivery systems used to deliver the hemostatic agents. The QC granules, ORC, and TC-325 were successfully applied resulting in hemostasis in all animals. These exploratory studies suggest that intraperitoneal hemorrhage might be easily and quickly controlled through endoscopic approaches [72].

**NOTES in autopsies**

A decrease in the number of relatives providing consent to perform a conventional autopsy has resulted in the development of virtual autopsy using CT or MRI-based imaging. There are limitations in the amount of information that can be obtained by imaging modalities. Denzer and colleagues reported a feasibility study of minimally invasive autopsy in 20 deceased subjects using various flexible endoscopic modalities including EUS [73]. Both intra- and extraluminal tissue was examined and biopsies were performed using standard endoscopic accessories. It is plausible that the combination of both cross-sectional imaging and endoscopy will be sufficient to provide the information that heretofore has only been possible by conventional autopsy. As the outer integrity of the deceased is not violated, this method of minimally invasive autopsy may be more acceptable to relatives.

**NOTES: evolving beyond the traditional operating room**

For NOTES to be the real next frontier in endoscopy, endoscopists will need to feel comfortable performing these procedures in a familiar environment, the endoscopy unit. There may be a potential cost reduction since the cost of using an operating room is obviated, as is the use of transportation staff and operating room costs. Hoffman and colleagues performed more than 1000 laparoscopies in an endoscopic unit, demonstrating that minimally invasive procedures can be safely performed outside the operating theatre [74]. The fact that NOTES has the potential to be performed under deep sedation rather than general anesthesia will have great impact in avoiding postoperative ventilator complications, including ventilator dependency. However, whatever facility is used for NOTES, considerations should be made for possible conversion to laparoscopy or open surgery.

**Robots for NOTES**

The concept of deploying a mobile robot via NOTES into the peritoneal cavity may appear very futuristic. This limitation may be solved by using robotics and this technique has been shown to be feasible by Rentschler and colleagues [75]. A 12-mm diameter in vivo robot was advanced into the gastric cavity using a sterile overtube and was able to traverse within the cavity under endoscopic guidance. Using its helical wheel the robot was able to navigate the gastric lumen with no apparent tissue injury. In the peritoneal cavity, the robot successfully navigated and maneuvered several organs, including the liver and small bowel. Development of an in vivo robot with camera and multipurpose arms capable of performing several tasks in addition to endoscopic imaging will enable performance of moderately complex surgery such as cholecystectomy. Furthermore, a robot with visual capabilities will help to overcome the problem of spatial orientation.

**Intrauterine fetal interventions**

Although transabdominal laparoscopic fetoscopy has proven to be a useful technique in human fetal surgery for such diseases as twin–twin transfusion syndrome and spinal meningomyelocele, it only allows anterior access to the uterine cavity and is limited by the use of rigid instrumentation. In addition, the performance of intraperitoneal procedures by the traditional percutaneous route can be followed by wound dehiscence and induce preterm labor. Theoretically, NOTES can provide superior access to the uterine cavity because of its flexibility and because the transgastric route allows a “straight shot” toward the uterus. Moreover, the absence of abdominal wall incision and general anesthesia also provide an added benefit for NOTES. Based on these assumptions, our group has evaluated the feasibility of NOTES for uterine interventions in pregnant sheep. During this acute nonsurvival experiment NOTES allowed visualization of the anterior, posterior, and lateral walls of the uterus. In addition, all intraperitoneal organs could be identified and were easily accessible. Using EUS, the fetus, various body parts, and the placenta could be easily identified. Amniocentesis and intracardiac fetal interventions were technically feasible with the EUS scope in the peritoneal cavity [76].

**Spinal procedures**

Surgical spinal procedures most commonly include transthoracic and posterolateral percutaneous approaches. Open surgical techniques require separation of musculoskeletal structures and traction of nerve roots to create an opening large enough to accommodate surgical tools. The morbidities associated with these surgical approaches include postsurgical neuralgia resulting from traction injuries to nerve roots, lacerations of the dura mater, scars from skin incisions, and muscular atrophy or trauma. Minimally invasive surgical techniques, including thoracoscopy and video-assisted thoracic spine surgery, have reduced the extent of percutaneous incisions and opening of the chest wall. Nevertheless, the consequences of percutaneous
access are not entirely avoided and complications such as lung atelectasis and retropleural effusions from single lung ventilation are additional morbidities [77].

The proximity of the esophagus to the vertebral column and anterior spine in particular may allow for interventions to the thoracic spine. NOTES provides direct anterior access to the vertebral column by transgastric and transesophageal approaches. In addition, the lumbosacral spine could also be approached for anterior endoscopic procedures via transgastric access. This may avoid the morbidity of a traditional anterior or posterior–lateral approach such as postsurgical neuralgia, rib resections, muscular atrophy, and trauma. Magno and colleagues reported the feasibility of transesophageal spinal interventions in four porcine models [78]. There was excellent visualization of the major vessels and anterior thoracic vertebrae and successful bone biopsy was performed.

This unconventional approach to the anterior vertebral column allows the development of novel spinal interventions under direct endoscopic guidance, such as vertebroplasty and kyphoplasty for osteoporotic or pathological vertebral bone fractures, discectomies and interbody fusion for herniated discs, and release of the anterior ligament at different levels of the vertebral column in patients with severe scoliosis. The advantages of NOTES for spinal interventions are similar to those for anterior laparoscopic spinal surgery but without the limitations of rigid instrumentation. These benefits include maintenance and ease of restoration of intervertebral disc height, avoidance of bone removal from the spine (an integral component of posterior spinal surgery), and preservation of normal spinal anatomy because this approach takes advantage of normal tissue planes with no removal of bone tissue.

**NOTES: the road toward clinical applicability**

Laparoscopic surgery has long been dependent on instrument triangulation that obviates internal and external clashing, the judicious placement of ancillary ports for optimized exposure, and the use of rigid operative instruments for secure tissue grasping and dissection. NOTES approaches have to overcome the disadvantage of generally being single incision and therefore inline placement of instruments, which generates clashing, suboptimal exposure, and at times imprecise tissue handling. Hybrid techniques combining laparoscopy with NOTES are currently the best solution. The hybrid approach can provide safe intraperitoneal access along with the essential triangulation and retraction. Once experience is gained, coupled with the development of new accessories, pure NOTES can then be tested against currently available techniques.

Additionally, NOTES must be proven to be safe and effective treatment before it can be widely used in humans. Currently, the uncertainty of optimal site for translumenal access hinders the clinical application of NOTES. Suitable devices and platforms, avoidance of infection, and the reliability of the closure must all be optimized [79].

There is currently not enough data from human studies to make recommendations regarding the training required to safely perform clinical NOTES. Training physicians to perform NOTES will need to incorporate both surgical and advanced endoscopic training. This will result in development of hybrid surgical and endoscopic training programs, blurring traditional borders between specialties and challenging traditional training programs.

NOTES offers the benefit of incisionless surgery, potentially leading to rapid recovery, less postoperative pain, absence of an abdominal wall scar or hernia formation, and fewer adhesions. It may have definite advantages in situations where the transabdominal route is not optimal, such as in patients with marked obesity where the risk of postoperative wound complications is high and in patients with anterior abdominal wall infection or severe scarring.

The true value of NOTES may emerge from shifting the focus of competing directly with currently satisfactory procedures, toward providing novel approaches to difficult problems where satisfactory solutions are currently lacking.

References are available at [www.yamadagastro.com/textbook](http://www.yamadagastro.com/textbook)

**Further reading**


Abdominal radiographs

Abdominal radiographs often play an important role in the evaluation of patients with abdominal pain or distention or clinical signs of an acute abdomen [1]. The purpose of this section is to review radiographic findings such as bowel dilation, pneumoperitoneum, and pneumatosis, and to discuss their significance. However, computed tomography (CT) and magnetic resonance imaging (MRI) are recognized as more sensitive techniques than abdominal radiography for diagnosing a host of conditions in patients with acute abdominal symptoms (see Chapters 147 and 148).

Technique

In patients with acute abdominal findings, both supine and upright radiographs of the abdomen should be obtained. The upright radiographs should be centered to include the diaphragms. This permits assessment of not only free intraperitoneal air beneath the diaphragms but also air-fluid levels within the bowel that can be detected only on horizontal-beam views. If patients are too sick or debilitated to stand, left lateral decubitus views should be obtained instead to detect free air between the liver and the right lateral abdominal wall.

Abnormalities

Bowel dilation

Bowel dilation is usually caused by obstruction or ileus. The small bowel is a more common site of obstruction than the colon. Other patients may develop an adynamic ileus without evidence of mechanical obstruction. These conditions are considered separately in the following sections.

Small bowel obstruction

Because of the increase in abdominal surgery in recent decades, most small bowel obstructions are caused by postoperative intraperitoneal adhesions [1]. Other less common causes include incarcerated hernias, metastases, radiation, Crohn’s disease, intussusception, and gallstone ileus.

In a mechanical small bowel obstruction, supine abdominal radiographs usually reveal multiple loops of dilated small bowel and a paucity of colonic gas (Figure 144.1a); multiple air-fluid levels are almost always seen on upright or decubitus views (Figure 144.1b). Dilated small bowel can usually be differentiated from dilated colon by its more central location in the abdomen as well as the presence of tightly spaced folds or valvulae conniventes that completely traverse the diameter of the bowel.

While advanced small bowel obstructions are easily recognized on abdominal radiographs, the diagnosis can be more difficult in patients who do not swallow a large amount of gas. In such cases, gaseous distention of bowel can be minimal or absent. Nevertheless, accumulation of fluid still occurs, and horizontal-beam views may yet demonstrate numerous air-fluid levels in nondilated bowel. Occasionally, a row of tiny gas bubbles or “string of pearls” may be seen on upright or decubitus radiographs due to small amounts of gas trapped along the
superior margin of small bowel loops almost completely filled with fluid [2]. In patients who swallow virtually no air whatsoever, abdominal radiographs may reveal a gasless abdomen with multiple fluid-filled loops of bowel appearing as tubular or sausage-shaped densities in the bowel that may be indistinguishable from true abdominal masses [2].

A simple mechanical obstruction does not usually cause bowel ischemia. However, a closed-loop obstruction due to an incarcerated hernia, volvulus, or other causes may occasionally produce a strangulating obstruction with ischemia or necrosis of the involved segment of bowel. CT has been recognized as a sensitive technique for detecting strangulation of bowel in patients with closed-loop obstruction [3].

It is important to recognize that advanced cecal carcinomas may obstruct the ileocecal valve, mimicking the radiographic appearance of a distal small bowel obstruction [1]. More distal colonic obstructions may also be masked by an incompetent ileocecal valve that allows gas to reflux from the obstructed colon into the small bowel. A barium enema may be performed on patients with radiographic evidence of a distal small bowel obstruction to rule out an unsuspected colonic carcinoma, particularly when there is no history of prior abdominal surgery.

**Colonic obstruction**

In colonic obstruction, supine abdominal plain radiographs usually reveal disproportionate colonic distention proximal to the obstructing lesion, with air–fluid levels in the dilated bowel on upright radiographs. The transition from dilated to nondilated bowel can often be recognized and most commonly occurs in the sigmoid colon because of an obstructing carcinoma. Primary colonic carcinoma accounts for 80%–90% of all colonic obstructions, but diverticulitis, metastases, and volvulus are other less common causes [1].

The most devastating complication of colonic obstruction is cecal perforation. Because of the high mortality associated with cecal perforation, colonic obstruction should be considered a surgical emergency. In general, a cecal diameter greater than 10–12 cm on abdominal radiographs is thought to be an indication for urgent colonic decompression because of the high risk of perforation [4].

Colonic volvulus should be distinguished from a simple colonic obstruction because it results from twisting of the colon around a fixed point on its mesentery, producing a closed-loop obstruction. The vast majority of cases involve the sigmoid colon or cecum [5]. Sigmoid volvulus is an acquired condition...
that often occurs in elderly patients who have chronic constipation or a high-residue diet [6]. In contrast, cecal volvulus tends to occur in younger patients due to congenital failure of retroperitoneal fixation of the cecum and ascending colon [6]. As a result, the right side of the colon has a persistent mesentery on which a volvulus can take place.

In sigmoid volvulus, abdominal radiographs usually reveal a massively dilated sigmoid colon that extends out of the pelvis into the upper abdomen with some degree of proximal colonic distention (Figure 144.2) [1,7]. In contrast, cecal volvulus usually produces a massively dilated cecum that flips into the left upper quadrant with a single air–fluid level on upright or decubitus horizontal-beam views [1,7]. Because colonic volvulus is a closed-loop obstruction, twisting of the mesentery may compromise the vascular supply of the bowel, leading to strangulation, infarction, and perforation of the involved loop. Early diagnosis is therefore essential so that colonic volvulus can be treated before strangulation occurs.

Because of the risk of cecal perforation in patients with colonic obstruction, a barium enema may be required as an emergency procedure to determine whether an obstruction is present and to delineate the nature and site of the obstructing lesion. Carcinoma of the colon typically manifests as an annular lesion with shelf-like overhanging borders, whereas diverticulitis produces a tapered area of narrowing with intact but distorted mucosal folds. In colonic volvulus, the barium enema reveals a typical “bird-beak” deformity at the site of the volvulus.

**Adynamic ileus**

In patients with an adynamic or paralytic ileus, there is interference with intestinal peristalsis without an actual mechanical obstruction. As a result, supine abdominal radiographs classically show diffusely dilated small and large bowel. Although the degree of distention depends on the degree of air swallowing, horizontal-beam views usually demonstrate air–fluid levels throughout the bowel [8]. However, for reasons that are unclear, abdominal radiographs sometimes reveal an isolated small bowel or colonic ileus. In such cases, the findings may be indistinguishable radiographically from a mechanical small bowel or colonic obstruction [1,8]. Ogilvie’s syndrome (also known as colonic pseudoobstruction) is characterized by acute colonic dilatation in the absence of mechanical obstruction in severely ill patients. It is a potentially life-threatening condition that can lead to massive cecal distention, resulting in ischemia, necrosis, and perforation. When the colon appears dilated, the presence

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**Figure 144.2** Sigmoid volvulus. (a) Supine abdominal radiograph shows a massively dilated sigmoid colon rising out of the pelvis into the abdomen. (b) Right lateral decubitus radiograph shows long air–fluid levels in both limbs of this dilated sigmoid loop. Source: Levine 1985 [1]. Reproduced by permission of Elsevier.
of a significant amount of rectal gas on left lateral views of the rectum should favor an ileus [9]. If it is unclear whether the patient has a distal colonic obstruction or an ileus, a single-contrast barium enema may be performed to differentiate these conditions.

**Pneumoperitoneum**

Upright chest and abdominal radiographs and left lateral decubitus radiographs of the abdomen are extremely sensitive for detecting free intraperitoneal air (i.e., pneumoperitoneum) and may demonstrate collections of intraperitoneal air as small as 1 mL [10]. In patients with an acute abdomen, the presence of free air (in the absence of a recent laparoscopic procedure involving peritoneal insufflation) almost always indicates a perforated viscus with subsequent peritonitis. The most common cause is a perforated duodenal ulcer [1]. Colonic perforation due to ischemic bowel disease, toxic megacolon, and diverticulitis is much less common but should be suspected in any patient with pneumoperitoneum and colonic distention on abdominal radiographs [11].

Pneumoperitoneum can readily be documented on upright chest radiographs or upright or left lateral decubitus radiographs of the abdomen by the presence of free intraperitoneal air directly beneath the diaphragms (Figure 144.3a) or between the liver and the right lateral abdominal wall. Unfortunately, some patients are too ill or debilitated to stand or lay on their side; supine abdominal radiographs may be the only images obtained in these patients. However, pneumoperitoneum can be recognized on supine radiographs by the presence of air on both sides of the bowel wall (Rigler's sign) (Figure 144.3b), by linear or triangular collections of gas in the subhepatic space, or by air outlining the falciform ligament as a linear density in the right upper quadrant [1,2]. In one study, one or more signs of free intraperitoneal air were present on supine abdominal radiographs in 59% of patients with pneumoperitoneum [12].

**Pneumatosis**

In patients with intestinal ischemia or necrosis, gas may dissect into the wall of the affected bowel, producing intramural bowel gas or pneumatosis. This finding is recognized on abdominal radiographs by mottled or linear gas shadows that have a characteristic radiographic appearance (Figure 144.4) [1,13]. CT has been recognized as a more sensitive technique than abdominal radiography for detecting pneumatosis [14]. It has classically been taught that the presence of pneumatosis indicates bowel infarction in the clinical setting of intestinal ischemia. However, studies have shown that pneumatosis can be detected on CT in patients with ischemic bowel disease who have viable bowel with partial mural ischemia rather than transmural infarction, so these individuals sometimes may recover without surgery [15,16].

In patients with intestinal necrosis, tiny, linear, peripherally branching gas shadows may occasionally be identified over the liver due to gas within the portal venous system [13]. This

![Figure 144.3 Pneumoperitoneum. (a) Upright chest radiograph shows large amounts of free intraperitoneal air beneath the diaphragm in this patient with a perforated duodenal ulcer. (b) Supine abdominal radiograph in a different patient shows an indirect sign of pneumoperitoneum with air on both sides of the bowel wall (Rigler sign) (arrows) following inadvertent perforation at colonoscopy. Source: Levine 1985 [1]. Reproduced by permission of Elsevier.](image)
studies utilize a smaller amount of high-density barium and gas to evaluate the en face appearance of the mucosal surface. As a result, double-contrast techniques have dramatically improved the radiologist’s ability to diagnose a variety of inflammatory and neoplastic diseases throughout the gastrointestinal tract. A major advantage of these techniques is their ability to demonstrate superficial mucosal abnormalities that cannot easily be recognized on conventional single-contrast examinations. In some cases, double-contrast studies may detect lesions that are missed or misinterpreted at endoscopy. Double-contrast radiography is less invasive and usually less expensive than endoscopy. Thus, it is a valuable technique for evaluating patients with suspected gastrointestinal disease.

**Pharynx**

**Indications**

With increased survival of the elderly, pharyngeal disorders have become an increasingly frequent problem in modern medical practice. Approximately 35% of nursing home patients have some form of swallowing dysfunction [17]. Resultant aspiration pneumonia and choking are particularly common causes of morbidity and mortality. Radiographic examination of the pharynx is now recognized as a valuable tool in the diagnostic workup of this large group of patients with pharyngeal disorders.

Contrast studies of the pharynx are most frequently performed on patients who have difficulty swallowing. However, disorders of the pharynx may also manifest by respiratory and speech problems. Laryngeal penetration or overflow aspiration may lead to recurrent pneumonia, asthma, chronic bronchitis, coughing, or choking. In other patients, soft-palate insufficiency may result in nasal regurgitation or may give the voice a nasal quality. A pharyngoesophagram may be helpful in patients who have a wide spectrum of respiratory, speech, and swallowing difficulties. Barium studies are also useful in assessing pharyngeal function and morphology in patients with a history of neuromuscular disease, stroke, pharyngeal tumor, or prior head and neck surgery or radiation.

**Normal anatomy**

The pharynx is a complex muscular tube suspended superiorly from the skull base and styloid process, posteriorly from the cervical spine, and anteriorly from the mandible and hyoid bone. At least 26 muscles and six cranial nerves participate in pharyngeal function [18,19].

The pharynx can be arbitrarily divided into three portions: the nasopharynx, oropharynx, and hypopharynx. The soft palate separates the nasopharynx from the oropharynx, and the pharyngoepiglottic fold separates the oropharynx from the hypopharynx. The tongue forms the anterior wall of the oropharynx. The larynx, with its associated epiglottic, thyroid, cricoid, and arytenoid cartilages, forms the anterior wall of the hypopharynx. This laryngeal complex often protrudes into the lower hypopharynx as an apparent mass.
The mucosal surface of the pharynx is thrown into a series of folds by underlying lymphoid and muscular tissue. The vertical surface of the base of the tongue often has a nodular appearance due to the circumvallate papillae and lingual tonsil. Nodular lymphoid tissue or linear webs may also interrupt the normally smooth surface of the valleculae. Although the anterior border of the hypopharynx usually has a smooth contour, close apposition of the longitudinal muscles of the pharynx to the overlying squamous mucosa results in longitudinal striations of the lateral and posterior walls of the hypopharynx [16]. Horizontal mucosal striations are seen in the redundant mucosa overlying the arytenoid processes and cricoid cartilages [19].

**Technique**

Complete radiographic examination of the pharynx includes a cine or video pharyngoesophagogram to evaluate motility and a series of spot images to evaluate morphology [20–22]. In patients with suspected foreign body, fistula, or abscess, frontal and lateral radiographs of the neck should also be obtained.

The barium study is initially performed with a high-density barium suspension for optimal visualization of the pharynx. The patient is asked to swallow barium in frontal, lateral, and, in some cases, oblique projections. A video recording of each swallow permits a frame-by-frame or slow-motion analysis of the various parameters of deglution. Movement of the tongue, soft palate, and epiglottis as well as laryngeal closure and cricopharyngeal opening are best evaluated in the lateral projection. However, symmetry of tongue motion, pharyngeal peristalsis, and epiglottic tilt are best evaluated in the frontal projection.

After individual swallows of barium, double-contrast spot images of the pharynx are obtained in frontal and lateral projections. The spot images are obtained during suspended respiration and during a modified Valsalva maneuver or phonation to optimally distend the pharynx [23]. The frontal view is best for demonstrating the contours of the valleculae and piriform sinuses, the lateral walls of the tonsillar fossae and hypopharynx, and the superior border of the base of the tongue. The lateral view is best for demonstrating the inferior border of the base of the tongue, the soft palate, the posterior pharyngeal wall, the anterior hypopharyngeal wall, the epiglottis, and the cricopharyngeus.

After the pharyngeal examination has been completed, upright double-contrast and prone single-contrast views of the esophagus are obtained to rule out associated esophageal disease.

**Abnormalities**

**Laryngeal penetration and aspiration**

Laryngeal penetration occurs when barium enters the laryngeal vestibule during swallowing. Penetration may be limited to the region of the subepiglottic space or may extend as far as the true vocal cords or trachea. Laryngeal penetration occurs because of poor timing of oral and pharyngeal events associated with swallowing or pharyngeal dysmotility due to neuromuscular disorders such as amyotrophic lateral sclerosis, multiple sclerosis, or cerebrovascular accidents. Inflammatory or neoplastic diseases that restrict pharyngeal motility may also cause penetration. One study found that patients with epiglottic carcinoma may present with signs and symptoms of aspiration because of decreased epiglottic excursion when this structure is involved by tumor [24].

Aspiration occurs when barium enters the laryngeal vestibule during normal breathing. Aspiration results from stasis and retention of pharyngeal contents because of tumor, diverticula, or neuromuscular disease in the pharynx. Aspiration may also be caused by gastroesophageal reflux or reflux of esophageal contents above an obstructing esophageal lesion such as a stricture or carcinoma. Penetration is primarily associated with dysmotility, whereas aspiration is associated with stasis. Some patients can have “silent” tracheobronchial aspiration that fails to elicit a cough reflex. It has been shown that the risk of developing aspiration pneumonia correlates directly with the degree of pharyngeal dysfunction on barium studies [25].

Video pharyngoesophagrams have increasingly been performed in conjunction with speech therapists as a joint procedure known as a modified barium swallow. When laryngeal penetration or tracheobronchial aspiration occurs during the study, the speech therapist will employ bariums of different viscosity (including nectar, honey, and pudding viscosity) as well as various compensatory maneuvers (e.g., swallowing with the head turned to one side or in a chin-tuck position) to prevent or minimize penetration or aspiration in patients with underlying swallowing dysfunction.

**Cricopharyngeal prominence**

The pharyngoesophageal segment, the radiographic equivalent of the manometrically defined upper esophageal sphincter (UES), is formed in conjunction with speech therapists as a joint procedure. During swallowing, a prominent cricopharyngeus appears as a smooth, 1 cm high, bar-like protrusion of the posterior pharyngeal wall into the barium column on lateral projections (Figure 144.5). The cricopharyngeus may show delayed opening, incomplete opening, or early closure. A prominent cricopharyngeus is detected on barium studies in about 5% of asymptomatic individuals [28,29]. However, some patients with this finding complain of dysphagia. In symptomatic patients, a prominent cricopharyngeus is often associated with pharyngeal paresis or occurs as a compensatory response to gastroesophageal reflux or esophageal obstruction.
barium collections or rings anteriorly in the upper hypopharynx just below the hyoid bone. In contrast, lateral pharyngeal diverticula appear as persistent protrusions in these areas.

**Zenker diverticulum**

Zenker diverticulum or posterior hypopharyngeal diverticulum is an acquired mucosal herniation through an area of anatomical weakness in the region of the cricopharyngeus (i.e., dehiscence of Killian). This area of anatomical weakness is located between the thyropharyngeus and cricopharyngeus or between the oblique and horizontal fibers of the cricopharyngeus [26,27]. Most patients with Zenker diverticulum have an associated hiatal hernia or gastroesophageal reflux. Rarely, these diverticula are complicated by ulceration or malignancy.

During swallowing, a Zenker diverticulum appears radiographically as a posterior bulging of the distal pharyngeal lumen above an anteriorly protruding cricopharyngeal bar (Figure 144.6a). At rest, the barium-filled diverticular sac often extends below the level of the cricopharyngeus posterior to the proximal cervical esophagus (Figure 144.6b).

**Inflammatory conditions**

Barium studies are of limited value in patients with viral, bacterial, or fungal infection of the pharynx [31]. Such patients usually have normal pharyngograms or nonspecific lymphoid hyperplasia of the palatine tonsil or base of the tongue. Occasionally, however, *Candida* or herpes pharyngitis may be manifested on double-contrast radiographs by plaques or ulcers in the pharynx, particularly in patients with acquired immunodeficiency syndrome (AIDS). Barium studies may also be helpful in a patient who has a chronic sore throat in order to determine whether there is underlying gastroesophageal reflux or reflux esophagitis.

**Tumors**

Double-contrast pharyngography has an important role in the initial detection and subsequent workup of pharyngeal tumors [32,33]. Double-contrast radiographs of the pharynx can accurately define the size, level, and extent of the lesion. Radiological examination is particularly helpful in demonstrating regions of the pharynx (e.g., valleculae, lower hypopharynx, cricopharyngeus) that are difficult to visualize at endoscopy. It also enables detection of submucosal masses that are easily missed at endoscopy. Although its accuracy is limited in the region of the palatine tonsils, the double-contrast examination is capable of detecting more than 95% of all mucosal neoplasms in the pharynx below the level of the pharyngoepiglottic fold [32].

Squamous cell carcinoma is by far the most common malignant tumor of the pharynx. With an overall 5 year survival rate of approximately 20%, this tumor has a somewhat better prognosis than esophageal carcinoma. These lesions may be manifested on double-contrast radiographs by an intraluminal mass, mucosal irregularity, or loss of distensibility [34]. An intraluminal mass may cause asymmetry or obliteration of the

**Lateral pharyngeal pouches and diverticula**

Lateral pharyngeal pouches are transient protrusions of the lateral pharyngeal wall at sites of anatomical weakness, such as the posterior thyrohyoid membrane and tonsillar fossae after a tonsillectomy [30]. These pouches are common findings, usually occurring as normal variants in asymptomatic patients. In contrast, lateral pharyngeal diverticula are persistent protrusions from the tonsillar fossae or region of the thyrohyoid membrane. These diverticula are much less common than pharyngeal pouches, occurring primarily in individuals who have markedly elevated pharyngeal pressure, such as glassblowers and tuba players. If stasis occurs in pharyngeal pouches or diverticula, subsequent spillage of pouch contents into the hypopharynx may result in aspiration into the larynx or tracheobronchial tree. Stasis with delayed spill into the hypopharynx may also cause mild neck discomfort or dysphagia after swallowing. Diverticula may also be manifested by neck masses and may occasionally be sites of ulceration or neoplasia.

Lateral pharyngeal pouches appear on frontal views as transient hemispheric protrusions of mucosa in the upper hypopharynx above the calcified edge of the thyroid cartilage. These pouches can be recognized on lateral views as transient ovoid
normal pharyngeal contour, barium-coated lines in unusual locations, or a superimposed radiodensity. Mucosal irregularity may be manifested by an irregular, lobulated, nodular, or granular surface pattern. Loss of distensibility may be associated with fixation of pharyngeal structures by infiltrating tumor. When malignant lesions are detected in the pharynx, the esophagus should be carefully evaluated radiographically because of the increased incidence of synchronous esophageal cancers in these patients [35].

**Upper gastrointestinal tract**

The development of routine double-contrast techniques for examining the upper gastrointestinal tract has dramatically improved our ability to diagnose a variety of inflammatory and neoplastic diseases in the esophagus, stomach, and duodenum. Despite increasing acceptance of this technique, some investigators advocate endoscopy as the initial screening study in patients with dyspepsia or other upper gastrointestinal symptoms. Although endoscopy has been recognized as a highly accurate technique for examining the upper gastrointestinal tract, it is also an invasive technique with a small risk of gastrointestinal perforation or other complications. Furthermore, it is an expensive technique, costing three to four times more in the United States than double-contrast upper gastrointestinal examinations. Because barium studies are safer and less expensive than endoscopy, radiological evaluation of the upper gastrointestinal tract remains a viable alternative as long as the fluoroscopist has the expertise needed to obtain examinations with an accuracy approaching that of endoscopy for clinically significant disease.

**Technique**

The routine double-contrast upper gastrointestinal examination should be performed as a biphasic study in which double-contrast and single-contrast views of the esophagus, stomach, and duodenum are obtained [36]. In the double-contrast portion of the study, a series of maneuvers is required to achieve adequate gaseous distention of the lumen while a thin layer of high-density barium is spread on the mucosa. The double-contrast examination is facilitated by the use of pharmacological agents (e.g., glucagon 0.1 mg intravenously) to induce gastric hypotonia. After the double-contrast portion of the study has been completed, prone or upright single-contrast views of the esophagus, stomach, and duodenum are obtained with a low-density barium suspension and various degrees of compression to supplement the double-contrast study. Because of its greater diagnostic yield, this biphasic study has been advocated as the

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**Figure 144.6**  
(a) Zenker diverticulum seen as a posterior outpouching of the hypopharyngeal wall (white arrows) above a prominent cricopharyngeus (black arrow) during swallowing.  
(b) A frontal view shows retention of barium in the diverticulum (arrow) at completion of the swallow.
best radiological technique for examining the upper gastrointestinal tract.

**Indications**

**Esophagus**

In patients with reflux symptoms, barium studies have traditionally been advocated to document the presence of a sliding hiatal hernia or gastroesophageal reflux, to detect complications such as strictures, and to exclude other abnormalities in the esophagus that can mimic reflux esophagitis. However, by permitting a more detailed assessment of the esophageal mucosa, double-contrast radiographic techniques have made it possible to detect superficial ulceration and other changes of esophagitis before the development of deep ulcers and strictures.

Because modern medical care is prolonging the survival of immunocompromised patients, infectious esophagitis has become an increasingly frequent problem. When infectious esophagitis is suspected on clinical grounds, double-contrast esophagography may be performed to confirm the diagnosis and differentiate the various underlying organisms. Dysphagia is an important indication for performing barium studies. If the sensation of dysphagia is localized to the pharynx, a careful pharyngeal examination should be obtained. However, some lesions involving the distal esophagus or cardia may cause dysphagia that is referred to the upper esophagus or even the pharynx. Thus, the gastric cardia and esophagus should be carefully evaluated radiographically in all patients with unexplained pharyngeal dysphagia to rule out a distal lesion masquerading as a pharyngeal disorder.

**Stomach and duodenum**

The most common indications for performing a double-contrast examination of the stomach and duodenum include epigastric pain or discomfort, bloating, belching, early satiety, and signs or symptoms of upper gastrointestinal bleeding such as hematemesis, melena, and guaiac-positive stool. If gastritis, duodenitis, duodenal ulcers, or unequivocally benign-appearing gastric ulcers are diagnosed radiographically, the patient may be able to be treated medically without need for endoscopic intervention. However, if the double-contrast examination demonstrates a gastric ulcer or other lesion that is equivocal or suspicious for malignancy, endoscopy and biopsy should be performed for a more definitive diagnosis. If the double-contrast examination is normal, the decision for endoscopy should be based on the severity of symptoms, age, and overall health of the patient.

**Contraindications and risks**

Because oral barium sulfate is contraindicated in patients with suspected esophageal or gastric perforation, water-soluble contrast agents should be used if there are clinical or radiographic signs of mediastinitis or peritonitis. Otherwise, the risks of the barium study are negligible. Nevertheless, a double-contrast examination may be difficult to perform on elderly or debilitated patients who cannot undergo the turning maneuvers required for this examination. These patients may be evaluated instead by conventional single-contrast barium studies.

**Abnormalities**

**Gastroesophageal reflux disease**

In patients with suspected gastroesophageal reflux disease, barium studies may be performed not only to detect gastroesophageal reflux but also to look for the morphological sequelae of reflux, including reflux esophagitis, peptic strictures, and Barrett esophagus. Conventional single-contrast esophagography has been considered an unreliable technique for diagnosing reflux esophagitis, with an overall sensitivity of only 50%–75% reported in the literature. However, the use of double-contrast esophagography has increased the radiographic sensitivity to almost 90% [37]. The single most common sign of mild reflux esophagitis on double-contrast studies is the presence of a nodular or granular mucosa due to mucosal edema and inflammation [36–38]. Other patients may have shallow ulcers and erosions appearing as one or more tiny collections of barium in the distal esophagus near the gastroesophageal junction (Figure 144.7). In more severe disease, the esophagus may have a grossly irregular contour, with serrated margins and decreased distensibility due to extensive ulceration, edema, and spasm.

Scarring from reflux esophagitis can lead to the development of reflux-induced or peptic strictures, most commonly seen as tapered areas of concentric narrowing in the distal esophagus above a hiatal hernia. Less frequently, peptic strictures may appear as ring-like areas of narrowing that can be difficult to differentiate from Schatzki rings [40].

Barrett's esophagus is a well-recognized complication of reflux esophagitis that is associated with a significantly increased risk of developing esophageal adenocarcinoma. Unfortunately, the classic radiological features of Barrett's esophagus (i.e., a high esophageal stricture or ulcer or a reticular mucosal pattern) occur in only a minority of patients [41]. However, data suggest that patients without reflux esophagitis or peptic strictures on double-contrast examinations rarely have Barrett's esophagus at endoscopy [42]. Thus, double-contrast esophagography may be a useful screening study for Barrett's esophagus to determine the relative need for endoscopy and biopsy in patients with reflux symptoms.

**Infectious esophagitis**

Esophagography has traditionally been considered an unreliable technique for diagnosing Candida esophagitis, with an overall sensitivity of less than 50%. With double-contrast techniques, however, esophagography has a sensitivity as high as 90% in diagnosing Candida esophagitis [43]. The major advantage of this technique is its ability to demonstrate mucosal plaques that cannot easily be recognized on conventional single-contrast studies. These discrete plaque-like lesions tend to be longitudinally oriented, appearing on double-contrast radiographs as linear or irregular filling defects with normal intervening mucosa (Figure 144.8a).
Patients suffering from advanced AIDS can develop a more fulminating form of *Candida* esophagitis, manifested by a "shaggy" esophagus with a grossly irregular contour due to multiple plaques, pseudomembranes, and ulcers (Figure 144.8b) [44]. Because this degree of esophagitis rarely occurs in other immunocompromised patients, the possibility of AIDS should be suspected when a shaggy esophagus is detected on barium studies. Herpes and, less frequently, cytomegalovirus (CMV) esophagitis also occur in immunocompromised patients with odynophagia; these conditions should be suspected in the same clinical setting as *Candida* esophagitis. More than 50% of patients with herpes esophagitis have discrete superficial ulcers on the esophageal mucosa that are readily detected on double-contrast radiographs (Figure 144.9a) [45]. In contrast, CMV esophagitis, which occurs primarily in patients with AIDS, is often manifested by the development of one or more large, relatively flat ulcers in the esophagus [44].

Human immunodeficiency virus (HIV) itself has also been associated with the development of giant esophageal ulcers in HIV-positive patients with odynophagia. The lesions typically appear radiographically as giant flat ulcers indistinguishable from those caused by CMV [46]. Because HIV-related ulcers may respond dramatically to treatment with oral steroids, endoscopy is required to differentiate HIV from CMV infection in the esophagus before initiating treatment.

**Eosinophilic esophagitis**

Eosinophilic esophagitis is an inflammatory condition characterized by intraepithelial eosinophilia, typically developing in young men and children with long-standing dysphagia and occasional food impactions. These patients often have an atopic history, asthma, or peripheral eosinophilia. The diagnosis is confirmed on endoscopic biopsy specimens from the esophagus showing a high number of intraepithelial eosinophils. Affected individuals often respond to treatment with steroids, especially inhaled steroid preparations. Barium studies may reveal esophageal strictures, a variable number of distinctive ring-like indentations (producing a so-called "ringed esophagus") [47], or
They may be plaque-like lesions or small sessile polyps with smooth or slightly lobulated contours. Other superficial spreading carcinomas may manifest radiographically by tiny coalescent nodules or plaques, causing localized nodularity or granularity of the mucosa. In contrast, advanced esophageal carcinomas appear as polypoid, ulcerated, or infiltrating lesions with mass effect, ulceration, or irregular narrowing of the lumen.

Some authors believe that endoscopy is warranted for all patients with dysphagia who have negative esophagograms because of the risk of missing esophageal cancer on barium studies. However, in one study, carcinoma of the esophagus or esophagogastric junction was diagnosed or suspected on double-contrast esophagography in 96% of patients with proven cancers. In the same study, endoscopy was recommended to rule out malignant tumors of the esophagus or esophagogastric junction in only about 1% of all patients who had barium examinations. Thus, a high sensitivity can be achieved in the radiographic diagnosis of these tumors without need for endoscopy.

long-segment narrowing of most or all of the thoracic esophagus (producing a so-called “small-caliber esophagus”) (Figure 144.9b) [48]. The ringed esophagus and small-caliber esophagus are radiographic findings that are highly suggestive of eosinophilic esophagitis.

\textit{Esophageal carcinoma}

Esophageal carcinoma is a deadly disease with an overall 5 year survival rate of only 5%–10%. This dismal prognosis is primarily related to the advanced stage of the disease at the time of clinical presentation. However, occasionally esophageal cancer may be discovered at an early stage. Unlike advanced esophageal carcinoma, early esophageal cancer is a readily curable lesion with reported 5 year survival rates approaching 90%. In Western countries, detection of these lesions is best accomplished by some form of radiological or endoscopic surveillance of patients known to be at increased risk for developing esophageal cancer.

Early esophageal cancers classically appear on double-contrast esophagrams as protruded lesions less than 3.5 cm in diameter [36]. They may be plaque-like lesions or small sessile polyps with smooth or slightly lobulated contours. Other superficial spreading carcinomas may manifest radiographically by tiny coalescent nodules or plaques, causing localized nodularity or granularity of the mucosa [36]. In contrast, advanced esophageal carcinomas appear as polypoid, ulcerated, or infiltrating lesions with mass effect, ulceration, or irregular narrowing of the lumen.

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**Erosive gastritis**

Gastric erosions may be classified radiographically as complete or incomplete erosions. Most patients have complete or varioliform erosions in which a punctate or slit-like collection of barium is surrounded by a radiolucent halo of edematous mucosa (Figure 144.10a) [50]. Varioliform erosions are most commonly found in the gastric antrum and are often aligned on the crests of the rugal folds. In the majority of patients, this finding is caused by ingestion of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) [51]. In contrast, incomplete or “flat” erosions appear as dots or streaks of barium without an edematous halo. Because the surrounding mucosa is normal, incomplete erosions have been extremely difficult to detect radiographically, accounting for less than 5% of all erosions seen on double-contrast studies.

Although erosions caused by aspirin or other NSAIDs are usually located in the gastric antrum, they sometimes occur in the gastric body, appearing as distinctive linear or serpiginous erosions that tend to be clustered together on or near the greater curvature (Figure 144.10b) [52]. In such cases, it has been postulated that these erosions result from localized mucosal injury as the dissolving tablets collect by gravity in the most dependent portion of the stomach.

**Helicobacter pylori gastritis**

*Helicobacter pylori* gastritis can be diagnosed on barium studies by the presence of thickened folds or thickened polypoid folds in the antrum, body or, less commonly, fundus of the stomach [51,53]. It is important to recognize that fold thickening is a nonspecific radiographic finding. Nevertheless, *H. pylori* gastritis should be a leading consideration in the differential diagnosis of thickened gastric folds (particularly in the gastric antrum) in patients with dyspepsia, epigastric pain, or other upper gastrointestinal symptoms [51].

Patients suspected of having peptic ulcer disease could be evaluated by a noninvasive *H. pylori* test combined with a double-contrast upper gastrointestinal examination. If the barium study reveals a duodenal ulcer or a benign-appearing gastric ulcer, a noninvasive *H. pylori* test could be performed to determine whether antibiotic therapy should be initiated as well as conventional antiulcer therapy. Such an approach might avoid the need for endoscopy in many symptomatic patients.

**Gastric ulcers**

In the past, some researchers have advocated endoscopy and biopsy of all radiographically diagnosed gastric ulcers to rule out cancer in these patients. However, several studies have found that virtually all gastric ulcers with an unequivocally benign appearance on double-contrast upper gastrointestinal examinations are benign lesions [54,55]. In these studies, about two-thirds of all benign ulcers had a benign radiographic appearance. As a result, unnecessary endoscopy could be avoided in the initial evaluation of most gastric ulcers diagnosed on double-contrast examinations. Instead, typically benign gastric ulcers could be followed radiographically to complete healing without need for endoscopic intervention.

Benign gastric ulcers classically appear en face as round or ovoid collections of barium, often surrounded by a smooth mound of edema or thin straight folds that radiate directly to the edge of the ulcer crater [55]. When viewed in profile, benign ulcers project beyond the contour of the adjacent gastric wall and are sometimes associated with an ulcer mound or collar. In contrast, malignant gastric ulcers classically appear en face as irregular ulcer craters within a discrete tumor mass, sometimes associated with nodularity or clubbing of adjacent folds due to
infiltration of the folds by tumor. When viewed in profile, malignant ulcers project inside the gastric lumen within a tumor mass that forms acute angles with the adjacent gastric wall rather than the obtuse, gently sloping angles expected for a benign mound of edema.

Most gastric ulcers detected on double-contrast studies are less than 1 cm in diameter [55]. Although some benign ulcers are round and symmetric, others have a rod-shaped or linear appearance. Almost all benign ulcers occur in the antrum or body of the stomach, and most are located on the lesser curvature or posterior wall (Figure 144.11) [55]. Occasionally, benign gastric ulcers may be found on the greater curvature of the distal stomach. The latter ulcers are almost always caused by ingestion of aspirin [55]. As these aspirin-induced greater curvature ulcers enlarge, they have a tendency to penetrate inferiorly into the gastrocolic ligament, occasionally leading to the development of gastrocolic fistulae [56].

Ulcer healing may be manifested radiographically by a decrease in the size of the ulcer and by a change in its shape. In most cases, ulcer healing produces a radiographically visible scar with a central pit or depression, radiating folds, or retraction of the adjacent gastric wall [55].

**Gastric carcinoma**

Gastric carcinoma has a relatively poor prognosis, with 5 year survival rates of only 10%–30%. Advanced tumors may appear radiographically as polypoid or infiltrating lesions or, less frequently, as scirrhous lesions with diffuse narrowing of the stomach, producing a linitis plastica appearance [57]. In contrast, early gastric cancer is a curable disease, with reported 5 year survival rates as high as 95%. The Japanese have developed an elaborate system for classifying these tumors based on whether they are predominantly elevated, flat, or depressed lesions. Unfortunately, most patients in the United States with gastric carcinoma already have advanced lesions at the time of clinical presentation. As a result, early gastric cancer is unlikely to be detected on double-contrast studies or endoscopy as long as these examinations are performed predominantly on symptomatic patients [58].

The average sensitivity of single-contrast barium studies for the diagnosis of gastric carcinoma has only been about 75% [59]. Concern about missing gastric cancers on barium studies has therefore been used as a rationale for performing endoscopy as the initial diagnostic test in patients with upper gastrointestinal signs or symptoms. However, in one study, gastric carcinomas were diagnosed or suspected on double-contrast examinations in 96% of patients with proven lesions [59]. In a separate part of the study, only 3.5% of all patients who had double-contrast examinations during this period underwent endoscopy because of findings that were equivocal or suspicious for gastric carcinoma. Thus, a high sensitivity can be achieved in the radiographic diagnosis of gastric cancer while referring only a small percentage of symptomatic patients for endoscopy.

**Gastric lymphoma**

It is well recognized that chronic *H. pylori* gastritis leads to the development of mucosa-associated lymphoid tissue (MALT) in the stomach. This lymphoid tissue is thought to be the precursor of low-grade B-cell gastric MALT lymphomas which, if untreated, may undergo transformation to more high-grade lymphomas [60]. Gastric MALT lymphomas can sometimes be recognized on double-contrast upper gastrointestinal examinations by variably sized, rounded, often confluent nodules in the stomach (Figure 144.12) [61]. However, focal gastritis due to *H. pylori* or other causes may produce similar findings, so that endoscopic biopsy specimens are required for a definitive diagnosis. In contrast, advanced gastric lymphoma may be manifested on barium studies by thickened folds, multiple submucosal
masses, centrally ulcerated bull’s-eye lesions, or giant cavitated lesions [62].

Other gastric tumors
Gastrointestinal stromal tumors (GISTs) are the most common benign submucosal tumors found in the stomach. These tumors usually appear on barium studies as smooth submucosal masses (with or without central ulceration) that form right angles or slightly obtuse angles with the adjacent gastric wall [36]. Most benign GISTs are less than 3 cm in diameter. In contrast, malignant GISTs usually appear as larger, more lobulated submucosal masses, often containing one or more ulcers or giant areas of cavitation [62]. Ectopic pancreatic rests are usually located on the greater curvature of the distal antrum, appearing as small submucosal masses, sometimes with central umbilication or ulceration [36]. Rarely, barium may reflux into rudimentary ductal structures. Gastric carcinoids may also be manifested on barium studies by one or more small submucosal masses, occasionally containing central ulcers.

Duodenitis
Duodenitis may be manifested radiographically by thickened folds, mucosal nodules, erosions, or deformity of the bulb [63]. Duodenal erosions are detected less frequently than gastric erosions on double-contrast studies because of difficulty differentiating these lesions from normal mucosal pits. However, erosive duodenitis can be diagnosed when double-contrast radiographs reveal central barium collections surrounded by radiolucent halos of edematous mucosa.

Duodenal ulcers
Unlike gastric ulcers, which occur primarily on the lesser curvature or posterior wall of the stomach, as many as 50% of duodenal ulcers are located in the anterior wall [36]. Because most double-contrast radiographs are obtained with the patient in a supine or supine oblique position, the anterior wall of the duodenum is not optimally coated with barium, and anterior wall ulcers can be missed on the double-contrast portion of the study. For this reason, double-contrast views of the duodenum should be supplemented with prone compression views obtained with a low-density barium suspension to demonstrate ulcers on the anterior wall. Thus, the biphasic technique is particularly important for evaluating the duodenum.

Small bowel
At many institutions, the conventional small-bowel follow-through examination consists of a series of overhead abdominal radiographs supplemented by spot images of the terminal ileum. Unfortunately, this technique is extremely unreliable in detecting pathology in the small bowel, as a host of morphologic abnormalities may be obscured on the overhead radiographs by overlapping loops of small bowel in the abdomen. A properly performed small-bowel follow-through therefore should include periodic fluoroscopic spot imaging of the jejunum and ileum with manual palpation to separate overlapping loops of small bowel and demonstrate abnormalities easily missed on the overhead radiographs. With this technique, the barium study can be a useful test for showing a variety of findings in patients with small bowel disease. Much less frequently, enteroclysis (i.e., a small-bowel enema) may be performed as a more detailed technique for detecting subtle small-bowel abnormalities. However, these techniques require time, effort, and interest by the radiologist. Barium studies of the small bowel therefore should be requested only if there are substantial clinical indications of small-bowel disease.

Techniques
Small-bowel follow-through
The dedicated or fluoroscopic small-bowel follow-through includes overhead radiographs but uses fluoroscopy as the primary means of examining the small bowel. Unless contraindicated, metoclopramide (20 mg) is sometimes administered orally 20 minutes before the examination to accelerate transit of barium through the stomach and small bowel. The patient then ingests 500–600 mL of an appropriate 35%–40% (weight/volume) suspension of barium sulfate. After a brief examination of the upper gastrointestinal tract, intermittent fluoroscopy is performed until all small bowel loops have been demonstrated. Periodic spot images are obtained to document the fluoroscopic findings.

Enteroclysis (small-bowel enema)
A more detailed study of the entire small bowel may be performed by enteroclysis [64]. If not contraindicated, the patient swallows 20 mg of metoclopramide to accelerate small-bowel transit. Surface anesthesia to the throat precedes intubation of the distal duodenum or proximal jejunum. Between 200 mL and 250 mL of a 75%–80% suspension of barium is then injected, followed by infusion of 1–2 L of a 0.5% solution of methylcellulose in water. These biphasic examinations first demonstrate the small bowel in single contrast (Figure 144.13a) and then in lumen-distended double contrast (Figure 144.13b). The radiologist must be present throughout the study to assess individual bowel loops by graded compression and to document the fluoroscopic findings with spot images. An overhead radiograph of the entire small bowel completes the examination.

Techniques
Small-bowel follow-through (SBFT)
The major advantage of an SBFT is that it does not require intubation. Transit acceleration by oral metoclopramide facilitates the examination by decreasing flocculation of barium and the time needed to perform the study. However, optimal distention of the bowel lumen cannot be achieved by this technique. The SBFT is an appropriate examination for evaluating established diseases of the small bowel, such as Crohn’s disease. It is also adequate for investigating pathological conditions not associated with luminal distention such as radiation enteritis,
Meckel diverticulum: increased luminal distention greatly improves its detection rate [66].

Normality: enteroclysis is the most reliable radiological examination for establishing morphological normality of the small bowel.

**Abnormalities**

**Small-bowel obstruction**

Concern has been expressed regarding the possible inspissation of barium within obstructed small bowel. Although animal studies and clinical experience have shown that such inspissation does not occur [67], it is often recommended that barium-based techniques be replaced by CT or by CT enteroclysis in patients who have high-grade or complete small-bowel obstructions [64]. With lower grades of obstruction, barium enteroclysis remains a useful test for delineating the site and cause of obstruction, particularly in patients with intermittent obstruction. If a decompression tube has already been positioned beyond the duodenum, it can be used to perform the enteroclysis examination.

**Adhesions**

Adhesions account for almost 75% of small-bowel obstructions. Enteroclysis can identify features that favor obstruction by a single band, multiple bands, or extensive adhesions. Single bands are more likely to produce high-grade obstruction. A closed-loop obstruction may be caused by prolapse of a bowel...
Bacterial overgrowth syndrome

Barium studies can accurately depict many structural abnormalities in the small bowel that cause stasis or contamination and lead to bacterial overgrowth. These abnormalities include strictures, blind pouch and blind loop syndromes, jejunoileal diverticulosis, and coloenteric fistulae. Other patients with bacterial overgrowth syndrome may have chronic intestinal pseudoobstruction due to scleroderma or other causes. Small-bowel involvement by scleroderma may lead to intestinal dilatation with crowded folds, producing the “hide-bound” sign that is virtually pathognomonic of this condition [69].

Intestinal lymphangiectasia

The primary and secondary forms of intestinal lymphangiectasia are manifested by nonspecific changes of fold thickening and fluid increase on conventional barium studies. With enteroclysis, it is possible to demonstrate 1–2 mm micronodules representing villi distended by dilated lacteals. Other patients with bacterial overgrowth syndrome may have chronic intestinal pseudoobstruction due to scleroderma or other causes. Small-bowel involvement by scleroderma may lead to intestinal dilatation with crowded folds, producing the “hide-bound” sign that is virtually pathognomonic of this condition [69].

Celiac disease

The diagnosis of celiac disease must be firmly established to justify placing the patient on lifelong dietary restrictions. A confident diagnosis can be made in patients who have characteristic mucosal changes on duodenal biopsy and have shown a satisfactory response to gluten withdrawal. However, more than 50% of patients have atypical clinical presentations. As a result, the diagnosis may first be suggested by enteroclysis, which can demonstrate a measurably increased separation of folds in the distended proximal jejunum (Figure 144.14). In one study, zero to three folds per 2.5 cm of jejunum were found by enteroclysis in 73% of celiac patients but in only 2% of controls [68]. Conversely, patients with five or more folds per 2.5 cm of jejunum rarely had celiac disease.

Enteroclysis is especially important in celiac patients who relapse after an initial dietary response; this technique can aid in the diagnosis of ulcerative jejunoileitis, T-cell lymphoma, and intestinal carcinoma as complications of long-standing celiac disease.

**Figure 144.14** Diagnosis of celiac disease on a small-bowel enema. The distended proximal jejunum shows an increased separation of folds, with only three folds per 2.5 cm (dotted line).
Enteroclysis is the best radiological technique for demonstrating these lesions (Figure 144.16).

Non-Hodgkin lymphoma Primary small-bowel lymphomas typically appear as cavitary lesions extending into the mesentery or as segmental infiltrating lesions. In other patients with disseminated lymphoma, barium studies may demonstrate submucosal nodules of various sizes. An enlarging mass of mesenteric nodal lymphoma also can secondarily infiltrate a loop of small bowel [64]. CT can be used to better delineate the extent of mesenteric and lymph node involvement.

Other malignancies Small-bowel carcinoids can be diagnosed by enteroclysis at the stage of incipient transmural extension of the primary tumor or tumors (Figure 144.17). More advanced carcinoids are typically associated with distorted folds. Enlarging mesenteric metastases produce mass effect and secondary fibrotic alterations in adjacent bowel loops. Early carcinoids may appear as small polypoid nodules, more often in the terminal ileum.

Both hematogenous and intraperitoneal-seeded metastases to the small bowel tend to occur as multiple lesions, often associated with signs of obstruction. GISTs may appear as excavated exenteric masses.

Meckel diverticulum Enteroclysis is the best radiological technique for diagnosing Meckel diverticulum, with an overall detection rate comparable to that found at autopsy [66]. The diverticulum arises from the antimesenteric border of the distal ileum, forming a blind sac, with a characteristic mucosal fold pattern at its site of origin. Occasionally, it is possible to identify a defect in the diverticulum due to ectopic gastric mucosa. It is also possible to identify
ties in the colon. As a result, the barium enema examination is performed far less frequently in modern radiology practice than it was in the past. However, because of its simplicity, low cost, safety, and accuracy, the barium enema remains a potentially useful diagnostic technique for investigating the colon.

**Single versus double contrast**
Radiological examination of the colon can be performed by single- or double-contrast technique. In single-contrast studies, the entire colon is filled with a low-density barium suspension. The examination is performed under fluoroscopic control, with extensive palpation and compression of the colon as it fills. A postevacuation radiograph is usually obtained to demonstrate additional mucosal detail. In double-contrast studies, a smaller volume of high-density barium is introduced into the colon, followed by insufflation of air. With this technique, the mucosal surface is coated by a thin layer of high-density barium, and the lumen is distended with air.

The double-contrast examination is considered to be a useful radiological technique for showing fine mucosal lesions such as small polyps and the early changes of inflammatory bowel disease (IBD) [73,74]. It can also better demonstrate segments of the large bowel that are inaccessible to palpation, such as the rectum and the hepatic and splenic flexures. The single-contrast barium enema is the preferred technique when careful control of the flow of barium is required in patients with suspected obstruction, acute diverticulitis, fistulae, or Hirschsprung disease. This technique is also frequently used in patients who are too old or debilitated to tolerate a double-contrast study.

**Radiology versus colonoscopy**
There is ongoing controversy about the relative roles of radiology and endoscopy in investigating colonic disease. In general, the choice of technique depends on the clinical setting and the relative skill and experience of the examiner. Nevertheless, it should be recognized that colonoscopy is primarily of value for detecting mucosal lesions. It should not be used as the primary diagnostic modality when the patient’s symptoms suggest an intramural or extrinsic lesion involving the bowel.

Colonoscopy is more accurate than radiology in demonstrating subtle mucosal abnormalities in the colon. When compared with high-quality double-contrast barium enemas, this benefit applies primarily to the detection of polypoid lesions less than 1 cm in diameter and the early changes of inflammatory bowel disease (IBD). However, this benefit must be balanced against the higher cost and complication rate of colonoscopy. The colonoscopist is unsuccessful in advancing the endoscope to the cecum in about 3% of patients [75], but the cecum is almost always visualized on barium enema studies.

The barium enema examination is a useful imaging test for patients with symptoms that could be caused by diseases of the colon, including abdominal pain, constipation, change in bowel habit, and anemia. Colonoscopy is generally the examination of choice for the evaluation of uncertain radiological findings, for
radiation or biopsy of lesions found at barium enema, and for the evaluation of patients at high risk for developing colorectal cancer or who have occult blood in the stool.

**Indications**

Although radiological examination of the colon may be performed for a wide variety of indications, the most common include detection of colorectal polyps and cancer; diagnosis of IBD and assessment of the type, extent, and severity of disease; diagnosis of diverticular disease and its complications; evaluation of extrinsic mass lesions involving the colon; and evaluation of the rectum.

**Colorectal polyps and cancer**

The barium enema is a useful diagnostic test for symptomatic patients with colorectal cancer. It is helpful not only for diagnosing the primary lesion but also for detecting synchronous cancers elsewhere in the colon. The double-contrast barium enema has an overall accuracy of about 95% in detecting colorectal cancer. However, there appears to be an irreducible minimum error rate of approximately 5%, primarily the result of perceptual error [76].

The double-contrast barium enema is also used to evaluate patients who have overt rectal bleeding or occult blood in the stool. In such cases, the goal is to detect invasive carcinomas as well as small adenomas that are precursors of colonic carcinoma (Figure 144.18). These adenomatous polyps should be removed endoscopically to prevent the development of cancer.

Similarly, the double-contrast barium enema has a role in the routine screening of average-risk patients for colorectal cancer [77]. However, in recent years CT colonography (i.e., virtual colonoscopy) has largely supplanted the double-contrast barium enema as a highly sensitive and less invasive imaging test for colorectal cancer screening [77].

**Inflammatory bowel disease**

Radiological examination of the colon serves a variety of purposes in patients with known or suspected IBD. It can establish the presence of disease in patients who have not had prior sigmoidoscopy or in those with negative sigmoidoscopy because the disease did not involve the rectosigmoid colon. It can also define the extent of disease in the colon. This information is particularly important in patients with ulcerative colitis, because the risk of developing carcinoma is related to the extent of colonic involvement.

Radiological examination of the colon can differentiate ulcerative from Crohn's colitis. In typical cases, ulcerative colitis is characterized on double-contrast radiographs by a granular mucosa involving the rectum and extending proximally to a variable degree (Figure 144.19a). In contrast, Crohn's colitis is characterized by progression from discrete aphthous ulcers (Figure 144.19b) to transmural disease with deep ulcers, fissures, fistulae, and abscesses. The rectum is often spared, and colonic involvement tends to be discontinuous and patchy.

Radiological examination can also detect complications of chronic ulcerative or Crohn's colitis, including strictures, abscesses, fistulae, and inflammatory or postinflammatory polyps. In patients who develop carcinoma as a complication of chronic ulcerative colitis, the tumor can be diagnosed and in some cases the development of macroscopic dysplasia can also be recognized on double-contrast studies [78].

**Diverticular disease**

Diverticular disease is one of the most common afflictions of Western society. The presence of massive diverticulosis poses a particular dilemma in interpreting double-contrast studies, because the multiplicity of ring shadows makes it difficult to differentiate diverticula from polyps. As a result, single-contrast studies may be easier to interpret than double-contrast studies in patients with severe diverticulosis.

Diverticulitis is a complication of diverticulosis in which a diverticular perforation leads to the formation of a pericolonic abscess. Because barium may extravasate into the abscess, it is important to control the flow of barium into the colon in these patients. Single-contrast technique is preferred when a barium enema is performed for suspected diverticulitis (Figure 144.20a). In recent years, CT has increasingly been used as the primary imaging modality in patients with signs and symptoms of acute diverticulitis because of its relatively high sensitivity and
Extrinsic mass lesions
In patients with abdominal or pelvic masses, the barium enema is a useful technique for determining whether the colon is displaced, compressed, or actually invaded by these lesions. The barium enema can also detect intraperitoneal seeding of the colon by metastatic tumor, inflammatory lesions, or endometriosis. In many cases, the barium study must be correlated with CT or other cross-sectional imaging modalities to determine the true extent of disease in the abdomen.

Rectum
When barium enemas were performed primarily by single-contrast technique, the rectum was not considered to be the province of radiology. However, with the use of double-contrast

Figure 144.19 Early findings of inflammatory bowel disease on double-contrast barium enemas. (a) Ulcerative colitis with typical granular mucosa in the sigmoid colon. (b) Granulomatous colitis with discrete aphthous ulcers in the transverse colon.

Figure 144.20 (a) Acute diverticulitis with pericolic abscess. Barium has extravasated from a perforated diverticulum into an abscess (arrows). Notice the diverticula in the sigmoid colon. (b) Chronic diverticulitis with circumferential narrowing of the sigmoid colon. The narrowed segment has a spiculated contour and tapered margins characteristic of this condition.

specificity for diagnosing this condition [79]. However, other patients with chronic diverticulitis may present with obstructive symptoms secondary to narrowing of the sigmoid colon. In such cases, the diagnosis can readily be suggested on barium enemas showing a relatively long segment of circumferential narrowing in the sigmoid colon with a spiculated contour and tapered margins, sometimes associated with retrograde obstruction (Figure 144.20b) [80].
only by a pneumoperitoneum without extravasation of barium into the peritoneal cavity. If these patients are aggressively treated with intravenous fluids and antibiotics, surgery may be avoided in some cases.

Retroperitoneal perforations usually result from laceration of the rectum by an inflated retention balloon on the enema tip in patients with diffuse rectal disease such as ulcerative or radiation proctitis. In such cases, barium may be observed in the rectal wall or in the perirectal soft tissues. Because of the risk of rectal laceration, the retention balloon should not be routinely inflated. When the balloon is required in patients who have poor anal sphincter tone, it should be inflated under careful fluoroscopic control after barium has been instilled into the rectum.

Despite occasional complications, the barium enema examination is a safe, simple, and relatively inexpensive procedure. It provides reliable information about the nature and extent of mucosal disease and about disease within and outside the bowel wall. Some patients undergo barium enemas to rule out colonic neoplasm or IBD, and a double-contrast study is the best radiological technique for evaluating these individuals. In other patients with suspected diverticulitis or colonic obstruction, a single-contrast barium enema may be performed. Whether a single- or double-contrast technique is used, the barium enema examination has few contraindications, and the complications can be minimized by careful attention to the clinical history and examination technique. In complicated or difficult cases, correlation of the radiological and endoscopic findings may be necessary to clarify the nature and extent of colonic disease.

References are available at www.yamadagastro.com/textbook

Further reading


**Introduction**

Sonography is one of the diagnostic imaging modalities that can be used to image intra-abdominal organs. Unlike computed tomography (CT), it does not utilize ionizing radiation in order to produce images. With increasing utilization of CT and concern for its associated cumulative radiation risk as well as cost, ultrasound provides a reasonable alternative that is not only less expensive and non-ionizing, but also portable and more universally available. Furthermore, as we will discuss later in this chapter, some abdominal organs such as the gallbladder are better evaluated with ultrasound than with CT; as such, ultrasound is the first line imaging modality in the evaluation of suspected gallbladder pathology. Ultrasound is portable, allowing the sonographer and the machine to come to the patient’s bedside rather than requiring the ill patients, especially those in an intensive care unit (ICU) setting, to travel to the CT or magnetic resonance imaging (MRI) scanner. Unlike the static images provided by CT and MRI, ultrasound can be used to dynamically image organs in real time, such as evaluating the compressibility of the appendix or to assess the hemodynamics of blood traveling through the liver vasculature.

Ultrasound is unique in that its performance characteristics are user dependent, requiring a trained sonographer or sonologist to recognize and capture images of the organs of interest while at the same time compensating for factors that may affect image quality such as patient body habitus, artifacts, and respiratory motion. A thorough understanding and knowledge of the appearance of normal anatomy and pathology is required to adequately image a patient in order to answer the clinical question. Unlike CT and MRI, sonography is not confined to imaging in the traditional axial, sagittal, and coronal planes and can image in any plane by rotating or angling the transducer. Thus, sagittal images of organs can be obtained even if they do not fully lie along the true sagittal plane of the body.

**Basic principles of diagnostic ultrasound**

**Gray scale imaging**

In ultrasound, sound waves are used to create images. Sound waves are emitted from the transducer and travel though the tissue of interest. How each sound wave travels through a piece of tissue – its speed and direction – is determined by the density of the tissue imaged. The higher the density of the tissue, the faster the sound wave moves through it. The sound waves can be reflected, refracted, scattered, or absorbed, again depending on the density of the tissue they encounter [1]. The sound wave

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between these two extremes and appear as differing shades of gray, again depending on the density of the tissue.

The appearance of tissue on ultrasound can be described with the suffix –echoic. Water containing structures that appear black are called anechoic whereas very bright structures are described as hyperechoic or echogenic. Hypoechoic, isoechoic, and hyper-echoic, can be used to describe the gray scale appearance of one tissue relative to another.

**Doppler imaging**

As stated earlier, one advantage of ultrasound is its ability to evaluate motion, allowing the user to evaluate not only the anatomic structure but also physiology and pathophysiology of an organ. One application is evaluating blood flow in an organ or vessel with Doppler imaging. When objects move, such as red blood cells in a vessel, the echo that returns to the transducer undergoes a frequency shift. That shift in frequency allows the calculation of the object's velocity and direction of movement relative to the transmitted sound wave [2].

Information regarding blood flow through a vessel can be displayed via color Doppler, power Doppler, and spectral Doppler. In color Doppler, the image will appear identical to a gray scale image of the blood vessel and surrounding tissues, but only the structures which are moving (i.e. blood in the vessel) fill in with color, usually set to a red-blue scale. The user can define how the scale is set so that one end of the color spectrum (e.g. red) will denote flow heading towards the probe and the other end (e.g. blue) will denote flow heading away from...
the probe (Figure 145.3). Power Doppler does not provide information on directionality of movement and so instead of a two toned scale, the areas with motion show one color (usually orange) regardless of the direction of flow. Power Doppler is slightly more sensitive than color Doppler in the detection of flow as it is less sensitive to noise [1]. In spectral Doppler, information regarding flow at a specific location in the vessel is displayed with a graph of velocity over time during a short period of time when the vessel is interrogated with a Doppler sound wave pulse. The graph displays the exact magnitude of the velocity of flow within the vessel as well as its directionality with respect to the probe.

**Equipment**

The workhorse probe of ultrasound imaging of abdominal organs is the curved array or phased array transducer, usually transmitting sound waves at frequencies between 2 MHz to 5 MHz. Higher frequency transducers can provide a higher resolution image; however, it comes at the sacrifice of imaging depth and penetration. Curved transducers also produce a wider field of view compared to linear transducers. High frequency linear transducers are helpful in the focused evaluation of superficial structures, such as the liver contour in cirrhotic patients.

**Limitations with respect to the other imaging modalities**

Air in the gastrointestinal tract causes significant artifact which can obscure the organ of interest. For example, air in the stomach can obscure the pancreatic body and tail located deep to the stomach. Bowel gas can obscure evaluation of the bowel itself, such that only the artifact created from air in the bowel is seen. For those reasons, optimal evaluation of the pancreas and bowel is not always possible and CT is the better modality of choice in the detection of pathologies in these organs. The role of ultrasound in the evaluation of a few specific bowel pathologies where radiation should preferably be avoided, such as in the pediatric population, is described further on.

As previously stated, ultrasound is user dependent, relying on the operator to obtain high quality images of the organ of interest and to recognize abnormalities of each organ in real time. This introduces variability in the quality and thus, the interpretation of a study. In contrast, user dependence is minimized in CT or MRI.

**Liver**

**Indications for sonography**

Primary indications for liver sonography include the evaluation of diffuse parenchymal disease, a focal liver mass, vascular disease, and transplantation. Sonography can be used to characterize abnormalities found on other imaging modalities such as CT or MRI. Its safety, relative low cost, and portability also make ultrasound a good modality for serial follow-up of indeterminate liver lesions and to assess the effect of therapy on known lesions. Sonography is also a simple and effective way to guide percutaneous aspiration, drainage, biopsy, or tumor ablation of liver lesions.
Abdominal sonography CHAPTER 145

intercostal scanning. The liver surface (usually the ventral left lobe in the subxyphoid region) should be evaluated for nodularity with a near field-optimized 7 MHz to 15 MHz linear array transducer. Routine color Doppler imaging is useful in patients with suspected liver pathology.

Focal liver masses
Sonographic features such as margins, echogenicity, and internal vascularity are important features in the characterization of focal liver masses. Typical sonographic appearances of common benign and malignant liver masses are reviewed in the following sections.

Benign masses
Cyst
The reported prevalence of simple liver cysts ranges from 2.5% as detected on ultrasound [3] to 18% as detected on multidetector CT [4]. Prevalence increases with age [3,4]. Simple cysts typically are well circumscribed thin walled anechoic structures with increased through transmission (see Figure 145.2). Thin septations are frequently seen. Some complex liver cysts may have internal echoes, thick walls, multiple thick septations, or calcification (Figure 145.5). Color Doppler is useful in confirming the absence of internal vascularity in complex cysts. Presence of internal vascularity is suggestive of a cystic neoplasm rather than a simple liver cyst.

Polycystic liver disease
Polycystic liver disease is usually associated with autosomal dominant polycystic kidney disease but may also occur as an

Anatomy
The liver has been divided anatomically into three lobes – the largest right lobe, the left lobe, and the small caudate lobe. Sonographic landmarks can be used to segregate the liver functionally into lobes and segments based on venous or ligamentous anatomy (Figure 145.4). Fissures and ligaments can be identified because they are echogenic, fat-containing structures. Portal veins, with their accompanying bile ducts and hepatic arteries, make up the portal triad. These triads are encased in echogenic fibro-fatty tissue. This associated echogenic tissue is the feature that allows differentiation of portal veins from hepatic veins. Portal veins, hepatic veins, hepatic arteries, and bile ducts can also be identified with Doppler imaging. Within the porta hepatitis, the common bile duct and hepatic artery lie anterior to the portal vein. More peripherally, this relationship is not constant and color Doppler imaging can be used to distinguish the bile ducts from the vascular structures.

Ultrasound technique
Hepatic sonography alone can usually be performed without special preparation. However, as the other upper abdominal organs are often evaluated with the liver, an overnight fast, or 6 to 8 hours of a clear liquid diet, is recommended to decrease bowel gas and distend the gallbladder. In some patients, it may be difficult to image the entire liver due to the patient's anatomy. Potential blind spots include the superficial liver above the costal margin, the left tip of the lateral segment of the left lobe, and the ventral subdiaphragmatic regions.

The liver is best imaged with the patient in the supine and left lateral decubitus positions, starting with 2 MHz to 5 MHz curved linear array transducers. A subcostal acoustic window should be used first, supplemented with intercostal scans. Small footprint sector transducers should be used to image areas inaccessible by the larger curved linear transducers, such as for
ill than patients with pyogenic abscess. Serum antibodies to *Entamoeba* species are present in more than 90% of cases. However, serologic findings may be negative in acute disease and may be positive if the patient had amebiasis in the past [6]. In many patients, it is difficult to differentiate amebic abscesses from pyogenic abscesses based on sonographic appearance. Amebic abscess may appear as a hypoechoic lesion with low-level internal echoes and absence of significant wall echoes. Amebic liver abscesses can also have sonographic patterns that are bizarre, including diffuse increased echogenicity, debris levels, and prominent heterogeneity [6].

**Parasitic abscess**

Hydatid disease is a parasitic disease that is endemic in many parts of the world, especially in South America, the Middle East, Africa, Australia, and the Mediterranean region. *Echinococcus granulosus* accounts for 95% of echinococcal infection [7]. Hydatid cysts are most commonly classified based on the Gharbi classification [8] and the World Health Organization (WHO) classification [9] systems. Hydatid cysts have a range of sonographic appearances depending on the stage of growth, ranging from simple unilocular cysts, cysts with multiple internal septations or floating membranes, mother cysts with multiple daughter cysts, heterogeneous degenerative cysts with no identifiable daughter cysts, and cysts with thick calcified walls [7]. Percutaneous drainage under sonographic guidance has become the treatment of choice as an alternative to surgery in the management of hydatid cysts [7].

**Fungal infection**

Fungal infection of the liver is a feature of disseminated fungal disease in patients with hematologic malignancies or compromise of the immune system. Most hepatic fungal microabscesses occur in leukemia patients and are caused by *Candida albicans*; other fungus-related diseases include *Cryptococcus* infection, histoplasmosis, and mucormycosis [6]. Four patterns of hepatosplenic candidiasis have been described. The most common pattern consists of a uniformly hypoechoic nodule, but it is the least specific sonographic appearance. Other less common patterns include “wheel-within-a-wheel”, bull’s eye, and echogenic foci with variable degrees of posterior acoustic shadowing [10]. The “wheel-within-a-wheel” consists of a central hypoechoic area of necrosis containing fungi surrounded by an echogenic zone of inflammatory cells, with a peripheral hypoechoic rim of fibrotic tissue. The bull’s eye configuration consists of a central echogenic nidus surrounded by a hypoechoic rim [6].

**Hemangioma**

Hemangiomas are the most common benign hepatic neoplasm, with an estimated prevalence ranging from 1% to 20% [11,12] and are usually discovered incidentally during abdominal imaging work-up. The typical sonographic appearance of a hemangioma is a homogeneous, hyperechoic mass with
hyperechoic on ultrasound [17]. Some lesions may show a hypoechoic halo, thought to represent compressed hepatic parenchyma or vessels surrounding the lesion [15]. The central scar is slightly hyperechoic but is often difficult to visualize on ultrasound [15,17]. On color Doppler ultrasound, one can see a central feeding artery with a stellate or spoke-wheel pattern of internal vascularity corresponding to the artery running from the central scar to the fibrous septa [17].

**Hepatic adenoma**

Hepatic adenoma is an uncommon benign neoplasm that is usually found in young women who are taking oral contraceptives, men who are receiving anabolic steroids, or patients with glycogen storage disease [18,19]. Unlike focal nodular hyperplasia, these tumors do not contain bile duct structures and very few Kupffer cells. Hepatic adenomas are reported to be solitary in 70% to 80% of cases, but it is not uncommon to see patients with two or three adenomas on multiphasic CT or MRI [18,20]. Patients with adenomatosis have multiple (more than 10) adenomas and have no associated glycogen storage disease, or steroid use [19]. Hepatic adenomas appear as heterogeneous masses on ultrasound. The heterogeneous appearance is due to a mixture of intratumoral fat, hemorrhage, necrosis, and calcifications [18]. Given the heterogeneous nonspecific sonographic appearance of hepatic adenomas, it is difficult to confidently diagnose hepatic adenomas on ultrasound. These masses need to be further evaluated with multiphasic CT or MRI and may need to be biopsied to confirm the diagnosis.

**Malignant masses**

**Hepatocellular carcinoma**

The majority of hepatocellular carcinomas arise in a background of cirrhotic liver, with only a minority of cases arising in a non-cirrhotic liver. They may present as a solitary mass, multiple masses, or a diffuse infiltrative pattern [21]. Hepatocellular carcinomas can be hypoechoic, isoechoic, or hyperechoic, and tend to be hypoechoic when small and become more echogenic and complex as they enlarge (Figure 145.8) [22]. Portal vein and hepatic vein invasion should suggest the diagnosis of hepatocellular carcinoma. The vessel may appear distended with echogenic material that is contiguous with the tumor. Color Doppler should be used to detect internal vascularity in the portal vein or hepatic vein tumor thrombus.

Contrast-enhanced ultrasound is a relatively new technique that uses a microbubble contrast agent for characterization of focal liver lesions. This technique has been shown to be useful in the diagnosis of hepatocellular carcinoma in a number of studies and in a recent meta-analysis [23]. On contrast-enhanced ultrasound, hepatocellular carcinoma is typically characterized by arterial hypervascularity and washout on portal venous and delayed phase images [24].

Fibrolamellar hepatocellular carcinoma is a rarely seen subtype of hepatocellular carcinoma that occurs primarily in young adults with noncirrhotic livers. It typically presents as a
large solitary mass with central scar and punctate calcifications [25].

**Metastasis**

Metastatic disease is the most common liver malignancy in a noncirrhotic liver. They are multifocal in 90% of patients. Ultrasound has reported sensitivity in detection of liver metastases ranging from 40% to 80%, depending on the size of the liver metastases and the experience of the sonologist [26]. Metastatic lesions, whether diffuse or focal, are usually heterogeneous. Target lesions with peripheral hypoechoic halos and “bull’s eye” lesions with concentric rings of varying echogenicity are common (Figure 145.9). Ill-defined infiltration with focal nodularity is another frequent pattern. Liver metastases can be hyperechoic, isoechoic, hypoechoic, or even cystic, depending on the tissue characteristics of the primary neoplasm. The most common hyperechoic metastatic lesions with peripheral hypoechoic halos are colorectal cancer, renal cell carcinoma, neuroendocrine tumor, choriocarcinoma, and Kaposi sarcoma. The most common hypoechoic liver metastases are from breast, lung, esophagus, stomach, pancreas, and non-Hodgkin lymphoma. Cystic metastases may arise from squamous cell carcinoma, sarcomas, and gastrointestinal stromal tumor [27]. Liver metastases from mucin-producing neoplasms such colon, ovarian, breast, and gastric cancer can calcify [28].

**Diffuse parenchymal disease**

Diffuse liver disease does not always cause distortion of liver anatomy or architecture, which can make sonographic detection difficult. Liver surface nodularity or atrophy of the right lobe, when present, can be useful signs of cirrhosis. Parenchymal echogenicity may be increased or coarsened in diffuse disease. This may be difficult to evaluate; echogenicity is judged relative to adjacent organs, and there is no absolute echogenicity standard on ultrasound.

**Hepatomegaly**

Hepatomegaly can be difficult to diagnose objectively with sonography. The normal span of the adult liver is 15 cm to 17 cm. Sagittal dimension from the dome to the tip of the right lobe, measured at the midclavicular line, is the most frequently used measurement. Hepatomegaly can also be diagnosed qualitatively when the liver extends caudal to the right kidney and the left lobe is of normal size or larger. A Riedel’s lobe is a normal variant of an elongation of the right lobe with a tongue of liver tissue extending below the right kidney and can clinically mimic hepatomegaly or a right upper quadrant mass.

**Hepatitis**

The imaging features of acute hepatitis are nonspecific and the diagnosis is usually based on serologic and clinical findings. In acute hepatitis, the liver is often enlarged and may demonstrate a diffuse decrease in parenchymal echogenicity [6]. The portal triads become echogenic. The “starry sky” pattern of increased periporal echogenicity coupled with decreased parenchymal echogenicity has been classically described in acute hepatitis [29,30]. However, a later study showed the starry sky pattern was nonspecific and was also seen in 31% of normal controls. It found no difference in the sonographic appearance of the liver between the normal control group and patients with hepatitis.
geneity, and nodularity of the liver. These signs are not sensitive or specific in the diagnosis of cirrhosis. High-resolution linear array transducer scanning of the liver surface is useful in detecting nodularity of the cirrhotic liver (Figure 145.11) [34,35]. Although liver biopsy remains the gold standard for assessment of liver fibrosis, there has been great interest recently in using ultrasound elastography as a noninvasive means to assess liver fibrosis. Several trials and meta-analyses have shown that ultrasound elastography may be helpful in the detection of liver fibrosis and provide additional information over conventional ultrasound techniques [36–38]. Additional validation studies are needed before ultrasound elastography becomes part of routine clinical practice.

Focal fatty infiltration, regenerating nodules, dysplastic nodules, and hepatocellular carcinoma may occur as mass lesions in a cirrhotic liver. A liver mass that does not have classic features of a benign mass raises the suspicion for hepatocellular carcinoma and needs to be further evaluated with CT, MRI, or percutaneous biopsy.

Cirrhosis
Sonographic findings of cirrhosis include changes in the lobes of the liver (atrophy of the right lobe with compensatory hypertrophy of the left lobe and caudate lobe), parenchymal inhomogeneity, and nodularity of the liver. These signs are not sensitive or specific in the diagnosis of cirrhosis. High-resolution linear array transducer scanning of the liver surface is useful in detecting nodularity of the cirrhotic liver (Figure 145.11) [34,35].慢性肝炎显示正常超声图像在许多病例中，它可能与粗大肝实质回声增强和周围血管增强性，导致门静脉分支变不明显 [6]。周围淋巴结病也可见。肝硬化
超声图像特征为肝叶变化（右叶萎缩，左叶和尾状叶代偿性增大），实质不均一性，和颗粒性表面。这些标志在诊断肝硬化时不敏感或不具体。高分辨率线性阵列探头扫描肝表面有助于检测肝硬化的颗粒性表面（图145.11）[34,35]。虽然肝穿刺活检仍然是评估肝纤维化的金标准，但该领域最近对使用弹性超声成像作为非侵入性手段来评估肝纤维化非常感兴趣。一些临床试验和meta分析表明，弹性超声成像可能在检测肝纤维化和提供关于常规超声技术的额外信息时是有帮助的 [36–38]。还需要进一步的验证研究，在弹性超声成像成为临床常规实践前。

脂肪肝
脂肪肝的患病率在一般人群中约为15%。导致脂肪肝的最常见条件包括过量饮酒，胰岛素抵抗，肥胖，及高血脂。其他相关条件包括乙型肝炎，丙型肝炎，类固醇，化疗药物，放射治疗，营养或饮食异常，及遗传性疾病 [32]。脂肪浸润的肝脏的特征是弥漫性肝实质回声增强（图145.10）。声波的声传播减少可能导致血管或膈肌边界不清。脂肪性浸润通常是楔形或地理性。脂肪性浸润或脂肪性高信号的区域也可能存在于肝膈膜，肝门，及胆囊窦 [32,33]。脂肪性浸润可能产生假性占位病变。影像学发现脂肪性浸润病灶的脂肪性高信号，特征性位置，缺乏对血管及结构的影响，及缺乏增生性血管化，支持脂肪性浸润而不是假性占位病变的诊断 [32]。

肝硬化
肝硬化时的影像学特征包括肝叶变化（右叶萎缩，左叶和尾状叶代偿性增大），实质不均一性，和颗粒性表面。这些标志在诊断肝硬化时不敏感或不具体。高分辨率线性阵列探头扫描肝表面有助于检测肝硬化的颗粒性表面（图145.11） [34,35]。
hepatic arteries typically range from 0.55 to 0.70. The resistive index of a vessel is calculated as the ratio of the difference between peak systolic velocity and end diastolic velocity to peak systolic velocity (S-D/S). The normal direction of flow in the portal vein is hepatopetal (towards the liver) throughout the cardiac cycle. The velocity of flow in the portal vein is relatively low (16 cm/sec to 40 cm/sec) compared to the hepatic artery and has a gently undulating waveform. The normal hepatic venous waveform is phasic with predominately anterograde flow. Fluctuations of the hepatic venous waveform are due to fluctuations in right atrial pressure that occur during systole and diastole that are transmitted to the hepatic veins [39]. Increased pulsatility in the portal vein may be caused by right sided heart failure and cardiac congestion.

Portal hypertension
Sonographic evaluation of portal hypertension includes evaluation of portal venous system and a search for portosystemic collaterals. Sonographic findings of portal hypertension include slow flow in the main portal vein (peak velocity <16 cm/sec), reversal of direction of flow in the main portal vein (hepatofugal flow), loss of phasicity of portal venous flow, and development of portosystemic shunts (Figure 145.12) [39]. The most common collaterals are left gastric (coronary) and paraumbilical veins. Left gastric collaterals are often difficult to image because of their deep location. Paraumbilical veins are superficial and arise from the ventral tip of the left portal vein and drain caudally through the ligamentum teres, where they communicate with superficial peritoneal collaterals. Other types of collaterals occur, including retroperitoneal, splenorenal, splenoretroperitoneal, short gastric, and omental.

Portal vein thrombosis
Portal vein thrombus is seen as a hyperechoic, isoechoic, or hypoechoic filling defect within the portal vein (Figure 145.13). The echogenicity of the thrombus varies depending on the age of the thrombus. Hypoechoic or anechoic thrombus can be difficult to detect on gray-scale images without color Doppler. Portal vein thrombus can be bland or malignant. Enlargement of the portal vein by an echogenic filling defect in conjunction with an adjacent suspicious liver mass is suggestive of a tumor thrombus [39]. The most specific sonographic feature of a malignant thrombus is the presence of an arterial waveform within the thrombus due to presence of tumor neovascularity. Chronic portal vein occlusion leads to cavernous transformation, with formation of collateral vessels in or around the occluded portal vein. The small collateral vessels may be difficult to detect on gray-scale images and are best appreciated on color Doppler images.

Budd-Chiari syndrome
Budd-Chiari syndrome is an uncommon condition characterized by obstruction of the hepatic venous outflow tract. Common causes of Budd-Chiari syndrome include inherited and acquired hypercoagulable states. Budd-Chiari syndrome may be classified into three types depending on the location of the occlusion. Type I is limited to the inferior vena cava (IVC). Type II lesions are within the hepatic veins. Type III is mixed type with involvement of both the IVC and hepatic veins [40]. Sonographic features of Budd-Chiari syndrome include hepatomegaly, enlarged caudate lobe, nonvisualization of the hepatic veins, collapsed IVC, enlarged intrahepatic collaterals,
splenomegaly, and ascites. In some cases, an enlarged caudate lobe vein (> 3mm) can be seen draining directly into the IVC [41]. A spider-web appearance of the hepatic veins or replacement of the hepatic veins by a fibrous, echogenic, or even calcified cord may be present [40]. Color Doppler shows absent or aphasic flow in the hepatic veins, IVC, or both and the presence of collateral vessels [42].

**Transjugular intrahepatic portosystemic shunts**

Transjugular intrahepatic portosystemic shunts (TIPS) are most commonly used for the treatment of severe portal hypertension causing refractory variceal bleeding or ascites. In a TIPS, a stent usually connects the right portal vein and right hepatic vein. This communication bypasses the hepatic sinusoids, creating a relatively low resistance pathway to divert portal vein blood flow and relieve portal hypertension. In a patient with functioning TIPS, there should be reversal of flow in the left portal vein as it heads centrally towards the shunt.

Shunt malfunction is the result of in-stent stenosis or occlusion caused by intimal hyperplasia or in situ thrombosis. Stenosis or occlusion can occur anywhere in the stent, but it is most common at the hepatic venous end. Stent occlusion is diagnosed by absence of flow within the stent on color Doppler. Stent stenosis is diagnosed by abnormally high (>190 cm/sec) or abnormally low (<90 cm/sec) velocity within the shunt, or an abnormal change in velocity (increase or decrease of more than 50 cm/sec) compared with the prior examination, or across the different portions of the shunt. A peak systolic velocity within the main portal vein of less than 30 cm/sec or reversal of the direction of the intrahepatic hepatofugal portal venous flow is also evidence of failure [39]. The left portal vein may show hepatopetal flow into the liver and away from the shunt. Patients may also present with symptoms of recurrent portal hypertension such as reaccumulation of ascites or upper gastrointestinal bleeding.

**Liver transplant and transplant complications**

Orthotopic liver transplantation is most frequently performed with end-to-end hepatic arterial, portal venous and biliary anastomoses. The use of a “piggyback” anastomosis between the donor and recipient IVC prevents the need for venovenous bypass and retrocaval dissection. In the “piggyback” technique, a length of the donor IVC is anastomosed to the stump of the recipient hepatic veins [43]. Doppler ultrasound is the first-line imaging modality for the evaluation of vascular complications following liver transplant.

Unlike in the native liver, the hepatic artery is the most important vascular supply to the transplanted liver as it supplies the biliary tree. Normal hepatic arterial spectral waveforms should show continuous anterograde diastolic flow, with normal resistive indices measuring 0.5–0.8. In the early postoperative period (<72 hours after transplantation), increased hepatic arterial resistance (resistive index > 0.8) is a frequent finding, but should return to normal level within a few days [44]. Hepatic artery complications include thrombosis, stenosis, and pseudoaneurysm. The estimated incidence of hepatic artery thrombosis is 4% to 12% in adults and 42% in children. Hepatic artery thrombosis is diagnosed based on absence of flow in the proper hepatic and intrahepatic arteries on Doppler ultrasound. Hepatic artery stenosis occurs in 5% to 11% of cases [44], and generally occurs at the anastomotic site within 3 months of the liver transplant. If left untreated, it can lead to hepatic artery thrombosis due to slow flow. Complications include liver ischemia or infarction leading to hepatic insufficiency, biliary strictures, biliary sepsis and cholangitis, and graft loss [45]. The site of stenosis will show a more than two- to three-fold increase in peak systolic velocity and turbulent blood flow. Sampled intrahepatic waveforms usually show a *parvus tardus* pattern with resistive indices of less than 0.5.

Thrombosis and stenosis of the portal and hepatic veins are relatively rare complications that occur in 1% of liver transplants [44].

**Bile ducts**

**Anatomy**

The biliary tree can be divided into intrahepatic and extrahepatic portions. As the intrahepatic portal triads contain the hepatic arteries, portal veins, and bile ducts, the bile ducts are seen running adjacent to the portal veins and hepatic arteries, usually anterior to the portal veins. This configuration may not be as consistent within the periphery of the liver. The extrahepatic bile ducts include the central most portions of the right and left ducts, the common hepatic duct, and the common bile duct. The insertion of the cystic duct denotes the boundary between the common hepatic duct and the common bile duct, with the common hepatic duct above the insertion and the common bile duct below. Sometimes it is difficult to distinguish the boundary between these two ducts as the nondilated cystic duct is usually not seen by ultrasound. The extrahepatic duct can alternatively be referred to as the common duct. In the region of the porta hepatitis, the proximal common duct is found anterior to the right and main portal vein as well as the right hepatic artery (Figure 145.14). At its mid portion, it travels posterior to the duodenum. Its distal portion courses through the pancreatic head before emptying into the second portion of the duodenum at the Ampulla of Vater.

**Ultrasound technique**

To minimize the effect of bowel gas obscuring the biliary tree, it is recommended that the patient fast for at least 6 hours. Either subcostal or intercostal approaches may be used in both the supine and left lateral decubitus positions. Color Doppler can be used to distinguish the vascular structures from the biliary tree.

The main portal vein in the region of the porta hepatitis is a useful landmark in the identification of the proximal common
duct. The bile duct will be seen as a tubular structure located anterior to the portal vein and right hepatic artery which does not fill with color on Doppler interrogation. Sometimes the gallbladder and cystic duct can be traced to its insertion into the common duct. Provided that there is no bowel gas obscuring the common duct, the duct can be followed into the pancreas where it courses through the pancreatic head before emptying into the duodenum (Figure 145.14). If duodenal gas is present and causing an artifact, the transducer can be used to apply pressure and displace the gas from the duodenum. Having the patient change position or drink water may also help to displace the gas.

**Biliary obstruction**

A common indication for a right upper quadrant ultrasound is to evaluate the biliary tree for obstruction, usually spurred by presence of abnormal liver function tests or clinical findings of jaundice. It is generally accepted that a common duct diameter of 6 mm or less is within normal limits [1,46]. However, as patients age, the biliary tree may also dilate. Post cholecystectomy patients may also show intrahepatic and extrahepatic biliary ductal dilation. In these patients, it is common to see a dilated mid portion that tapers to a normal diameter distally. However, when a patient with a dilated duct presents with elevated bilirubin or alkaline phosphatase levels, it is important to evaluate the biliary tree fully for an obstructing process.

As the intrahepatic bile ducts travel parallel to the portal veins, dilated ducts appear as nonvascular tubular channels adjacent to the vasculature. Peripheral ducts should be no more than 2 mm in diameter or greater than 40% of the adjacent portal vein [1,46]. With increasing dilation, the walls may appear more irregular or tortuous. Furthermore, because of the branching pattern of the biliary tree, the dilated tubular structures will have a stellate pattern, converging centrally.

While ultrasound is highly accurate in detecting extrahepatic obstruction, between 78% to 98%, it is less accurate in determining the cause of obstruction. Reported accuracies of ultrasound in identifying the cause of obstruction have ranged between 23% to 88% [47]. This is due to the difficulty in evaluating the distal common bile duct because of overlying bowel gas. The most common cause of biliary obstruction is a common duct stone. Other causes include tumors and stricture. Stents are commonly placed to relieve the obstruction.

If a patient has abnormal bilirubin or alkaline phosphatase levels and the cause of obstruction is not visible on ultrasound, magnetic resonance cholangiopancreatography (MRCP) can be performed. It is a noninvasive alternative to endoscopic retrograde cholangiopancreatography (ERCP) (see Chapter 148).

**Choledocholithiasis**

Ultrasound sensitivities for choledocholithiasis have ranged from 20% to 78% [48]. Choledocholiths appear as echogenic foci within the bile duct causing posterior acoustic shadowing. It is best seen when the patient is scanned in a right posterior oblique position and the common duct is dilated and filled with anechoic fluid, outlining the bright echogenic stone (Figure 145.15). However, when the duct is not diluted, it may be difficult to differentiate the echogenic stone from the adjacent walls of the biliary tree. Smaller stones also may not shadow or their shadow may be obscured by adjacent bowel gas.
Furthermore, in as many as one-third of patients, stones may be present in nondilated ducts [46]. MRCP or ERCP would be the next imaging step in the evaluation for common duct stone.

**Neoplasms**

Another cause of biliary obstruction could be the presence of a tumor, either from a primary biliary lesion or due to secondary mass effect from an adjacent tumor in the pancreas or duodenum. The most common malignancy of the biliary tree is cholangiocarcinoma. As they can arise anywhere in the biliary tree, cholangiocarcinomas may be intrahepatic or extrahepatic. Most commonly they arise at the bifurcation of the biliary tree into the left and right ducts and are referred to as Klatskin tumors. These comprise about 50% to 60% of all cholangiocarcinomas. Intrahepatic cholangiocarcinomas account for 10% of the total, with the remaining 30% being extrahepatic [46].

The actual lesion may be difficult to see under imaging, presenting as wall irregularity or thickening resulting in narrowing. The location of the lesion may be determined by the abrupt termination of the dilated bile ducts with normal sized bile ducts centrally and distally (Figure 145.16). As the lesion expands outside of the confines of the bile duct there may be involvement of the adjacent vascular structures. Intrahepatic cholangiocarcinomas can result in focal intrahepatic ductal dilation peripheral to the mass and if long term, the liver may also show lobar atrophy [46].

Benign neoplasms of the biliary tree include adenomas and biliary cystadenomas. Both entities are rare. Like cholangiocarcinoma, adenomas may obstruct the biliary tree, causing pain and jaundice. They are usually homogeneous and isoechoic to the liver parenchyma [46]. Biliary cystadenomas are typically found intrahepatically as cystic masses in middle aged women. They are usually large and can either be simple and unilocular in appearance or may appear more complex with septations, mural nodularity, complex fluid, and calcification.

Lesions in the pancreatic head or ampulla can also cause upstream biliary ductal dilation. Tumors in these locations can also cause pancreatic ductal dilation, and therefore it is important to evaluate the pancreas as well for the presence of a dilated duct or mass lesion.

**Stricture**

In addition to malignant causes of stricture, there are benign causes of stricture, such as post inflammatory changes and scarring from prior episodes of pancreatitis, choledocholithiasis, or sclerosing cholangitis.

**Pneumobilia**

Air may be present in the biliary tree for many reasons. The most common causes are endoscopic sphincterotomy and after surgical procedures such as hepaticojejunostomy. Stent placement in the biliary tree may also result in pneumobilia. On ultrasound, pneumobilia is seen as multiple echogenic foci within the liver parenchyma, following the branching pattern of the biliary tree. It can be seen centrally as well as peripherally (Figure 145.17). Sometimes it may be difficult to differentiate between pneumobilia and portal venous gas on ultrasound. In addition to correlation with any history of prior procedures, Doppler imaging may be helpful to correctly place the location of air within the biliary tree rather than within the portal venous system.

**Inflammatory processes of the biliary tree**

In acute bacterial cholangitis, patients usually present with right upper quadrant pain and fever. There is most often an
underlying biliary obstruction leading to biliary stasis. On ultrasound, there may be wall thickening and debris within the biliary tree [46]. Hepatic abscess is a complication of cholangitis, so the liver should also be evaluated for any focal lesions.

Sclerosing cholangitis may be idiopathic, but also may be associated with inflammatory bowel disease. Secondary sclerosing cholangitis may also occur from prior inflammatory processes of the biliary tree such as choledocholithiasis. The inflammation of the biliary tree results in fibrosis and stricture formation. Due to stricture formation, biliary stasis occurs, which predisposes patients to infection and hepatic abscess formation. Long-term complications include cirrhosis and liver failure. On ultrasound the bile ducts may be dilated, thickened, and tortuous. There may be features of cirrhosis with a nodular contour of the liver. Acquired immune deficiency syndrome (AIDS) related cholangitis may also present with these features [46].

Mirizzi syndrome is a rare condition in which a gallstone becomes impacted in the cystic duct or neck of the gallbladder causing compression of the common bile duct (CBD) or common hepatic duct, resulting in obstruction and jaundice.

Gallbladder

Anatomy

The gallbladder is usually located at the inferior edge of the right lobe of the liver, in the interlobar fissure. The interlobar fissure separates the left and right hepatic lobes. An intrahepatic gallbladder is a common variant, with the gallbladder located superior to the interlobar fissure. The gallbladder is filled with bile, which appears anechoic under ultrasound. The gallbladder is oval shaped, measuring up to 10 cm sagittally and 4 cm transversely. Normal gallbladder wall thickness is 3 mm or less [1]. Folds in the gallbladder may also be present near the neck (junctional fold) or in the fundal region (Phrygian cap).

Ultrasound technique

Since the gallbladder contracts, ejecting bile when the patient eats, it is recommended that the patient fast for at least 6 hours prior to the exam to allow the gallbladder to be adequately distended for evaluation.

A 3 MHz to 5 MHz sector transducer is used to initially view the gallbladder either from a subcostal or intercostal approach from a supine position [1]. A higher linear frequency transducer can also be used to evaluate the gallbladder wall of the fundus for better resolution. The patient should be imaged in multiple positions, most commonly the supine and right side up decubitus or erect positions, in order to evaluate for stones adequately. Stones may be obscured in one position, but demonstrable in the other position. Demonstrating the mobility of stones or sludge also requires imaging in more than one position. Care should be taken to adequately visualize the gallbladder neck for the presence of stones.

Cholelithiasis and sludge

Ultrasound has high sensitivity in the detection of gallstones with an estimated sensitivity of 95% in patients with gallstones [49]. As gallstones contain dense or calcified material, they usually appear as echogenic structures within the lumen of the gallbladder casting posterior acoustic shadows as long as they are greater than 3 mm in size (see Figure 145.1). Gallstones are mobile and patients should be evaluated in the supine and right side up decubitus or erect positions to demonstrate their mobility. Stones may vary in size and may be solitary or multiple. They may fill the entire lumen of the gallbladder. Depending on their size and density they may be seen floating within the bile.

Sludge is the result of increased density of the viscous bile fluid, usually due to the presence of calcium bilirubinate granules or cholesterol crystals [1]. Sludge appears as internal echoes within the usually anechoic lumen of the gallbladder, resulting in a sludge-bile fluid level. Sometimes the presence of internal echoes within the gallbladder lumen may be related to reverberation artifact. Sludge, if present, will be seen as internal echoes within the gallbladder lumen that persist on multiple images taken from different angles. Due to its increased density relative to the bile, sludge will always layer dependently within the gallbladder, even when the patient is repositioned.

Sludge may coalesce into focal masses, referred to as sludge balls or tumefactive sludge, which can be mistaken for cholelithiasis, or a gallbladder tumor. While tumefactive sludge may be mobile like stones, it does not cause posterior acoustic shadowing and unlike gallbladder tumors, it is avascular on color Doppler imaging.

Patients may present with episodes of biliary colic, in which the cystic duct is temporarily occluded by a stone. Patients will usually present with pain as well as nausea and vomiting for a couple of hours. When the stone either passes into the bile duct or back into the gallbladder, relieving the obstruction of the cystic duct, the pain usually resolves [49].

In addition to biliary colic and acute cholecystitis, other complications of gallstones include pancreatitis, choledocholithiasis, and gallstone ileus [49].

Cholecystitis

Occlusion of the cystic duct or gallbladder neck for a prolonged period of time can result in acute cholecystitis. Additional sonographic findings beyond the presence of cholelithiasis are required to diagnose acute cholecystitis. A sonographic Murphy’s sign is the presence of increased pain and tenderness when the transducer is placed over the gallbladder. The presence of gallstones and a positive Murphy’s sign has been shown to have a positive predictive value of 92% [49]. Additional findings include pericholecystic fluid, gallbladder wall thickening greater than 3 mm, and gallbladder enlargement (Figure 145.18). Use of color Doppler ultrasound to evaluate the gallbladder wall may show hyperemia. The absence of stones and absence of a sonographic Murphy’s sign has been reported to have a negative predictive value of 95% [49]. Patients presenting...
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with abdominal pain not attributable to acute cholecystitis may demonstrate diffuse abdominal pain rather than a focal area of tenderness. When evaluating for a sonographic Murphy’s sign the examiner should ensure that the maximal pain is elicited when the transducer is over the gallbladder rather than the liver or epigastric area to avoid a false positive. Situations where a false negative sonographic Murphy’s sign occur include the prior administration of pain medication or a confused or obtunded patient. Patients with denervated gallbladders, either due to diabetes or gangrenous cholecystitis, can present without a sonographic Murphy’s sign. In addition when acute cholecystitis progresses to perforation in order to relieve the obstruction, pain may resolve.

It should be noted that the presence of pericholecystic fluid and gallbladder wall thickening are nonspecific findings. Wall thickening can be seen in acute hepatitis, ascites, congestive heart failure, and hypoalbuminemia [50]. A decompressed gallbladder may also show wall thickening. If findings are equivocal on ultrasound, biliary scintigraphy may be helpful.

Unrecognized or untreated cholecystitis may present with sloughed mucosal membranes, appearing as echogenic curvilinear foci within the gallbladder, focal ulcerations of the mucosa, and intramural abscesses.

Complications of acute cholecystitis include gangrenous and/or emphysematous cholecystitis, where the gallbladder wall becomes ischemic and necrotic. These patients only show a positive Murphy’s sign in 33% of cases [49]. When the gallbladder wall thickening of acute cholecystitis progresses to a multilaminar striated appearance of alternating hyperechoic and hypoechoic layers with internally sloughed membranes, this should prompt concern for gangrenous cholecystitis.

Emphysematous cholecystitis is caused by the presence of gas forming organisms, and air may collect within the gallbladder wall, or the lumen. Unlike the sharply demarcated posterior acoustic shadowing caused by a gallstone, air will appear as echogenic foci causing dirty acoustic shadowing arising from the nondependent area of the gallbladder.

Bleeding may occur into the gallbladder as a result of acute cholecystitis or after interventional procedures, causing hemorrhagic cholecystitis or hemobilia. Focal perforation of the gallbladder usually occurs near the fundus, resulting in a pericholecystic collection or intrahepatic abscess. Unlike the crescentic fluid along the longitudinal axis of the gallbladder seen with uncomplicated cholecystitis, this fluid will be focal or loculated in appearance. The fluid may appear complex and have internal echoes suggestive of debris.

Acute cholecystitis is caused by acalculous cholecystitis in 5% to 10% of patients. These patients are quite sick and usually in the ICU. Risk factors include diabetes, vascular insufficiency, hyperalimentation, trauma, burn, or surgery [51]. Instead of a stone causing obstruction of the cystic duct, it is thought to be due to the increased bile viscosity from stasis causing functional obstruction of the gallbladder. The findings of distended gallbladder, gallbladder wall thickening, and pericholecystic fluid may be seen. Biliary scintigraphy has been reported to have significant false positive rates, with one study showing a specificity of 38% [52]. If there is high index of suspicion for acalculous cholecystitis, patients should undergo cholecystostomy tube placement.

Chronic cholecystitis may be difficult to differentiate from acute cholecystitis by imaging. It is the result of chronic inflammation due to cholelithiasis leading to fibrosis and gallbladder wall thickening. This wall thickening impedes the normal contractility of the gallbladder and the gallbladder may appear contracted [48]. Biliary scintigraphy may be helpful in differentiating acute from chronic cholecystitis and can evaluate gallbladder ejection function.

Gallbladder polyps
The most common type of gallbladder polyp is the cholesterol polyp, a nonneoplastic polyp. It is the result of cholelithosisis, in which cholesterol precursors deposit within the wall of the gallbladder. It is part of the hyperplastic cholecystoses, the other being adenomyomatosis. If numerous polyps are present, they can cause the appearance of a “strawberry gallbladder,” due to the mucosa being carpeted by the polyps. This is usually seen on pathologic specimens rather than on imaging. On ultrasound, single or multiple polyps can be detected. They are differentiated sonographically from gallstones by their lack of mobility and shadowing. There may be overlap in the gray scale appearance of a polyp and an adherent stone that is too small to cause posterior acoustic shadowing. It has also been reported that many small polyps diagnosed at ultrasound are found to be small stones during cholecystectomy [53]. Internal vascularity may be identified, although commonly it is not seen in small polyps.
Other types of gallbladder polyps such as adenomatous ones are less common, larger in size, and usually solitary. They are found in 0.3% to 0.5% of cholecystectomy specimens [46]. Unlike cholesterol polyps, adenomas are true neoplasms, and those lesions have the potential of malignant transformation especially if they are larger in size. Once polyps reach 10 mm or larger, it is recommended that they be removed as the risk of malignant transformation to adenocarcinoma outweighs the risk of cholecystectomy [53]. Lesions below 10 mm have a low potential for malignant transformation [54]. It has traditionally been recommended that polyps between 5 mm to 10 mm should be followed yearly to ensure stability. A study by Corwin in 2011 of 346 patients with gallbladder polyps who underwent sequential imaging for growth and malignant transformation found no neoplastic polyps less than 7 mm, and suggested no follow-up for polyps 6 mm or less [53]. Other features besides growth and size that may suggest malignancy include sessile appearance and associated gallbladder wall thickening [53].

Metastatic lesions may also present as gallbladder polyps. Melanoma is the most common malignancy to spread to the gallbladder, and polyps in these patients should be treated more conservatively [1]. Evaluation for liver metastases and lymphadenopathy should be performed as these may coexist with gallbladder metastases.

**Adenomyomatosis**

This entity is relatively common, seen in about 5% of cholecystectomy specimens [55]. There is no potential for malignant transformation. There is no treatment for adenomyomatosis, but on occasion it may cause pain, and cholecystectomy may be performed to relieve the patient’s symptoms. Patients with adenomyomatosis often have associated cholelithiasis.

Adenomyomatosis is the result of hyperplasia of the layers of the gallbladder walls and can be either focal or diffuse in its involvement. Sinuses form within the hyperplastic walls, called Rokitansky-Aschoff sinuses, where cholesterol crystals may deposit. The crystals within these sinuses cause a characteristic appearance under ultrasound. Best seen along the nondependent wall of the gallbladder, echogenic foci are present which produce a “comet tail” or “ring down” artifact posterior to the foci (Figure 145.19). It is best seen along the nondependent wall because the artifact projects into the gallbladder lumen and the anechoic bile within the gallbladder provides a nice contrast to the bright artifact. Artifacts arising from the sinuses along the dependent wall may be obscured.

If focal, adenomyomatosis may manifest as focal gallbladder wall thickening, typically within the fundus. However, because both may present with gallbladder wall thickening, focal adenomyomatosis may be difficult to differentiate from gallbladder carcinoma. MRI is useful in making this distinction by demonstrating intramural cystic spaces and calculi [53].

**Porcelain gallbladder**

Calcification of the gallbladder wall is known as porcelain gallbladder. Patients with a porcelain gallbladder usually also have cholelithiasis. There is an increased incidence of gallbladder carcinoma in patients with porcelain gallbladder, and patients with porcelain gallbladder should undergo cholecystectomy. It has been estimated that 10% to 25% of patients with porcelain gallbladder have gallbladder carcinoma [56].

Porcelain gallbladder can have a variable appearance on ultrasound depending on the degree of calcification present. Classically, only the anterior wall is seen, appearing as a thick echogenic crescent causing complete posterior acoustic shadowing such that the internal contents of the gallbladder and posterior wall are obscured. If the calcification is not as severe, then both walls may be appear echogenic.

Porcelain gallbladder may be difficult to differentiate from a contracted gallbladder filled with stones. The key to differentiating between these two entities is the ability to demonstrate the gallbladder wall separate from the calcification, the so-called “wall-echo-shadow sign.” The presence of a distinct non-calcified wall favors a gallbladder full of stones. The diffuse shadowing on ultrasound caused by the gallbladder wall calcification limits evaluation for internal masses or abnormal gallbladder wall thickening, and tumors may be missed on ultrasound.

**Gallbladder carcinoma**

Gallbladder carcinoma often is an incidental diagnosis as clinical symptoms can be quite nonspecific, presenting as abdominal pain, weight loss, or anorexia. Due to its indolent presentation, patients often present with advanced disease, resulting in a poor prognosis. Gallbladder carcinoma may also present as an incidental finding during pathologic evaluation of a gallbladder removed during cholecystectomy. It has been estimated that 1%
Pancreas

Anatomy

The pancreas is comprised of multiple parts: the uncinate process, head, body, and tail. The pancreatic head and uncinate process are located just to the right of midline, anterior to the IVC, while the pancreatic body and tail cross over the aorta and superior mesenteric artery into the left upper quadrant extending into the splenic hilum. The pancreas usually lies posterior to the stomach, and the lateral segment of the left hepatic lobe may extend anterior to the pancreatic head. The tail of the pancreas abuts the splenic hilum. The splenic vein courses along the posterior pancreatic body and tail, joining the superior mesenteric vein to form the portal vein at the portosplenic confluence in the region of the pancreatic head. The uncinate process is located inferior to the pancreatic head, posterior and lateral to the superior mesenteric artery and vein. The common bile duct courses through the pancreatic head, emptying into the second portion of the duodenum with the pancreatic duct.

The maximum anterior-posterior (AP) dimension of the pancreas can be up to 3 cm in the pancreatic head, and 2.5 cm in the rest of the pancreas. A pancreatic duct diameter of 3 mm or less is normal. Both the pancreatic duct and common bile duct may dilate over the normal limits as patients age. In those cases, it is important to evaluate for and exclude an obstructing process such as a tumor or a stone that may alternatively cause the ductal dilation.

Ultrasound technique

Due to its location posterior to the stomach, the pancreas is a difficult organ to evaluate adequately under ultrasound. The presence of air within the stomach may cause artefactual shadowing that obscures structures deeper to the stomach such as the pancreas. If the left hepatic lobe extends anterior to the pancreatic head, it may act as an acoustic window to allow echoes to reach the pancreas so that it can be imaged. Likewise the spleen may also act as an acoustic window to evaluate the pancreatic tail and distal body. If feasible, it is recommended that the patient fast overnight, or for at least 6 hours, to limit the amount of gastrointestinal gas.

The best way to image the pancreas is to use a subxiphoid approach with the patient in a supine position. The left hepatic lobe may act as an acoustic window to allow echoes to reach the pancreas so that it can be imaged. Likewise the spleen may also act as an acoustic window to evaluate the pancreatic tail and distal body. If feasible, it is recommended that the patient fast overnight, or for at least 6 hours, to limit the amount of gastrointestinal gas.

Patients may present with acute symptoms suggestive of acute cholecystitis and there may be difficulty in differentiating between the two entities if there is no distinct mass. The possibility of an abnormal gallbladder being related to gallbladder carcinoma rather than acute cholecystitis should be discussed with the referring clinician so that during cholecystectomy a wider excision can be performed to provide for adequate negative margins.

Evaluation of the adjacent liver should be performed to search for direct extension of the tumor. Liver metastases or nodal metastases could also be present and should be evaluated for as well.

Figure 145.20 Gallbladder adenocarcinoma. A 1.2 cm polypoid mass (calipers) is seen along the nondependent wall of the gallbladder projecting into the gallbladder lumen. Interrogation with color Doppler (not shown) showed internal vascularity within the mass, confirming a solid mass.

of patients undergoing cholecystectomy will have an incidental carcinoma [56].

Cholelithiasis is a risk factor in the development of gallbladder carcinoma as the stones cause chronic irritation and inflammation of the gallbladder wall. Congenital anatomic anomalies including the presence of a choledochal cyst, low insertion of the cystic duct, and abnormal junction of the pancreatic and common bile duct also predispose patients to gallbladder carcinoma. Patients with primary sclerosing cholangitis also may show increased risk [56].

Gallbladder carcinoma can have a variable appearance on ultrasound. They may present as an area of focal gallbladder wall thickening, an intraluminal polypoid mass (Figure 145.20), or a mass replacing the gallbladder. Wall thickening is a nonspecific finding but it has been suggested that gallbladder wall thickening greater than 1 cm with associated mural irregularity should prompt concern for malignancy or complicated cholecystitis [56].

Patients may present with acute symptoms suggestive of acute cholecystitis and there may be difficulty in differentiating between the two entities if there is no distinct mass. The possibility of an abnormal gallbladder being related to gallbladder carcinoma rather than acute cholecystitis should be discussed with the referring clinician so that during cholecystectomy a wider excision can be performed to provide for adequate negative margins.

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The echogenicity or the gray scale appearance of the pancreas may vary among patients. The degree of fatty replacement within the pancreas affects its echogenicity. The normal pancreas may be isoechoic or slightly hyperechoic relative to the liver (see Figure 145.21). With fatty replacement, the pancreas may become more echogenic, sometimes such that it is difficult to differentiate it from the surrounding retroperitoneal fat. In this situation, vascular landmarks may be helpful in localizing the pancreatic head.

The pancreatic duct and common bile duct can be seen on ultrasound within the pancreatic parenchyma. On transverse images of the pancreas, the pancreatic duct may appear as either a single echogenic line or two parallel lines (a tram-track appearance) within the pancreatic body located anterior to the splenic vein and portosplenic confluence. The common bile duct will appear as a round anechoic structure within the pancreatic head, located to the left of the portosplenic confluence on transverse images.

**Pancreatitis**

The main purpose of a right upper quadrant ultrasound in a patient diagnosed with acute pancreatitis is to evaluate for the presence of gallstones or common bile duct stones as a cause of the patient's pancreatitis. Ultrasound features of acute pancreatitis include diffuse enlargement, heterogeneity, and hypoechogenicity of the gland. Peripancreatic fluid may be seen [57]. However, the ultrasound appearance of acute pancreatitis may also be normal. Therefore, a normal appearance of the pancreas on ultrasound does not exclude the diagnosis of pancreatitis.

Since evaluation of the entire pancreas is almost always difficult secondary to gastrointestinal gas, detection of complications of acute pancreatitis should be performed with CT [58]. Ultrasound has limited utility in the evaluation of pancreatic necrosis. Ultrasound may be used as an adjunct to monitor complications so as to avoid further radiation exposure. Vascular complications include splenic or portal vein thrombosis as well as splenic artery aneurysm. Doppler and gray scale ultrasound can be used to evaluate the size and patency of these vessels. Focused evaluation for peripancreatic or left upper quadrant fluid collections can also be performed. Ultrasound is useful to guide drainage of such collections.

In chronic pancreatitis, pancreatic atrophy, ductal dilation, and parenchymal calcifications may be seen (Figure 145.22). It is important to evaluate if these findings are focal such as an abrupt cutoff of the pancreatic ductal dilation or the presence of an isolated cluster of calcification as these findings could suggest a more sinister process as the cause, such as pancreatic adenocarcinoma. Stones within the dilated pancreatic duct may also be seen.

**Pancreatic tumors**

Pancreatic adenocarcinomas can appear as focal masses within the pancreas or be more infiltrative in appearance, especially if large. Tumors are typically hypoechoic relative to the normal pancreatic parenchyma. Again features such as focal pancreatic atrophy, calcifications, or ductal dilation should be treated with suspicion and careful evaluation for a mass lesion should be performed. Masses within the pancreatic head may also cause common bile duct dilation as well as pancreatic ductal dilation – the so called “double duct” sign. Pancreatic adenocarcinoma may also affect the pancreatic vasculature. If a mass is suspected, patency of the superior mesenteric, splenic, and portal vessels...
Abdominal sonography

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With fluid, wall thickening may be better evaluated with ultrasound. Therefore, as with sonographic evaluation of the other abdominal organs, fasting for 6 hours or more is recommended to minimize bowel gas artifact.

For screening purposes, a 2 MHz to 5 MHz curved transducer is initially used to survey the abdomen and to perform a focused exam over any focal areas of pain or tenderness. If an abnormality is found within the bowel, the operator should switch to a higher frequency linear transducer (7.5 MHz to 13 MHz) in order to gain better resolution in evaluating the bowel. As switching to a higher frequency transducer limits penetration, this strategy works best for relatively superficial loops of bowel, such as the appendix and in thin patients.

Indications

The most common indications for focused sonographic evaluation of the bowel occur in the pediatric population in the diagnosis of appendicitis and intussusception. Both are used as first line imaging to avoid radiation exposure produced by CT or abdominal x-ray/fluoroscopy.

Appendicitis

To diagnose appendicitis, the appendix must first be visualized. A blind ending tubular structure typically in the right lower quadrant is identified (Figure 145.23). The abnormal appendix will have a diameter of 7 mm or greater and pain will be elicited should be assessed as tumor may occlude, extend into, narrow, or encase these vessels. Metastatic peripancreatic lymph nodes may also be seen separate to the mass, but have a similar sonographic appearance to the primary tumor.

Islet cell tumors may also present as hypoechoic masses on ultrasound. Twenty percent contain calcification [1]. Due to their hyperfunctioning status as in insulomas or gastrinomas, they may cause symptoms leading to their early discovery when small. Nonfunctioning islet cell tumors, on the other hand, may present later with larger masses and with metastatic disease.

Cystic pancreatic neoplasms can be divided into macrocystic lesions and microcystic lesions. Macrocystic lesions include mucinous cystadenomas and cystadenocarcinomas. These mucinous tumors appear as well defined cystic masses on ultrasound. They are most commonly found within the pancreatic body and tail in middle aged women. There may be internal septations and calcification present; the presence of mural nodularity or solid components is suggestive of a malignant tumor. Microcystic lesions include serous cystadenoma. These are benign lesions usually found in the pancreatic head in middle aged women. If the cysts are small, this neoplasm may appear as a solid mass on ultrasound. If the cysts are larger, in the range of 1 cm, ultrasound may resolve the cysts and the lesion may appear as a multicystic mass. They usually are large and well defined.

Masses incidentally seen on ultrasound should be referred to CT for further characterization. In addition, CT is the modality of choice in determining the resectability of a pancreatic tumor. Ultrasound is a useful modality to guide a pancreatic biopsy.

Gastrointestinal tract

Anatomy

The bowel has a multi-laminar appearance of alternating hypoechoic and hyperechoic layers under ultrasound correlating to the various tissue layers of bowel. This appearance is referred to as “gut signature.” The superficial mucosa, the inner-most layer, is typically hyperechoic, whereas the deeper muscularis mucosa is hypoechoic. Next a hyperechoic layer separates the muscularis mucosa from the hypoechoic muscularis propria. The outermost layer, the serosa, is hyperechoic [59]. All of these layers may not be seen consistently when imaged, but this multilaminar appearance is typical of bowel. The typical bowel wall thickness is 2 mm to 4 mm.

Ultrasound technique

The use of ultrasound in the diagnosis of intestinal abnormalities is limited by the presence of intraluminal air which can cause significant artifact, obscuring the walls of the bowel. Bowel wall thickening is a nonspecific finding, but may be seen in appendicitis, diverticulitis, and infectious or inflammatory enteritis or colitis. When the bowel is decompressed or filled with fluid, wall thickening may be better evaluated with ultrasound. Therefore, as with sonographic evaluation of the other abdominal organs, fasting for 6 hours or more is recommended to minimize bowel gas artifact.

For screening purposes, a 2 MHz to 5 MHz curved transducer is initially used to survey the abdomen and to perform a focused exam over any focal areas of pain or tenderness. If an abnormality is found within the bowel, the operator should switch to a higher frequency linear transducer (7.5 MHz to 13 MHz) in order to gain better resolution in evaluating the bowel. As switching to a higher frequency transducer limits penetration, this strategy works best for relatively superficial loops of bowel, such as the appendix and in thin patients.

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Appendicitis

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Intussusception is one of the most common and most serious causes of abdominal pain in children. Children between the ages of 6 months to 2 years are typically affected. Patients present with colicky abdominal pain and bloody stools. The stool may appear a "currant jelly" appearance. Patients may also present with an abdominal mass in the area of intussusception [60]. Intussusception occurs when one part of the bowel telescopes into an adjacent part of bowel. Transient intussusceptions may occur; complications and symptoms occur when intussusceptions persist. In children, the most common type of intussusception is an ileocolic intussusception. Mostly thought to be idiopathic, there may be a lead point in the involved bowel that may predispose the bowel to intussusception. In children it is thought to be related to lymphoid tissue hyperplasia in the terminal ileum. In older patients, this may be related to a mass such as a lipoma, or a tumor. Intussusceptions must be reduced in order to avoid complications such as bowel ischemia and obstruction.

Regardless of the location of the intussusception (colo-colic, ileo-colic, or small bowel intussusception), the ultrasound appearance of the intussusception remains the same. On transverse images, the mass created by the intussusception has a donut-like, or target-like appearance with multiple concentric rings. The intussuscipiens (receiving segment) is located on the outside and the intussusceptum (the telescoping bowel) in the inside. The intussusceptum is accompanied into the intussusception by adjacent mesenteric fat and vasculature. Together the two segments of bowel yield two hypoechoic concentric rings, separated by a hyperechoic rim of mesenteric fat [59]. Sagittal images will show the intussusceptum partially enveloped by the intussuscipiens (Figure 145.24).

Once a diagnosis of intussusception has been made on ultrasound, the pediatric patient is usually referred for air reduction enema. Ultrasound can be repeated once the intussusception is reduced to monitor for recurrence. In children with long-standing intussusception with the possibility of complications or in adult patients with underlying masses, surgery may be required to reduce the intussusception and resect the predisposing mass.

**Intussusception**

Intussusception occurs when one part of the bowel telescopes into an adjacent part of bowel. Transient intussusceptions may occur; complications and symptoms occur when intussusceptions persist. In children, the most common type of intussusception is an ileocolic intussusception. Mostly thought to be idiopathic, there may be a lead point in the involved bowel that may predispose the bowel to intussusception. In children it is thought to be related to lymphoid tissue hyperplasia in the terminal ileum. In older patients, this may be related to a mass such as a lipoma, or a tumor. Intussusceptions must be reduced in order to avoid complications such as bowel ischemia and obstruction.

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**Other causes of bowel wall thickening**

In adults, abdominal ultrasound is not routinely used in the evaluation of small or large bowel pathologies in the United States. However, in the course of imaging the solid organs of the abdomen, the bowel may be imaged and bowel pathologies may be manifested by bowel wall thickening or dilation. Bowel wall thickening is a nonspecific finding and can be seen in diverticulitis, inflammatory bowel disease, and infectious enteritis or colitis. These etiologies may be accompanied by pain when the transducer is placed over the site. As with appendicitis, once diverticulitis or inflammatory bowel disease is suspected, evaluation for adjacent collection or abscess should be performed. Small bowel dilation and fluid filled bowel may be seen in small bowel obstruction.

**Peritoneal cavity**

Besides evaluation of the solid organs, ultrasound can be used to evaluate the peritoneal cavity for fluid. Common indications include the evaluation for ascites or focal fluid collections such as abscesses or hematomas. Solid peritoneal masses such as omental implants or mesenteric lymph nodes can be seen with ultrasound on occasion. While these masses are better detected with CT, ultrasound can be used to locate and target these lesions for biopsy once diagnosed.

**Intraperitoneal fluid**

Simple free fluid as in transudative ascites from congestive heart failure or cirrhosis is anechoic, or completely black, on ultrasound. More complex free fluid, containing higher amounts of protein, such as in malignant ascites, bacterial peritonitis, or intraperitoneal hemorrhage, may appear hypoechoic with low
Due to the presence of internal debris within the abscess, the lesion may not show increased through transmission, and therefore may mimic a solid mass. Use of color Doppler may help differentiate solid from fluid containing masses. Internal vascularity will confirm the presence of a solid mass, although the lack of internal vascularity found within a lesion does not exclude a solid mass. A mass deep within the peritoneal cavity or a hypovascular mass may not show internal vascularity due to its deep location relative to the transducer.

Evaluation for a focal fluid collection is limited by the availability of sonographic windows. In postoperative patients with drains, open wounds, and bandages who cannot move, the ability to image the region of interest may be hampered and collections can be missed. Overlying bowel gas may also obscure the collection. In these cases, CT should be performed to completely evaluate the peritoneal cavity for such collections.

**Peritoneal masses**

There is limited utility of ultrasound in the diagnosis of peritoneal masses when compared to CT. However, in cases of suspected peritoneal carcinomatosis with peritoneal or omental implants on CT, ultrasound may be useful in the targeting of such lesions for tissue confirmation. The omentum is a fat containing structure deep to the anterior abdominal wall, attaching like an apron over the transverse colon. The normal omentum appears as homogeneous echogenic tissue posterior to the abdominal wall musculature. Solid omental implants will appear as solid hypoechoic masses disturbing this homogeneity. Peritoneal carcinomatosis manifested by stranding within the omentum on CT will not be seen under ultrasound as there will not be sufficient soft tissue tumor to distinguish it from the hyperechoic omentum on ultrasound.

In patients with inflammatory conditions of the bowel or mesentery, such as appendicitis, Crohn’s disease, or mesenteric adenitis, enlarged mesenteric lymph nodes may be visualized with ultrasound.

**Intraoperative sonography**

Due to its portability, sonography can be used in the operating room to provide real time imaging guidance to the surgeon. The most common organs evaluated in the operating room are the liver and the pancreas. Due to the ability to image the organ of interest directly without intervening soft tissue or air, there is significantly improved ability of ultrasound to resolve lesions as little as 2 mm as compared to lesions in the 5 mm to 10 mm range on preoperative ultrasound imaging [61]. Dedicated transducers with sterile probe covers are used. The ideal transducers have a small footprint and allow for flexible positioning. Commonly used probes include the fingertip probe and the hockey stick probe owing to their handling and shape, respectively. With the fingertip probe, the user is able to mount the probe onto his or her finger, guiding the transducer over the

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**Figure 145.25** Exudative ascites surrounding loops of bowel (arrows) in the left lower quadrant. Instead of the fluid being anechoic, note internal echoes within the fluid, suggesting complex free fluid (H). In this patient, it was caused by hemoperitoneum.
organ using only his or her fingertips. Tactile sensation is an important intraoperative tool that the surgeon uses to guide the procedure; use of a fingertip ultrasound probe provides corresponding imaging information over the area in question. Typical frequencies of a fingertip probe are 5 MHz to 10 MHz range. Hockey stick probes are shaped like their name implies; which allows flexibility in positioning of the tip and ability to image tight locations. Frequencies are higher than the fingertip probe, usually between 7 MHz to 13 MHz, allowing for better resolution. Hockey stick probes are commonly used to image small parts and vascular flow [62].

Common indications for intraoperative sonography of the liver include: survey for primary and metastatic lesions; guidance for tumor resection, biopsy, or ablation; evaluation of vessel patency and vascular anatomy; and evaluation for extrahepatic disease [61]. Common indications for intraoperative ultrasound of the pancreas include evaluation of masses and their resectability. This is especially useful for nonpalpable pancreatic masses, especially in small lesions such as the islet cell tumors.

References are available at www.yamadagastro.com/textbook

Further reading

CHAPTER 146

Endoscopic ultrasonography

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Introduction

Endoscopic ultrasonography (EUS) is an established diagnostic and therapeutic modality in gastroenterology with increasing widespread use. Although most gastroenterologists are not trained in the practice of EUS, it is important that they all understand the principles of the technique and the indications (diagnostic and therapeutic) for EUS to offer optimal patient care.

This chapter outlines the principles of EUS, provides a brief overview of the equipment, and details the indications for EUS in commonly encountered clinical scenarios. Particular attention is paid to the role of EUS and EUS-guided tissue sampling in relation to other imaging modalities. This is not a comprehensive chapter on the practice of endosonography and the authors recommend that anyone interested in learning EUS should review textbooks dedicated to the practice of EUS and to seek out an established EUS training program.

Technical considerations

Basic properties of sound waves

EUS is the addition of an ultrasound transducer to the tip of an endoscope, which allows ultrasound-generated imaging of the gastrointestinal tract and adjacent anatomical structures. The ability to image in real time from inside the gastrointestinal tract has led to diagnostic and therapeutic indications. A basic knowledge of the principles of ultrasonography is required to understand EUS. Chapter 145 is a detailed review of sonography, and this section reviews those ultrasound principles related to EUS generation and interpretation.

Sound is mechanical energy generated in the form of vibrations as they propagate through a medium such as air, water, or tissue [1]. The frequency of a sound wave is measured in Hertz (1 Hz = 1 cycle/s) and the ultrasound frequency used in medical technology is in the range 1–30 MHz (1 MHz = 1 000 000 cycles/s). The velocity of an ultrasound wave is a product of the frequency and wavelength, and the velocity in a specific tissue depends on the acoustic impedance of that particular tissue. Hence, each tissue, based on its density and elastic properties, propagates sound waves at a particular velocity. Tissues with similar acoustic impedance will propagate similar amounts of sound waves, whereas tissues with different acoustic impedance will reflect the majority of sound waves. Air, bone, and fat have different acoustic impedances compared with soft tissue [2].

Ultrasound waves interact with tissue in four ways: reflection, refraction, scattering, and absorption:

- Reflection is when the sound wave strikes a surface at a non-perpendicular angle and is thus reflected at an angle equal to the angle of incidence. If a sound wave encounters a medium interface with different acoustic impedance, a proportion of the ultrasound waves will be reflected back to the transducer while the remainder of the waves will be transmitted to the second medium.
• Refraction is the amount of bending the transmitted wave experiences. This occurs when there is a difference in the acoustic velocities of the incident and transmitted mediums, and is analogous to light traveling through a prism.
• Scattering occurs when a propagating ultrasound wave interacts with different components in a tissue that are smaller than the wavelength and with different acoustic impedance than the propagating medium. When scattering occurs, only a small portion of the scattered wave is reflected back to the transducer. Examples of scatterers include collagen, fat goblets, and individual cells [1].
• Absorption is when tissue assimilates the ultrasound wave and generates heat. Higher frequencies cause more tissue vibration resulting in greater absorption of the ultrasound energy and more heat generation.

Components of an echoendoscope
The main components of an EUS system include the transducer, processor, and display monitor. A transducer is a device that generates the ultrasound pulse by converting electrical energy into mechanical energy. The piezo ceramic element is the component responsible for the conversion of energy. The piezo electric crystals vibrate when an electrical impulse is applied to them, generating an ultrasound wave that is propagated toward the surrounding tissue. A proportion of the ultrasound waves are reflected back to the transducer and subsequently converted back into an electrical impulse that is processed and displayed as an image on the monitor. The intensity of the returning echoes determines the brightness of the pixels on the screen, thus generating shades of black and white [2].

There are two types of the transducers, single element and phased array. Single-element transducers are mechanically rotated 270°–360° on an axis that is perpendicular to the axis of the endoscope; these are referred to as mechanical echoendoscopes. This is in contrast to phased-array transducers, where the piezo ceramic crystals are stimulated by electric pulses sweeping along the long axis of the endoscope; these are referred to as electronic echoendoscopes [2].

The processor controls the transducer and amplifies the returning signal. When a transducer is perpendicular to the reflected waves, the greatest quantity of echoes are garnered by the transducer and the resulting image is optimized. As a result of scattering and absorption (see previous section for details), echoes that are returning to the transducer from greater distances are attenuated. These weak signals may require amplification (i.e., time gain compensation [TGC]). TGC allows the EUS operator to adjust the amplification (gain) of the signal at varying distances from the transducer. Increasing the gain will increase detection of weak echoes while sacrificing resolution [2]. The operator can also increase the frequency of the ultrasound, which improves the resolution of the image. However, higher frequencies result in greater ultrasound wave absorption and decreased penetration, which leads to a reduced range of imaging.

Principles of imaging
It is important that the endosonographer has a basic understanding of the characteristics involved in determining image quality and the various modes available for imaging. These characteristics include resolution and artifacts of imaging, and modes such as A-mode and B-mode scanning, and Doppler.

Spatial resolution (the ability to discriminate two points as separate) is vital for quality imaging. Axial resolution is the ability to discriminate between two points along the beam path and is dependent on the frequency of the ultrasound wave. Axial resolution is the most important property in imaging the layers of the gastrointestinal tract. Lateral resolution is the ability to discriminate between two points in the same plane perpendicular to the transmitted ultrasound wave [1]. To achieve optimal lateral resolution, the ultrasound beam from the object of interest must lie in the narrowest portion, termed the focal zone. Radial echoendoscopes have a fixed focal zone (1.5 cm–3.5 cm), which requires that the operator manipulate the EUS endoscope such that the target being imaged is located within the focal zone. Electronic array echoendoscopes have a variable fixed focal zone that is adjusted using the processor [2].

Since EUS imaging and interpretation are performed in real time, the endosonographer must be able to recognize image artifacts. Ultrasound waves can interact with adjacent tissue and fluid to create artifacts of imaging. An artifact is any phenomenon that does not accurately represent the target being imaged. The most common image artifacts are listed in Box 146.1, and several of these are reviewed further on. A trained endosonographer must accurately identify and interpret such artifacts, so as to provide an accurate assessment of the ultrasound image and procedure.

Reverberation can occur when a single ultrasound beam is bounced back and forth between the transducer and a highly reflective surface until the signal is attenuated beyond detection of the processor. This can result in a false image deep to the true image; this artifact can be mitigated using TGC [1,2]. Acoustic shadowing occurs when a large impedance mismatch is encountered by the ultrasound wave, and there is intense hyperechoic reflection at the surface associated with an anechoic signal.

Box 146.1 Artifacts of ultrasound imaging.
Reverberation: multiple reflections between transducer and a strongly reflective surface
Reflection (mirror image): an air–water interface acts as a mirror, placing image at deeper depth than in reality
Refraction: difference in the acoustic velocities of the incident and transmitted mediums, resulting in objects placed erroneously at locations different from their true location
Acoustic shadowing: large impedance mismatch results in hyperechoic signal at interface and anechoic signal beyond interface
Acoustic enhancement: enhancement of structure beyond a fluid-filled structure
Side-lobe artifacts: a hyperechoic signal within an anechoic structure that disappears with scope repositioning
by the interface. Acoustic shadowing is a phenomenon often seen when imaging calcified lesions, such as in chronic pancreatitis or gallstones. Acoustic enhancement is the relative increase in ultrasound transmission in structures beyond a fluid-filled structure, and is due to less attenuation of the ultrasound wave as it travels through a fluid-filled structure in comparison to the surrounding tissues. This is commonly seen in the gallbladder, urinary bladder, vascular structures, and cysts [2]. The mirror image artifact occurs in the setting of a highly reflective surface behaving as a mirror. The EUS machine places the image at a deeper depth than in reality, and is commonly seen when visualizing the rectum or intraluminal gas in the rectum.

Scanning is the processing of the received signal, which can be visualized in several imaging modes. The received signal is amplified (A-mode, or amplitude mode) by the processor to yield an A-mode signal. Most clinicians do not image using A-mode but it forms the basis of the most common type of imaging, B-mode (brightness mode). B-mode scanning is created by processing a series of A-mode signals, the amplitude of the signal being reflected by the brightness of the dot on the display monitor. EUS systems generate images from a compound B-mode scan [1].

Doppler is a feature available on all EUS processors and takes advantage of the Doppler shift phenomenon. This states that an object in motion relative to the transducer will reflect an ultrasound wave at a different frequency relative to the frequency transmitted by the transducer. Hence, the returning wave reflected from an object moving toward the transducer will contain a higher frequency, and vice versa. The most common application of Doppler is imaging of blood flow, and assisting in the identification of blood vessels. Continuous-wave Doppler is the simplest configuration of Doppler ultrasound, consisting of a receiving and transmitting transducer. However, continuous-wave Doppler does not provide information about the depth at which the movement is occurring. Pulsed-wave Doppler consists of a single transmitting and receiving transducer that emits and receives a lengthy pulse wave and uses electronic gating to calculate depth information. Using pulse-wave Doppler with B-mode imaging is called duplex scanning. Color Doppler combines the principles of pulse-wave Doppler and shades of red or blue to reflect the relative velocities of blood flow. Immobile objects are represented on gray-scale B-mode imaging, and on this background, information regarding direction and relative velocity of blood flow are obtained. Power Doppler is the most sensitive Doppler for detecting blood flow, providing information on the presence of blood flow but no information on the relative velocity or direction of blood flow [1].

**Equipment**

Echoendoscopes can be broadly classified into two types, radial (or sector) and linear (convex array); each type is available with either a mechanical or electronic transducer. A variety of EUS catheter probes are available for imaging of small submucosal lesions and from within the biliary and pancreatic ducts. Along with the echoendoscope, the standard equipment must include an EUS processor, balloons, and needles for tissue sampling if fine-needle aspiration (FNA) is planned. This section focuses on the main types of echoendoscope and their uses. It does not focus on the specific competing products available for purchase in the market (Figure 146.1a–c).

**Radial echoendoscopes**

Radial echoendoscopes provide circumferential views at right angles to the echoendoscope. The mechanical radial echoendoscope has been the workhorse of EUS by providing cross-sectional anatomical images with a 270°–360° field of imaging coupled with an oblique-viewing endoscope. Current generations of radial echoendoscope include electronic array with oblique or forward-viewing endoscopic optics. The electronic technique allows for the addition of Doppler to the radial echoendoscope. A balloon is situated over the transducer tip to allow for water-filled acoustic coupling to the wall of the gastrointestinal tract, and imaging can be performed at a variety of frequencies from 5 MHz to 20 MHz with a range of up to 12 cm (Figure 146.1a). Typically, radial echoendoscopes are used for evaluation of gastrointestinal cancer staging, mucosal and subepithelial lesions, bile duct stones, and peripapillary lesions.

**Linear echoendoscopes**

The linear echoendoscope provides an imaging view analogous to transabdominal ultrasonography. The ultrasound waves are transmitted in the same axis as the long shaft of the transducer, which allows for real-time therapeutic intervention, most commonly FNA. By advancing the FNA needle in the plane of the ultrasound wave, the endosonographer can visualize the needle in real time as it is inserted into the lesion for cellular acquisition. The linear echoendoscope has a 120°–180° field of imaging, and biopsy channel diameters range from 2.0 mm to 3.8 mm (therapeutic) (Figure 146.1b). The therapeutic channel has enabled significant advances in interventional EUS.

**Catheter probes**

Ultrasound probes vary in their design and capabilities. They consist of a flexible shaft with a central wire that drives the rotation of the mechanical transducer at the tip. The transducer is surrounded by oil, which provides the acoustic interface with tissue, providing a 360° view. Techniques to improve probe-based imaging include close apposition of the probe to tissue with air aspiration; instillation of liquid into the gut lumen; use of a condom over the tip of the endoscope; and use of a balloon sheath over the probe. Catheter probes are available in various diameters (2–2.9 mm) and frequencies (12–30 MHz) [3–5]. A 2.9 mm guidewire-based EUS probe is available with imaging at 20 MHz that can be advanced via a side-viewing duodenoscope.
Figure 146.1 Types of echoendoscopes. (a) Radial imaging electronic echoendoscope. (b) Linear (convex array) echoendoscope. (c) Over-the-wire esophagoprobe.

into either the biliary or pancreatic duct for intraductal imaging. The most common applications for catheter-based probes include assessment of small superficial lesions of the gastrointestinal tract, evaluation of submucosal nodules, and examination of pancreaticobiliary ductal pathology including choledocholithiasis and ductal strictures.

**FNA needles and techniques**

Various standard FNA needles are available for use, ranging from 19-guage to 25-guage. The 22-guage and 25-guage needles are most often employed for FNA sampling and the 19-guage needle is most often employed for obtaining larger samples, such as core biopsies, and therapeutic interventions, such as celiac plexus neurolysis and pancreatic pseudocyst drainage. The 19-guage needle can accommodate a standard guidewire for interventional procedures. There is no single needle diameter or technique that is proven to result in higher cytological yield.

There has been increased interest in recent years to improve the amount and quality of tissue obtained with FNA needles, leading to development of different needles and sampling techniques. In particular, a distinction is now made between fine needle aspiration (FNA) using standard needles and fine needle biopsy (FNB) using core biopsy needles. However, comparisons of the needle gauge have shown that the needle size (smaller vs. bigger gauge) does not influence the diagnostic yield.

The EUS Tru-Cut biopsy needle (Quickcore, Cook Medical, Winston-Salem, NC, USA) is designed to provide core tissue sampling through a linear echoendoscope, including benign liver parenchyma (as an alternative to percutaneous liver biopsy). However, this needle is soon to be removed from the market. A relatively newer core biopsy needle (Cook Medical, Winston-Salem, NC, USA), 25-, 22- or 19-guage, has been shown in randomized trials to lead to comparable accuracy for cytologic diagnosis of solid pancreatic masses, with fewer number of passes (including one study demonstrating high single pass yield even with smaller 25-guage needle) but varying results on sample quality.

The specific technique for performing EUS-FNA and EUS-FNB has also been debated. Traditionally, endoscopists have used either a “jabbing” (multiple to-and-from movements of the needle tip within the same area of the lesion) or “fanning” technique (needle is moved back-and-forth in four different areas within the lesion). The use of suction (and how much, as well as whether continuous versus intermittent), or no syringe suction on the needle during FNA has been studied, with some studies showing more blood but not much more diagnostic tissue when suction is used. Hence, many endosonographers use suction only for cysts and not solid lesions. More recently, a “stylet slow pull-back” (capillary) technique involving no suction and gradual slow pull back of the stylet while the needle is moved to-and-fro within the target lesion multiple times can lead to acquisition of multiple mini-core biopsies.
Endoscopic ultrasonography CHAPTER 146

Needle-based confocal laser endomicroscopic and fiberoptic imaging

Novel approaches to EUS needle-based tissue imaging have been developed in recent years. A very thin fiberoptic probe that enables contrast-enhanced confocal laser endomicroscopy (nCLE) of tissues has been developed (Mauna Kea Technologies, France). This fiberoptic probe is passed through a 19-gauge standard FNA needle after it has been advanced into a solid or cystic lesion. Intravenous fluorescein is injected (off label use). A pilot study reported technical challenge in 30% and pancreatitis in 11% [10]. Another small pilot study including lymph nodes, cystic and solid pancreatic masses reported visualization of irregular tumor vessels, fluorescein leakage, and dark malignant cells [11]. A larger multicenter study in 66 pancreatic cyst patients reported technical failures but visualization of villous type structures, with nCLE sensitivity of 59%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 50% [12]. Moreover, the adverse event rate was high (9%) compared to EUS-FNA, and including pancreatitis, pain, and bleeding [12]. The role of nCLE in relation to diagnostic EUS/FNA is uncertain and is still under evaluation.

Diagnostic EUS general considerations

The ultrasound image of the normal gastrointestinal tract is dependent on the ultrasound frequencies used. Frequencies of 5–12 MHz produce five layers, while frequencies of 20–30 MHz depict seven to nine layers (Figure 146.2) [12]. Most commonly, there are three echogenic layers separated by two echo-poor layers. The first echogenic layer, beginning at the mucosal surface, is thin and is produced by the interface between lumenal fluid or the balloon and the mucosa. The second layer is echo-poor and represents the remainder of the mucosa. This layer was formerly attributed to the muscularis mucosae; however, the normal muscularis mucosae is too thin to account for entire second layer [12]. The muscularis mucosae is usually obscured by an echo occurring at its interface with the lamina propria so that the location of the muscularis mucosae corresponds to the most superficial part of the third (submucosal) layer. If the muscularis mucosae is thicker than the interface echo, a separate thin hypoechoic layer is seen between this interface echo and the underlying submucosal layer [13]. The third ultrasound layer is easily recognizable because it is the most echogenic. This layer corresponds to the submucosa but is thicker because it also includes the interface between the submucosa and muscularis propria [12]. The fourth layer is echo-poor and corresponds to the muscularis propria. In areas with a well-developed inner circular and outer longitudinal muscle component, a small amount of connective tissue between the muscle layers may produce a line of echoes within the muscularis propria [12,13]. The fifth layer is echogenic but of variable thickness. If no subserosal fat or inflammation is present, this echogenic layer corresponds to the serosa and the interface between the serosa and the surrounding tissue. The layer can be thick in the rectum, where there is often abundant echogenic perirectal fat.

The appearance of organs in the mediastinum and abdomen is roughly similar to that seen by transcorporeal ultrasound, but often in greater detail. The posterior mediastinum, the aortopulmonary and subcarinal regions, portions of the heart, and the great vessels can be visualized with the transducer in the esophagus. The liver and spleen are homogeneous and of intermediate echogenicity; the liver can usually be differentiated from the spleen by the bright echoes adjacent to the anatomical layers and from the acoustic interfaces between tissue layers.

Figure 146.2 The five layers of the stomach wall. (a) Normal five-layer endoscopic ultrasonography image of the stomach wall: m, mucosa; sm, submucosa; mp, muscularis propria. (b) The layers of the normal gastrointestinal wall as seen on ultrasound images. The ultrasound image comprises echoes arising from the anatomical layers and from the acoustic interfaces between tissue layers.
echogenicity, internal echo pattern, and the character of their outer margin have been reported [14–16]. Malignant lymph nodes are usually echo-poor with sharply defined borders. The internal echoes from the nodes can be homogeneous or inhomogeneous. Benign nodes tend to have poorly defined boundaries and may be hyperechoic (Figure 146.4). When nodes are over 1 cm in diameter, hypoechoic, and have a rounded distinct border, there is an 80%–100% probability of malignant involvement [17,18]. However, it is increasingly clear that the diagnosis of a malignant lymph node by EUS appearance alone has limitations, which has led to the increased use of EUS-guided needle aspiration for pathological confirmation of suspicious nodes [6,19].

Additional modalities for improving the sensitivity of EUS for distinguishing benign from malignant pancreatic masses [13], suspected gastrointestinal stromal cell tumors (GIST) [14,15], lymph nodes [16,17] include administration of intravenous contrast agents (contrast-enhanced EUS) and elastography. Contrast-enhanced EUS is more commonly performed outside the United States where regulatory issues and cost prevent routine use of contrast agents approved for cardiovascular imaging. One prospective multicenter trial showed comparable performance of contrast-enhanced EUS with EUS-FNA cytologic diagnosis of pancreatic adenocarcinoma (accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 95%, 96%, 94%, 97%) [18]. Overall, contrast agents appear to be comparable to EUS-FNA and studies show that it cannot replace cytologic tissue sampling. Elastography can be performed only with the Pentax echoendoscope and Hitachi ultrasound processor. It involves detection of differential stiffness (or low elasticity) of diseased tissue (such as cancer) using either qualitative differences in coloration (blue is bad, green is good) or quantitative differences in the strain ratio of the target lesion compared to a reference normal adjacent tissue.

Multiple studies [19–23] and a metaanalysis [19] underscore the concept that elastography has modest diagnostic utility and should be considered an ancillary technique. Like contrast EUS, it cannot replace EUS-FNA for differential diagnosis of benign versus malignant lesions. One interesting potential application of elastography for benign disease is the quantitative analysis of stiffness as a predictor of pancreatic fibrosis when compared to MRI and functional testing [24] as well as histologic resection specimens [25].

**Diagnostic EUS Indications**

**Esophageal cancer**

It is estimated that in 2007, esophageal cancer will affect over 14,000 individuals in the USA and result in over 13,000 deaths.
for T-stage is 80%–85%, with highest accuracy in staging T3 and T4 disease [32,39–47]. EUS is superior to CT and PET for assessing T-stage of esophageal malignancy, and should be the test of choice.

Although less than 5% of T1m tumors are associated with nodal spread, 60% of T2 and more than 80% of T3/T4 lesions are associated with malignant nodal spread [48–50]. The presence and number of malignant lymph nodes portends poor prognosis and often shifts the treatment paradigm toward neoadjuvant therapy [51,52]. CT and FDG-PET are inferior to

The International Union against Cancer and American Joint Committee on Cancer updated the guidelines in 2002 for staging esophageal cancer. The involvement of cervical or celiac axis lymph nodes is classified as metastatic disease (M1a or M1b, depending on tumor location). Tumor of the lower esophagus with celiac axis lymph node spread is classified as M1a disease, as is tumor of the upper esophagus with cervical lymph node involvement. Tumor of the mid esophagus with either cervical or celiac axis lymph node spread is classified as M1b disease, and also stage IV disease [28]. In general, early lesions (T1N0, T2N0) undergo surgery while presence of any lymph nodes usually mandates neoadjuvant therapy. Esophageal cancer patients who undergo EUS are associated with improved survival, probably due to accurate staging resulting in the use of stage-appropriate adjuvant therapy and surgical resection [29].

**Early esophageal cancer**

Early esophageal cancer (carcinoma-in-situ or T1N0Mx) is most commonly detected in patients undergoing aggressive surveillance. When such lesions are identified, high-frequency EUS demonstrates excellent cross-sectional gastrointestinal tract images to assess T and N stage. In patients with Barrett esophagus with high-grade dysplasia or intramucosal carcinoma, EUS is more sensitive than CT for T and N stage. It can detect previously unknown submucosal involvement (sensitivity 100%, specificity 94%) and lymph node metastasis (sensitivity 100%, specificity 81%), and the absence of these findings on EUS is reassuring to physicians that the patient has early esophageal cancer or carcinoma-in-situ (NPV 100%) [30,31]. EUS confirmation of early malignant lesions allows nonoperative curative endoscopic ablative techniques, if desired.

**Advanced esophageal cancer**

Patients with locally advanced esophageal cancer should initially be evaluated with CT (and FDG-PET if available), searching for distant metastatic disease. The accuracy of CT ranges from 63% to 90% [32,33], and is not as sensitive in detecting small hepatic lesions or peritoneal metastases compared with diagnostic laparoscopy [34,35]. EUS can complement CT by improving the accuracy for M-staging by detecting cervical or celiac axis lymphadenopathy (M1a or M1b disease) [32], adrenal gland or liver metastases, or malignant ascites. FDG-PET is superior for detecting distant metastasis and nonregional lymph nodes compared with CT plus EUS (82% vs. 64%), and may up-stage patients to stage IV [36–38] (Figure 146.5).

The locoregional staging of a malignant esophageal stricture is a common indication for EUS. The overall accuracy of EUS for T-stage is 80%–85%, with highest accuracy in staging T3 and T4 disease [32,39–47]. EUS is superior to CT and PET for assessing T-stage of esophageal malignancy, and should be the test of choice.

Although less than 5% of T1m tumors are associated with nodal spread, 60% of T2 and more than 80% of T3/T4 lesions are associated with malignant nodal spread [48–50]. The presence and number of malignant lymph nodes portends poor prognosis and often shifts the treatment paradigm toward neoadjuvant therapy [51,52]. CT and FDG-PET are inferior to
EUS in the evaluation of locoregional lymphadenopathy. The accuracy of CT is estimated to be only 51%–70% [32,53], and FDG-PET lacks the spatial resolution to differentiate local nodal involvement from adjacent primary tumor, and reactive inflammatory lymph nodes can lead to false-positive results. The sensitivity of PET for detection of N1 disease is approximately 33% [36].

EUS assessment of lymphadenopathy is accomplished by visualization and FNA. The accuracy of EUS in classifying a lymph node as malignant based on appearance is approximately 80% [17,18,28] and the overall sensitivity of EUS in detecting malignant lymphadenopathy ranges from 50% to 75% with an accuracy of 65% [17,18,32,46]. The accuracy is increased to 85%–93% with the addition of FNA [54,55]. It should be noted that when performing FNA of a lymph node, a false-positive sample can be obtained if the needle tract penetrates through primary tumor, thus contaminating the FNA sample. Hence, FNA of peritumoral lymph nodes may not be always feasible. Common hiding places for metastases from esophageal malignancies are the region above the aortic arch (outside the cervical esophagus), the gastrohepatic ligament, and the celiac axis region.

A common clinical scenario is the nontraversable malignant esophageal stricture, where the standard echoendoscope is unable to pass beyond the stricture without prior dilatation to 14–16 mm. Although perforation is a risk, dilation can be performed safely, and is indicated. Wallace and colleagues reported that 32% of their 132 patients required dilation for adequate staging, and only one patient suffered a perforation. In addition, 19% of patients would have been under-staged if dilation had not been performed [56]. In cases when the stricture is so tight that dilation and passage of the standard echoendoscope is not feasible, a catheter ultrasound probe or an over-the-wire esophagoprobe (Olympus MH-908, Tokyo, Japan) can be used [28] (see Figure 146.1c). Unfortunately, if celiac lymphadenopathy is detected, FNA cannot be performed.

Submucosal lesions
A submucosal lesion is an endoscopically visible, often incidental finding (i.e., a “bump”) with normal overlying mucosa. The estimated prevalence of gastrointestinal submucosal findings is less than 1%, and is most commonly found in the stomach [57,58]. EUS is well suited for evaluating submucosal lesions because of its ability to visualize gut wall layers and abdominal structures and to safely perform FNA. Table 146.1 lists the common etiologies of submucosal gastrointestinal lesions and their descriptive EUS features.

Causes of extrinsic compression include adjacent organs, bowel, blood vessels, retroperitoneum, omentum, and lymph nodes [57,59–67]. The frequency is approximately 30%. The accuracy of CT and transabdominal ultrasonography for differentiating between extrinsic compression and a true submucosal lesion is 22% and 28% respectively compared with an EUS accuracy of 100% [65].

After excluding extrinsic compression, the approximate frequency of gastrointestinal submucosal lesions is as follows: smooth muscle neoplasm (53%), aberrant pancreas (8%), carcinoid (6%), cystic lesion (7%), granular cell tumor (4%), lymphangioma or hemangioma (4%), Brunner gland hyperplasia (1%), malignant lymphoma (1%), and other (8%) [57]. Most smooth muscle neoplasms are gastrointestinal stromal cell tumors (GISTs), but older studies do not differentiate GISTs from other mesenchymal tumors.

When evaluating a submucosal lesion by EUS, a variety of clinical issues need to be addressed. In many cases, the endosonographic appearance and characterization of which gut layer(s) the lesion originates from will narrow the differential. However, issues regarding differentiation between benign and malignant lesions, role of FNA and surveillance of lesions need further clarification. Several of the submucosal lesions are discussed in further detail.

Gastrointestinal stromal cell tumor
Gastrointestinal stromal tumors, the most common mesenchymal tumors, arise from the interstitial cells of Cajal and often express a protooncogene called c-kit, which confers a gain-of-function mutation to such lesions. Immunohistochemical staining can differentiate GISTs from other related lesions [68]. Approximately 80% of gastrointestinal mesenchymal tumors are GISTs, and 10%–30% of GISTs are malignant [68,69]. All GISTs are considered to be potentially cancerous, and are stratified
into low-, medium-, or high-risk category depending on tumor size and mitotic count. However, GISTs can be unpredictable, and low-risk lesions have been reported to metastasize [57,70].

Most GISTs are located in the stomach or duodenum [71] and under EUS appear as a homogeneous, hypoechoic, well-circumscribed lesion that originates from either the muscularis mucosae or muscularis propria (Figure 146.6). EUS features suggestive of malignancy include tumor size more than 4 cm, an irregular extraluminal border, echogenic foci, and cystic anechoic spaces (suggestive of necrosis). If two of the four features are present, the sensitivity ranges from 80% to 100% for detecting a malignant GIST [72]. Additional notable features suggestive of malignancy include malignant-appearing lymph nodes, ulcerated mucosa, and nonoval shape [59,72–75]. The lack of these features does not rule out malignancy. Recent use of contrast agents to visualize tumor vessels in suspected GISTs raised the possibility of differentiating benign from malignant GISTs with sensitivity of 100% in one prospective single center study [15].

Current guidelines recommend resection of symptomatic or large suspected GISTs and surveillance of smaller lesions ≥2 cm. Hence, tissue sampling of FNA of suspected GISTs <2 cm should be performed [76], when possible, to assist with decision-making regarding surgery or surveillance. For the diagnosis of small GIST <20 mm, the sensitivity and positive predictive value (PPV) of EUS-FNA were 81.3% and 100%, respectively, in one study, but other studies report lower diagnostic rates (67.8%) even with adequate on-site cytological evaluation [77]. EUS-FNA/FNB with immunohistochemical staining is the only reliable method for diagnosing a GIST. Approximately 90% of GISTs express CD117 (c-kit) and its presence confirms the diagnosis but does not assess malignant potential [78]. A new ancillary technique to EUS-FNA for improving diagnosis of GISTs is a jumbo biopsy “unroofing” technique.

The question remains of how to manage an asymptomatic mesenchymal lesion, particularly if it is less than 1 cm in size, where the risk of malignancy is believed to be low. It may be useful to perform FNA on a small suspected GIST for immunohistochemical confirmation. Medications that target CD117-positive GISTs are available. There is no proven EUS-based strategy for optimal surveillance of suspected GISTs; however, a reasonable strategy may be annual EUS surveillance for small asymptomatic lesions without any features of malignant transformation.

**Lipoma**

Lipoma, a benign tumor composed of mature lipocytes, is most often asymptomatic. It appears as a well-circumscribed, homogeneous, hyperechoic lesion arising from the submucosa (third layer). FNA is not required to confirm the diagnosis as its appearance is pathognomonic [79,80].

**Carcinoid**

Carcinoids are slow-growing, premalignant, neuroendocrine tumors primarily found in the lung and gastrointestinal tract. Approximately 17% of carcinoids are found in the rectum and 3% are located in the stomach, both sites amenable to EUS evaluation. Sporadic gastric carcinoids tend to behave more aggressively than the multifocal gastric carcinoids seen in hypergastrinemic states.

The EUS appearance is a well-circumscribed, mildly hyperechoic or isoechoic mass arising from either the mucosa (second layer) or submucosa (third layer). EUS identifies carcinoid

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Figure 146.6 Gastrointestinal stromal cell tumor (GIST). (a) A submucosal lesion visualized on upper endoscopy. (b) Typical endoscopic ultrasonography appearance of a GIST.
lesions amenable to endoscopic versus surgical resection [81–83].

Granular cell tumor
Granular cell tumors are uncommon lesions of neural derivation that appear endoscopically as yellowish mucosal or submucosal nodules. The majority of these lesions are less than 2 cm in size [84] and typically considered to be benign, although approximately 2%–3% of lesions are malignant [85]. Under EUS, these tumors appear as homogeneous, hypoechoic, well-circumscribed lesions originating from the mucosa (second layer) or submucosa (third layer) [86,87].

Stomach
Gastric cancer
Worldwide, gastric cancer accounts for approximately 10% of all malignancies, and in 2006 over 21 000 patients were diagnosed with gastric cancer in the USA [26]. Despite a reduction in mortality during the 1980s and 1990s, gastric cancer remains the second leading cause of cancer-related mortality worldwide [88]. A major clinical challenge is to diagnose gastric cancer in its early curable stages, a feat unfortunately rarely accomplished in the absence of a screening program. The Japanese have the most experience with early gastric cancer. They use the Japanese classification for management while worldwide the TNM (tumors, nodes, metastasis) system is most commonly used.

Because gastric cancer confined to the mucosa and submucosa can be treated with surgical resection, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD), EUS plays a role in local staging. Cancers with involvement of only the mucosa (m) and submucosal invasion less than 500 μm (sm1) have negligible risk of metastasis and are ideal for EMR. Some conservative authorities advocate EMR and ESD only for lesions with mucosal involvement and less than 2 cm in diameter [89]. Stage T2 or T3 tumor is treated with surgical resection and T4 lesions are managed with neoadjuvant chemotherapy and radiation.

EUS is an accurate method for local staging of gastric cancer: it can visualize infiltrating scirrhoues malignancies, which appear as diffuse thickening of the normal layers of the gastric wall, or assess tumor invasion based on disruption of wall layers [90–100] (Figure 146.7). The accuracy of dynamic CT and magnetic resonance imaging (MRI) for T-staging is 50%–70% [101–105], whereas the overall accuracy of EUS for T-stage ranges from 70% to 93% [32,91,99,106–112]. In particular, the accuracy for detecting submucosal invasion has been reported to be as high as 90% with a highfrequency catheter probe [107,113]. EUS T-staging is lowest for T2 lesions (accuracy 60%–70%), and the difficulty is in differentiating between subserosal (T2) from serosal (T3) involvement, particularly since the entire stomach is not covered by a serosa.

EUS has long been the test of choice for assessing T-stage in gastric cancer; however, with the advent of multidetector CT and the advanced imaging techniques of MRI, the accuracy of T-staging among the different modalities has been reevaluated. Table 146.2 shows the performance characteristics of EUS, multidetector CT, and MRI in assessing tumor stage in gastric cancer. These imaging modalities appear to be equivalent, although the greatest expertise remains with EUS and further experience needs to be gained with multidetector CT and MRI [44,99,100,106,109,111,112,114]. A limitation of EUS is that depth of invasion may be overestimated if there is an ulcer scar or inflammatory reaction below the cancer (peritumorous inflammation) or a protruding lesion, and underestimated if there is microinvasion [97].

The overall accuracy of EUS nodal staging in gastric cancer ranges from 50% to 87% [44,98,99,106,110,111,115–122], and is highest for T3 and T4 lesions, for lymph nodes located within 3 cm of the tumor, and along the lesser curvature. Only 15% of T1 lesions are associated with malignant lymph nodes, but detection of these lymph nodes is critical, particularly if EMR or ESD is contemplated. The overall accuracy of EUS for detection of lymph nodes is approximately 69%, and FNA should be employed, if needed. Nodal staging with CT and MRI is not clearly superior to EUS [105,112,123,124].

Gastric wall layer abnormalities
EUS is indicated in the presence of thickened gastric folds. By definition, the gastric folds are considered thickened if they fail to flatten with endoscopic insufflation or if an upper gastrointestinal series or CT suggests a thickness greater than 1.5 cm [125]. The normal thickness of the gastric wall ranges from 0.8 mm to 3.6 mm [12] and is considered to be thickened when the diameter of the five-layer EUS image of the gastric wall is greater than 4 mm [126,127]. The differential diagnosis (Box 146.2) includes benign and malignant conditions. A clear diagnosis may not always be possible; however, based on the EUS origin of the lesion, the differential can be narrowed.

Multiple studies have reported EUS findings in patients with large gastric folds [128–131]. The presence of gastric varices is diagnostic and biopsy specimens can be avoided. If EUS demonstrates abnormalities in layers three and four, malignancy needs to be strongly considered, even if biopsies are negative [128,129]. Most cases with a scirrhoues carcinoma have a thickened third and fourth layer [129], and the second and third layers can be thickened in benign or malignant conditions [129]. Endoscopic biopsy of an abnormality in layer two should be diagnostic and if biopsies are negative for cancer, follow-up studies report that malignancy will often not develop [128] (Figure 146.8).

EUS can diagnose early infiltrative gastric lymphoma, which is typically a non-Hodgkin lymphoma. An early-stage lymphoma can be subtle in its endoscopic and endosonographic appearance, revealing only a thickened second layer with preservation of the gastric layers and endoscopically normal-appearing mucosa [132,133]. More advanced stages show a diffuse hypoechoic thickening with distortion of the gastric layers. The accuracy of EUS for staging gastric lymphoma is
approximately 95% [116,134], and EUS can also be used to evaluate tumor response to chemoradiation [135–138].

### Ampullary and pancreatic neoplasms

The role of EUS in the management of suspected ampullary or pancreatic neoplasms is to identify the lesion, assess for surgical resectability, and acquire cytological confirmation if needed.

#### Ampullary neoplasm

Ampullary adenomas, the most common tumors of the ampulla of Vater, can be sporadic or part of a genetic polyposis...
PART 5 Diagnostic and therapeutic modalities in gastroenterology

PART 5 Diagnostic and therapeutic modalities in gastroenterology

EUS sensitivity is higher in symptomatic patients and patients at risk for adenomas. Accurate staging is critical in the management of ampullary neoplasms, since endoscopic options are feasible in selected cases. According to the TNM classification used to stage ampullary neoplasms, T1 corresponds to tumors not extending beyond the sphincter of Oddi, T2 to tumors invading the muscularis propria of the duodenal wall, T3 to tumors with less than 2 cm of invasion into the adjacent pancreas, and T4 tumors deeply invade the pancreas or adjacent vasculature [151].

EUS is the most reliable modality for local preoperative staging of ampullary neoplasms, including assessing for portal venous involvement. It is superior to MRI, CT, transabdominal ultrasound, and angiography, regardless of whether the radial or linear echoendoscope is used [148,150,152–154]. Peritumoral pancreatitis due to the desmoplastic reaction of malignant cells can lead to under-staging of true T3 lesions or over-staging of true T2 lesions, but typically the surgical treatment for both lesions is identical [147]. The accuracy of EUS in determining whether endoscopic resection for a T1 lesion can be performed with curative intent ranges between 87% and 94% [146,147,152,155,156]. The Japanese staging system subdivides T1 lesions into d0 (tumors limited to the sphincter of Oddi) and d1 lesions (tumors extending into the submucosa). The prevalence of malignant lymph nodes varies from 0 to 30% in T1 tumors, with the highest risk associated with tumors that invade the submucosa [146,147,153,157].

Intraductal ultrasonography (IDUS) complements radial or linear EUS. Imaging at 20 MHz demonstrates the muscle layer of the sphincter of Oddi as a distinct hypoechoic layer, which allows greater tissue layer resolution and the ability to discern d0 lesions from d1 lesions with an approximate accuracy of 89% [156]. IDUS is nearly 100% accurate in visualizing tumor invasion into the pancreaticobiliary ductal system [156]. The combination of EUS and IDUS is believed to provide the most accurate staging information, and reliably select candidates eligible for curative endoscopic ampullectomy versus surgical treatment.

Pancreatic neoplasms
One of the first targets for EUS imaging was pancreatic cancer. The early detection of this usually lethal neoplasm has eluded other diagnostic abdominal modalities such as transabdominal ultrasound. The increased spatial resolution of EUS allows detection of smaller resectable neoplasms in patients with vague symptoms [158] and is the most sensitive imaging modality for the detection of a pancreatic mass. Numerous studies have documented the high sensitivity (98%–100%) of EUS for detection of pancreatic tumors [159–170]. EUS may play a role in the screening of asymptomatic high-risk populations for early cancer detection [171–175].

As an imaging modality, EUS is not as widely available as transabdominal ultrasound, CT, and PET. Transabdominal ultrasound...
ultrasound is inferior to EUS for detection of pancreatic masses, particularly those located in the pancreatic head or uncinate [150]. Despite the advent of multidetector CT [176,177], studies suggest that EUS remains a superior imaging modality, particularly for small lesions. Compared with multidetector CT, EUS is more sensitive (98% vs. 86%) [167], and more accurate (94% vs. 74%) [169]. In patients with indeterminate findings on CT, EUS has an accuracy of 92% for detection of a pancreatic tumor and an NPV of nearly 100% for excluding a focal pancreatic mass [178,179]. A normal EUS of the pancreas in the setting of subtle radiological findings, nonspecific symptoms, or laboratory values effectively rules out a pancreatic neoplasm [180].

MRI and PET may detect small pancreatic tumors; however, inflammatory conditions such as chronic pancreatitis can result in glucose uptake and false-positive PET [181,182]. The anatomical resolution from PET is inferior to CT and MRI for determining locoregional tumor spread. However, PET can identify distant metastases that can alter clinical treatment in up to 40% of patients with pancreatic cancer [183–185].

For locoregional staging of pancreatic cancer, multidetector CT and MRI provide excellent assessment of tumor staging, vascular involvement, and nodal staging [154,186,187]. Both modalities are superior to EUS for detection of metastatic disease, but EUS can provide information suggesting metastatic disease by detecting previously unknown hepatic metastases [188–192], small pockets of ascites [193], and malignant mediastinal lymphadenopathy [194]. These findings preclude surgical resection.
maximize diagnostic yield [222,223]. The overall risk of complications from an EUS-FNA of a pancreatic mass is 0.5%–2% [55,201,214,224–226], with a higher complication rate for cystic lesions (14%) compared with solid tumors (0.5%) [55]. Complications of EUS-FNA include pancreatitis, perforation, bleeding, and infection. Sampling of solid pancreatic masses is one of the most common indications for EUS-FNA/FNB, with high diagnostic accuracy [201], and high clinical impact for distinguishing benign and malignant disease and decision-making with respect to surgery and chemoradiation therapy. Current needles and techniques using cytology (slide smears) and histology (cell block analysis) lead to about 90% sampling adequacy, sensitivity of 84%, and specificity of 100%, with overall accuracy of 90% [201].

Islet cell neoplasm
The anatomical localization of hormone-producing pancreatic tumors is important for guiding their surgical resection. Most of these neoplasms arise from islet cells within the pancreas, and conventional transabdominal imaging with ultrasound and CT detects less than one-third of tumors. In particular, insulinomas are less likely to be detected by CT. MRI and selective arteriography may also fail to localize the neoplasm. Careful examination of the pancreas with EUS detects about 77%–94% of islet cell neoplasms within the pancreas not found on CT or MRI [227–237]. Islet cell neoplasms are usually round, well-circumscribed, homogeneous, and hypoechogenic compared with the surrounding parenchyma, and lesions as small as 5 mm in diameter have been imaged by EUS [227,237,238]. All patients diagnosed with a resectable pancreatic neuroendocrine tumor should undergo preoperative EUS and octreotide scanning to localize the neoplasm and facilitate surgical planning.
EUS-FNA is not required in the setting of a well-defined clinical syndrome and documented excessive hormone secretion.

**Chronic pancreatitis**

Chronic pancreatitis is an ongoing inflammatory process that results in irreversible destruction of pancreatic tissue leading to exocrine and endocrine insufficiency. It can be a diagnostic challenge, particularly in nonsevere cases when radiological imaging tests and functional diagnostic tests are equivocal or negative. There is no perfect test (imaging or functional) that accurately diagnoses early chronic pancreatitis, but EUS offers several advantages because of its minimal risk of causing pancreatitis and its ability to characterize both pancreatic parenchymal and ductal abnormalities (Figure 146.11).

The endosonographic criteria and the histological correlates for chronic pancreatitis are listed in Table 146.3 [241–243]. Additional proposed criteria include gland contour (lobular vs. smooth), echogenic foci with and without shadowing, and accentuation of the gland’s lobular pattern [242,244]. Despite the specific terminology of these EUS features, the interobserver agreement for these features and the collective assessment of an EUS examination is only moderate [243] and clinical bias exists in the interpretation of the examination as it applies to each patient [245].

When evaluating the performance characteristics of EUS for the diagnosis of chronic pancreatitis, the best reference standard is pathological confirmation of the presence of inflammation, atrophy, or fibrosis, but only a few studies have tried to correlate EUS features of chronic pancreatitis with microscopic findings. Most studies have compared EUS with morphological tests such as CT, MRI/magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) and with the functional secretin test [245–249].

EUS has an approximate sensitivity and specificity of 85% and 75% respectively when ERCP is used as the gold standard to diagnose chronic pancreatitis [241,242,244,245,250]. Wiersema and colleagues enrolled 69 patients with suspected pancreatic

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**Table 146.3** Histological correlates for endoscopic ultrasonography (EUS) findings as related to chronic pancreatitis.

<table>
<thead>
<tr>
<th>EUS finding</th>
<th>Histological correlate</th>
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<tr>
<td><strong>Parenchymal features</strong></td>
<td></td>
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<tr>
<td>Hyperechoic foci</td>
<td>Focal areas of fibrosis</td>
</tr>
<tr>
<td>Hyperechoic strands</td>
<td>Linear areas of fibrosis</td>
</tr>
<tr>
<td>Pseudolobule</td>
<td>Linear fibrosis containing focal edema</td>
</tr>
<tr>
<td>Cysts</td>
<td>Cysts or cyst side branches</td>
</tr>
<tr>
<td><strong>Ductal features</strong></td>
<td></td>
</tr>
<tr>
<td>Main pancreatic duct dilation</td>
<td>Dilated duct</td>
</tr>
<tr>
<td>Side-branch dilation</td>
<td>Dilated side branches</td>
</tr>
<tr>
<td>Irregular duct contour</td>
<td>Periductal fibrosis</td>
</tr>
<tr>
<td>Hyperechoic duct wall</td>
<td>Periductal fibrosis</td>
</tr>
<tr>
<td>Stones</td>
<td>Calcified stones</td>
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pain and noted that the sensitivity and specificity of EUS was 80% and 86% respectively when three or more criteria were used [244]. Sahai and colleagues [241] performed EUS in a prospective blinded study of patients with unexplained pain who were referred for ERCP. They noted that patients with five or more EUS features correlated with at least moderate chronic pancreatitis on ERCP. Fewer than three features essentially ruled out moderate or severe chronic pancreatitis (NPV > 85%), and three to four EUS features was equivocal. However, three to four EUS features in patients with history of alcohol intake or pancreatic pain symptoms may be significant [241,251]. When compared with secretin testing, the overall sensitivity and specificity of EUS is 80% and 70% respectively [242,244,245]. Catalano and colleagues [242] compared EUS with ERCP and secretin testing in patients with recurrent pancreatitis. There was 100% agreement between EUS findings for normal pancreas (no EUS features of chronic pancreatitis were seen) and severe chronic pancreatitis (more than five EUS features) when compared with ERCP and secretin testing. For moderate chronic pancreatitis (three to five EUS features), there was 92% agreement with ERCP and 52% agreement with secretin testing [242]. In 2009, an expert group published standardized criteria for the diagnosis of chronic pancreatitis (Rosemont classification) grouping major and minor criteria [54].

It is unclear if focal chronic pancreatitis is a normal variant, a sign of focal fibrosis, or early malignancy. When the clinical suspicion and EUS features of moderate chronic pancreatitis are present throughout the gland, performing FNA does not improve the accuracy of the examination [252]. However, EUS-FNA should be considered in patients with focal chronic pancreatitis, despite the relatively low sensitivity of EUS-FNA in chronic pancreatitis (54%) [253]. A nondiagnostic FNA may eliminate an underlying malignancy, and careful follow-up is mandated in 1–3 months.

The EUS diagnosis of chronic pancreatitis depends on the threshold set for the number of positive criteria required to establish a definitive diagnosis. Changing the threshold affects the performance characteristics of EUS. In general, if less than two criteria are present, chronic pancreatitis is highly improbable. If three or four criteria are present, the test outcome is equivocal. If more than five criteria are present, the probability of chronic pancreatitis is high.

**Pancreatic cysts and intraductal papillary mucinous neoplasms**

Asymptomatic pancreatic cysts are increasingly recognized due to widespread imaging of the abdomen. While the majority of cysts are benign, approximately 10% represent cystic neoplasms [254,255]. Accurate characterization of the malignant potential of a pancreatic cyst remains challenging. EUS-FNA is often used in the management of such lesions. This section reviews the diagnostic accuracy of the various imaging modalities and recommends a current clinical algorithm. A recent updated consensus international white paper provides guidelines for management of suspected intraductal papillary mucinous neoplasms, including use of EUS [256].

The potential advantages of EUS and FNA include the ability to evaluate lesions for high-risk stigmata (e.g., thick septae and mural nodules) and to obtain specimens for cytological analysis and fluid for cyst fluid analysis. The EUS examination should note the following cyst characteristics: size; location (including relationship to adjacent vasculature); wall thickness; presence of focal wall irregularity, papillary projections, associated mass, or septae, echogenic debris or mucus; and dilation of the main pancreatic duct. Some of these findings are considered high-risk EUS features suggestive of malignant transformation; however, they do not reliably differentiate between benign and malignant cysts [257–261]. In addition, the absence of these features does not exclude the presence of malignancy.

When performing FNA of pancreatic cysts, the recommendation is to undertake a single puncture, aspirate the cyst dry, describe the appearance of the aspirated cyst fluid, and analyze the cyst fluid for specific proteins, tumor markers, or genetic changes. All patients should receive antibiotic prophylaxis prior to FNA followed by 1–3 days of oral antibiotic treatment to theoretically reduce the risk of infection.

A multicenter trial [262] of 341 patients showed the accuracy of EUS morphology to be 51%, with the addition of FNA increasing the accuracy to 59%. A smaller trial of 67 patients found the overall EUS accuracy to be 73% (range 43%–88%). Cytology improved the sensitivity for mucinous lesions (94%), malignant mucinous lesions (100%), serous lesions (100%), and pseudocysts (100%), with a specificity of 98%–100% [263]. Additional findings were that a low carcinoembryonic antigen (CEA) level (<5 ng/mL) was predictive of a serous cystadenoma, and high amylase or lipase concentration was associated with pseudocysts. Studies have reported a wide accuracy of EUS with or without FNA, ranging from 40% to 96% [257–259,261–266]. Studies have evaluated a variety of cyst fluid tumor markers or cyst fluid properties (CEA, CA19-9, CA72-4, CA125, amylase, lipase, viscosity, mucin stain). CEA is found in high levels in mucinous tumors, whereas levels are low in pseudocysts (unless infected) and serous cystadenomas [264,267,268]. A large, prospective, multicenter trial reported that a CEA level of 192 ng/mL or more was 79% accurate for differentiating mucinous neoplasms from other types of cysts. In this study, no combination of morphological features, cytology results, and cyst fluid analysis improved the accuracy rate over that obtained with CEA alone [262]. Other studies have reported variable accuracies with CEA [263,269,270]. It has also been reported that an elevated CEA (≥480 ng/mL) and viscosity (≥1.6) accurately predicted mucinous cystic neoplasm from serous cystadenoma and pseudocysts. Mucinous cystadenocarcinoma lesions had a CEA level greater than 6000 ng/mL in one study [271].

CA19-9 (>50 000 units/mL) has been associated with sensitivity of 86% and specificity of 85% in distinguishing cystadenocarcinoma from other lesions. However, CA19-9 is often elevated in inflammatory conditions and biliary obstruction,
which limits its usefulness [264,267]. Amylase has been found in high concentrations in pseudocysts and intraductal papillary mucinous neoplasms (IPMNs), and amylase levels greater than 5000 U/L are associated with varying sensitivity (61%–94%) and specificity (58%–74%) in differentiating pseudocysts from other cystic lesions [263,268,272]. Recently, whole exome sequencing studies have demonstrated specific genetic mutations detectable in small amounts of pancreatic cyst fluid, such as KRAS, GNAS, and Von Hippel Landau genes [273,274], which may soon allow improved differentiation of mucinous and nonmucinous cysts.

The ideal diagnostic approach to patients with pancreatic cysts is unclear and not validated, and is variable among medical institutions. Management often depends on local expertise. An international consensus guideline for management of IPMNs and mucinous cystic neoplasms has been published [275], and this algorithm should serve as a general framework in the management of patients with pancreatic cysts.

**Biliary tract indications and cholangiocarcinoma**

The common bile duct and gallbladder are in close proximity to the antrum and duodenum, allowing EUS to image these organs. EUS is a safe and accurate alternative imaging modality to ERCP, the traditional method most often used to evaluate the biliary tract. In many cases, EUS-guided therapy can be performed and can nearly eliminate the need for diagnostic ERCP.

A common indication for endoscopic biliary intervention is for suspected choledocholithiasis. An ERCP is often performed in such cases, but the risk of complications is significant [276–279] and it should be performed only in cases requiring therapeutic intervention.

**Choledocholithiasis**

EUS is superior to other imaging modalities for evaluation of the extrahepatic biliary tree for suspected choledocholithiasis. Transabdominal ultrasound detects approximately 30% of common bile duct stones [280,281], and helical CT has a reported diagnostic accuracy of 86%–94% [282,283], but with reduced accuracy for small bile duct stones. EUS and MRCP are both accurate imaging modalities for detection of common bile duct stones, with EUS slightly more accurate (approximately 96% vs. 90%) [284–292]. EUS has greater resolution than MRCP, and hence EUS can detect stones as small as 1–2 mm without the loss of accuracy seen with MRCP [285,293]. EUS is the most accurate imaging test available for detection of microlithiasis [290,293].

Although long considered the gold standard for detection of choledocholithiasis, ERCP is less accurate and more invasive and has a higher failure rate compared with EUS. The NPV (the ability to rule out a common bile duct stone) of EUS is nearly 100%, with up to 32 months of patient follow-up [294–298].

When managing patients with suspected choledocholithiasis, adopt a treatment algorithm of performing EUS on patients with low or intermediate risk for choledocholithiasis, and proceed directly to ERCP in patients with a high clinical suspicion for choledocholithiasis. The EUS-based approach reduces the number of unnecessary ERCP procedures and is cost-effective [285,294,299].

**Indeterminate biliary strictures**

The critical question in the characterization of an indeterminate bile duct stricture is whether the stricture is malignant. Brushings or forceps biopsy obtained at ERCP has an accuracy that ranges from 30% to 70%, primarily due to the desmoplastic reaction associated with such tumors [300–305]. EUS (radial, linear, and IDUS) can visualize the extrahepatic biliary tree and extrinsic masses [306,307]. A prospective study of 40 patients with an indeterminate biliary stricture who underwent various imaging and endoscopic techniques found that the combination of MRCP and EUS had the highest specificity for diagnosis of an indeterminate biliary duct stricture [308].

For bile duct lesions, radial or linear EUS provides excellent visualization and ability to obtain tissue [309,310]. For lesions located in the porta hepatitis region, the 20-MHz IDUS mini-probe provides accurate images of the bile duct wall and surrounding structures. The IDUS miniprobe is advanced to the stricture without a prior papillotomy. The first hyperechoic layer corresponds to the mucosa in addition to a border echo, the second hyperechoic layer is smooth muscle fibers with fibroelastic tissue, and the third hyperechoic layer is the thin and loose connective tissue with a border echo [311]. IDUS findings concerning for malignancy include disruption of the bile duct wall, sessile lesions, and tumor size greater than 10 mm. The accuracy of IDUS in differentiating between benign and malignant strictures ranges from 76% to 92% [312–316]. The presence of two of these three features is considered specific for the diagnosis of malignancy, and the absence of all these features carries a very high NPV for ruling out malignancy [315]. However, IDUS is not accurate when evaluating for metastatic lymphadenopathy [314]. The linear EUS echoendoscope is still required for FNA. Studies have shown that EUS-FNA may aid in the diagnosis of a hilar cholangiocarcinoma when other standard methods of tissue acquisition have failed [317].

**Cholangiocarcinoma**

When cholangiocarcinoma is diagnosed, EUS can assist in staging and assessment of surgical resectability. Bile duct cancer T-staging is as follows: T1, limited to the wall of the common bile duct; T2, invasion beyond the wall of the common bile duct; and T3, invasion to adjacent structures. The accuracy of IDUS is higher than EUS for assessing T-staging (77.7% vs. 54.1%) [318], particularly for hilar or common hepatic duct strictures.

When assessing for surgical resectability, the key question is longitudinal extent of tumor spread and involvement of adjacent structures, particularly the portal vein and right hepatic artery. The accuracy of IDUS for assessment of longitudinal tumor spread ranges from 72% to 86%, when using notching of
the outer margins and asymmetric wall thickening as visualized endosonographic features. However, thickening due to inflammation can reduce the accuracy [319]. IDUS is highly accurate at visualizing portal vein and right hepatic artery involvement, and is more accurate than angiography [320,321].

**Anorectal EUS**

Common indications for rectal EUS include evaluation of suspicious polyps and locoregional staging of rectal cancer, assessment of submucosal lesions, and evaluation of incontinence (for possible anal sphincter defects). Most patients can be adequately prepared for this unsedated procedure with enemas.

Malignancy often appears as an irregular hypoechoic lesion with disruption of the rectal wall layers (Figure 146.12). Since neoadjuvant therapy in locally advanced rectal cancer is associated with an improvement in recurrent-free survival, the accurate preoperative staging of such lesions is critical [322–329]. EUS is indicated in the locoregional staging of patients with rectal cancer and in the evaluation of patients with recurrent malignancy [330,331].

When M0 rectal cancer has been established, EUS is the next step in staging because it has superior performance characteristics to CT and MRI [332]. The accuracy of EUS for T-staging ranges between 80% and 95%, with a mean sensitivity of 87.5% and specificity of 83.5%; this compares with an accuracy of 65%–75% for CT and 75%–85% for MRI [331,333–338]. The accuracy of EUS for determining nodal metastases is approximately 70%–75%, whereas that for CT is 55%–65% and MRI 60%–70% [331,334,336]. The presence of perirectal lymph nodes often warrants FNA, which can be performed safely with low risk of infection [339,340]. EUS has been shown to alter the treatment plan in nearly one-third of rectal cancer cases [341].

A common submucosal rectal lesion may be rectal carcinoid, often an incidental finding [342,343]. Poor prognosis is associated with larger tumor size, deep invasion of tumor, and lymphovascular invasion [343]. EUS can assess lesions to determine eligibility for local excision versus surgical resection [344].

Anorectal EUS also plays a role in detecting sphincter defects in patients with fecal incontinence, and helping to assess whether the defect is amenable to surgical correction [345]. EUS findings have been correlated accurately with operative findings [346]. EUS may also be useful in assessing perianal inflammatory conditions [347].

**Lung cancer**

The annual incidence and mortality of lung cancer worldwide is estimated to be 1.35 million and 1.18 million respectively [20]. The prognosis and treatment depends on histology (small cell vs. nonsmall cell), accurate assessment of mediastinal lymph node spread, and the presence or absence of T4 disease (tumor invasion into adjacent organs, central vessels, or vertebrae). Nearly half of patients diagnosed with nonsmall cell lung cancer (NSCLC) present with advanced disease. It is clinically relevant to differentiate malignant spread to the ipsilateral lymph nodes or subcarinal lymph nodes (N2, stage IIIA) from spread to the contralateral lymph nodes (N3), or T4 disease (stage IIIB). Although 5-year survival in stage III NSCLC is dismal, neoadjuvant chemoradiation for stage IIIA improves median survival [21–23].

In patients with suspected lung cancer, EUS can visualize the following lymph node stations: station 4L (left paratracheal), station 5 (aortopulmonary window), station 7 (subcarinal), station 8 (lower paraesophageal), and station 9 (pulmonary ligamentum). Since ultrasound cannot penetrate the air-filled trachea, EUS cannot reliably assess anterior mediastinal lymph nodes at levels 2R (upper paratracheal), 4R (lower paratracheal), 3 (prevascular, retrotracheal), and 6 (paraaortic) [24,25].

Figure 146.12 Rectal carcinoma. (a) Endoscopic image of ulcerated rectal mass. (b) Endoscopic ultrasonography image demonstrates T3N1 stage: m, mass; mln, malignant lymph node.
Posterior mediastinal assessment

The most common clinical indication for EUS in NSCLC is for mediastinal staging. Prior to the advent of EUS-FNA, patients underwent various procedures including bronchoscopy with transbronchial FNA, computed tomography (CT), positron emission tomography (PET), video-assisted thoracoscopy, and mediastinoscopy to accurately assess metastatic disease. EUS-FNA (as opposed to EUS alone) [18,76,77,171] provides accurate evaluation of the posterior mediastinum, and is complementary to those imaging modalities that assess the anterior mediastinum.

The performance characteristics of EUS-FNA have been reported in numerous studies [54,171,180,201,256,273,274,348–357], and a metaanalysis of over 1200 patients [25]. EUS-FNA for mediastinal staging or in suspected mediastinal malignancy has a pooled sensitivity of 83%, specificity of 97%, negative predictive value (NPV) of 78%, and positive predictive value (PPV) of 98%. EUS-FNA is more sensitive (88% vs. 57%) and specific (91% vs. 82%) than CT for the detection of suspected malignant lymph nodes [76,77], and detects malignant lymphadenopathy in 35% of patients without lymphadenopathy on prior CT. This reduces the number of patients requiring mediastinoscopy and exploratory thoracotomy [25,273,348,352,356] (Figure 146.13).

Fluorodeoxyglucose (FDG)-PET and CT are comparably sensitive for the detection of enlarged mediastinal lymph nodes; however, in cases where lymph nodes are not enlarged on CT, FDG-PET had a higher sensitivity than both CT and EUS-FNA (82% vs. 58%). Due to the false-positive rate of benign granulomatous disease on PET, a positive PET should be confirmed with tissue diagnosis. When available, EUS-FNA is a more accurate and a preferential alternative to “blind” transbronchial FNA [76,171,348,355,358].

EUS-FNA can assess intrapulmonary lesions in the posterior mediastinum. The accuracy of EUS-FNA for such lesions is 97%-100% [9,359], and EUS is more accurate than CT or PET for assessing T4 disease (sensitivity 88%, specificity 98%, PPV 70%, NPV 99%) [360]. CT and PET have limited sensitivity and specificity for T4 detection [361,362].

Impact on clinical care

The clinical impact of EUS-FNA in patients with NSCLC is its ability to accurately stage the posterior mediastinum, subsequently reducing the number of invasive mediastinoscopies and thoracotomies. EUS-FNA prevents further invasive staging procedures in up to 70% of cases [274,351,353,354,363,364]. The role for EUS-FNA in the clinical algorithm for NSCLC patients continues to evolve, but the general consensus is that it should be utilized early in the clinical staging algorithm since EUS, by itself, can demonstrate T4 disease or mediastinal metastases in 25% of patients regardless of CT findings [352,356]. PET, if available, should be performed before EUS-FNA.

The future staging of NSCLC is likely to involve endobronchial ultrasound (EBUS). Compared with CT and PET, EBUS with transbronchial needle aspiration has high sensitivity and specificity for mediastinal and hilar lymph node evaluation [365,366]. The challenge will be for bronchoscopists and endoscopists to integrate the two techniques efficiently and to work together to achieve complete mediastinal staging.

EUS-FNA plays a vital role in the management of patients with suspected NSCLC. Given that it is minimally invasive, safe, more accurate than CT and transbronchial FNA, and more specific than FDG-PET, EUS-FNA impacts patient care by reducing the number of invasive diagnostic surgical procedures. Indications for EUS-FNA in the diagnosis and staging of NSCLC include the evaluation of mediastinal lymphadenopathy, identification of adjacent intrapulmonary lesions and diagnosis of T4 disease, and mediastinal FNA of PET positive lesions, and should be the first invasive procedure performed after CT [114]. Since EUS cannot visualize the anterior mediastinal structures, it is most appropriate to proceed to mediastinoscopy if EUS-FNA is nondiagnostic. Mediastinoscopy provides evaluation of the upper and lower paratracheal regions (stations 2 and 4). In a comparison of EUS-FNA and mediastinoscopy, both procedures demonstrated a comparable accuracy rate of 90%, and the combination detected significantly more patients with lymph node metastases than either technique alone [353]. The role of EBUS remains to be clearly defined.

Interventional EUS

Background

Improvements in echoendoscope design, imaging quality and accessories have collectively led the evolution of EUS from a diagnostic to a therapeutic modality [367]. As a result, EUS is now a well-established technique for tissue sampling, fine-needle injection and drainage of fluid collections and abscesses adjacent to the gastrointestinal (GI) tract. Widespread adoption of minimally invasive surgery and radiologic procedures has naturally led to the increased use of EUS in treatment and/or
palliation of gastrointestinal and pancreaticobiliary diseases. This section will describe different applications of interventional EUS, including EUS-guided biliary drainage (EUS-BD), EUS-guided pancreatic duct interventions, EUS-guided drainage of peripancreatic fluid collections, EUS-guided celiac plexus neurolysis, EUS-guided fiducial placement and EUS-guided angiotherapy.

**EUS-guided biliary drainage (EUS-BD)**

In patients with normal, nonobstructed upper GI anatomy, selective bile duct cannulation by experts at ERCP is successful in over 90% of cases. When bile duct access is not possible due to failed cannulation, altered upper GI tract anatomy, distorted ampulla, gastric outlet obstruction (GOO), periampullary diverticulum, or in-situ enteral stents, EUS-BD has been increasingly used as a less-invasive alternative to surgery, or radiology [368–373]. EUS-BD can be performed by one of three methods. First, a rendezvous technique may be considered whereby a wire is placed into an intrahepatic or extrahepatic bile duct, passed through the papilla and is retrieved by a duodenoscope for biliary interventions. Second, direct transluminal stenting using a transgastric or transduodenal approach may be performed without accessing the papilla [374,375]. EUS-guided antegrade transpapillary (or trans-anastomotic) biliary stent placement is a third, less widely used, approach [376,377].

**Rendezvous technique**

A linear echoendoscope is used to achieve initial biliary access within a segment of dilated bile duct proximal to the site of obstruction. The tip of the echoendoscope is positioned in the gastric fundus or duodenal bulb when accessing the intrahepatic or extrahepatic bile duct, respectively. A 19-gauge or 22-gauge FNA needle is used to puncture the bile duct with access confirmed by contrast injection and fluoroscopic imaging. A 0.035-inch, 0.025-inch, or 0.018-inch guidewire is then advanced into the bile duct. The smaller 0.018-inch wires need to be exchanged for larger wires before stent placement. The echoendoscope and needle are angled to facilitate antegrade guidewire passage through the site of obstruction and across the papilla and coiling of the wire within the duodenum is preferred to enable REN technique. The echoendoscope is withdrawn leaving the guidewire in place. A side-viewing endoscope is passed to the papilla and a snare or biopsy forceps is used to grasp the guidewire and withdraw it through the endoscope with subsequent stent placement (Figure 146.14) [378].

**Direct transluminal (TL) technique**

In TL cases, the entire procedure is performed using the echoendoscope. After the bile duct is accessed as described above, the puncture track is dilated with a dilating catheter or dilation balloon and a variety of devices are used to facilitate stent placement. These devices are selected based on the patient’s anatomy and features of the obstructing stricture. Stent insertion is then performed via antegrade approach (Figure 146.15) [378,379].

**Antegrade stenting**

The EUS-guided antegrade stenting technique involves the following steps. The dilated biliary ductal segment is punctured with an FNA needle and contrast is then injected through the needle to provide a cholangiogram. A hydrophilic guidewire is advanced through the needle and manipulated across the stricture. The FNA needle is then removed, and the tract is dilated over the wire to 7-Fr or 8.5-Fr using an ERCP catheter (e.g. Soehendra Biliary Dilation Catheter, Wilson-Cook Medical, Winston-Salem, NC, USA). With the dilation catheter tip within the bile duct, the hydrophilic wire is exchanged for a stiffer instrumentation guidewire (e.g. 0.035-inch Jagwire, Boston Scientific, Natick, MA, USA). Antegrade stent placement is performed by advancing the stent through the therapeutic channel of the echoendoscope over the guidewire and stent is then deployed across the stricture transpapillary or trans-anastomotic.

**Outcomes of EUS-BD**

Despite growing international experience and peer-reviewed publications of EUS-BD in recent years, concern still remains about the safety and efficacy of these techniques compared to the standard, widely available alternative procedures. Small series from expert centers suggest that EUS-BD can be performed with high therapeutic success (87%) but is associated with 10%–20% morbidity (most mild-moderate) and rare serious adverse events [380]. Recently, Artifon et al. [381] published the first prospective, randomized trial comparing EUS-BD to percutaneous transhepatic biliary drainage (PTBD) in 25 patients (13 EUS-choledochoduodenostomy or EUS-CDS and 12 PTBD) with malignant biliary obstruction and failed ERCP. The two groups were similar before EUS-BD in terms of quality of life, total bilirubin (16.4 vs. 17.2; \( P = 0.7 \)), alkaline phosphatase (539 vs. 518; \( P = 0.7 \)), and gamma-glutamyl transferase (554.3 vs. 743.5; \( P = 0.56 \)). All procedures were technically and clinically successful in both groups. At 7-day follow-up, there was a significant reduction in total bilirubin in both groups (EUS-CDS, 16.4 to 3.3; \( P = 0.002 \), and PTBD, 17.2 to 3.8, \( P = 0.01 \)), although no difference was noted between the two groups (EUS-CDS to PTBD, 3.3 vs. 3.8, \( P = 0.2 \)). There were no differences in complication rates between the two groups (\( P = 0.44 \)): EUS-CDS (2/13, 15.3%), and PTBD (3/12, 25%). Cost was similar for both groups ($5673, EUS-CDS vs. $7570, PTBD; \( P = 0.39 \)). Therefore, this randomized study showed that EUS-BD performed via transluminal approach (choledochoduodenostomy) had a similar success rate, complication rate, and cost as compared to PTBD. Although this small prospective, single center study suggests that EUS-BD may be an acceptable alternative to PTBD, large prospective studies are still needed to definitively determine procedure-related complications, efficacy and modifications employed to improve patient outcomes.

Shah and colleagues reported their large experience with EUS-BD in patients with altered anatomy due to surgery or
failed ERCP [373]. A total of 70 patients had attempted EUS-guided cholangiography and this was successful in 68 (97%) patients; 66 patients had cholangiographic findings requiring interventions. EUS-BD using the rendezvous technique was attempted in 50 patients and was successful in 37 (74%), and failed in 13. Direct EUS-guided interventions (hepatogastrostomy, choledochoduodenostomy, antegrade stenting) were attempted in the remaining 16 patients and were successful in 13 (81%). A total of six complications occurred most of which were managed conservatively. One perforation that required subsequent surgical intervention occurred and was related to sphincterotomy after successful rendezvous ERCP.

Recently, Park and colleagues described a large prospective cohort who underwent EUS-BD by one experienced operator at a large, busy tertiary center in Korea [382]. These authors have previously reported a relatively high adverse event rate of 20% [368] for EUS-BD and in the more recent study they aimed to evaluate whether a modified technique of “enhanced guidewire manipulation” could improve the safety and efficacy of EUS-BD. The modified approach by Park et al. included:

- optimizing angle of bile duct puncture with the EUS needle
- use of smaller-diameter wires to avoid wire shearing
- introducing a 4-Fr catheter to manipulate direction of wire towards/distal stricture/ampulla; and
- preference for puncturing a segment to intrahepatic duct to allow advancement of wire towards the hilum [382].

In this study, 45 patients with benign or malignant biliary obstruction underwent same session EUS-BD after failed ERCP. Technical success, which was defined as successful stenting or balloon dilation along with the flow of contrast medium and/or bile through the stent, was achieved in 41 (91%) patients. Functional success, defined as decrease of cholestatic indices to less than 75% of pretreatment value within 1 month of the procedure, was achieved in 39 (95%) of these patients. A total of five (11%) adverse events occurred in four patients: one each of pancreatitis, focal bile peritonitis, limited pneumoperitoneum, intraperitoneal stent migration and biloma. The latter complication was managed by an EUS-guided approach with stent-in-stent placement. In all, three patients experienced mild complications and one patient experienced a moderate

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**Figure 146.14** EUS-guided biliary drainage using the rendezvous technique. (a) The common bile duct (CBD) was punctured with a 19-gauge needle under endosonographic guidance and antegrade cholangiography revealed dilated CBD with distal obstruction. (b) Antegrade passage of guidewire can be seen passing via the stomach (red arrow), duodenal bulb (yellow arrow), through the papilla and coiled in the distal duodenum (white arrow). (c) The wire was grasped through a duodenoscope and a sphincterotomy was passed over the wire (white arrow). The wire was withdrawn from the duodenal bulb (yellow arrow) and re-advanced in a retrograde fashion to facilitate transpapillary stent placement. (d) Dark bile flowing through transpapillary self-expandable metallic biliary stent. (e) Coronal CT showing self-expandable metallic stent placed across distal biliary stricture due to pancreatic mass.
complication per the ASGE lexicon's severity grading system [383]. Technical success and complications in this study were similar to other reports.

As stated above, the primary intent of the Park's study [382] was to evaluate whether “advanced guidewire manipulation” may decrease the 20% (n = 11) adverse event rate the authors reported in a prior study of 55 patients who underwent either EUS-guided hepaticogastrostomy or choledochoduodenostomy [368]. To evaluate whether the authors’ successfully met their goal, it is important to evaluate potential reasons for complications in these 11 patients (graded as mild in seven and moderate in four). Interestingly, nine of these 11 patients underwent fistula dilation using a needle knife and its use was independently associated with occurrence of adverse events (odds ratio [OR] 12.4; P = 0.01). In the more recent study, fistula dilation with needle knife was used in only five patients. Therefore, it is recommended that use of needle knife cautery for tract creation/dilation during EUS-BD should be avoided when possible.

Gupta et al. reported a multicenter experience on long-term outcomes of EUS-BD in 246 patients [384]. The intrahepatic approach was used in 60% of the cases. Successful biliary drainage was achieved in 87% of cases, with a similar success rate in extrahepatic and intrahepatic approaches (84.3% vs. 90.4%; P = 0.15). A higher clinical success rate was noted in patients with malignant diseases compared with benign diseases (90.2% vs. 77.3%; P = 0.02). Complications for all techniques included pneumoperitoneum 5%, bleeding 11%, bile leak/peritonitis 10%, and cholangitis 5% without a significant difference between the intrahepatic and the extrahepatic approaches and between benign and malignant diseases.

It is important to note that results of the above discussed studies come from tertiary centers where all procedures were performed by high-volume, highly-qualified interventional endoscopists. We believe these procedures are ideally performed by experienced endoscopists trained in both ERCP and EUS and carried out at institutions where appropriate surgery and radiology backup are available should complications arise.

**EUS-BD vs. PTBD**

Outcome data comparing EUS-BD and alternative procedures (e.g. PTBD) are limited. One small randomized controlled trial comparing EUS-BD and PTBD in 25 patients with malignant biliary obstruction and failed ERCP [381]. This study concluded that both procedures had equivalent efficacy, safety and cost.
The primary limitation of this study was that only direct procedural costs were calculated. This likely overestimated the cost-effectiveness of EUS-BD which is associated with increased downstream costs due to the requirement for frequent reinterventions. In another study, Khashab and colleagues recently compared efficacy, safety, and cost of EUS-BD to that of PTBD in 73 jaundiced patients with distal malignant biliary obstruction who underwent EUS-BD or PTBD after failed ERCP [385]. Although technical success was higher in the PTBD group (100% vs. 86.4%; \( P = 0.007 \)), clinical success was equivalent (92.2% vs. 86.4%; \( P = 0.40 \)). PTBD was associated with higher adverse event rate (index procedure: 39.2% vs. 18.2%; all procedures including reinterventions: 80.4% vs. 15.7%). Stent patency and survival were equivalent between both groups. Total charges were more than two times higher in the PTBD group (\( P = 0.004 \)) mainly due to significantly higher rate of reinterventions (80.4% vs. 15.7%, \( P = 0.001 \)). The authors concluded that EUS-BD and PTBD are comparable effective techniques for treatment of distal malignant biliary obstruction after failed ERCP. However, EUS-BD is associated with decreased adverse events rate and in this study was significantly less costly due to the need for fewer reinterventions.

One of the advantages of EUS-BD is the possibility of accessing the biliary ductal system from multiple routes. The dilated intrahepatic biliary radicals can be accessed from the liver via the distal esophagus, or stomach, or the common bile duct can be punctured from the proximal duodenum (and occasionally from gastric antrum) [386]. This choice of access routes allows for successful endoscopic biliary drainage even in patients with duodenal obstruction or duodenal bypass surgeries. Other advantages include feasibility of EUS-BD in patients with ascites and liver metastasis, avoidance of percutaneous catheters, and their associated complications (e.g. skin irritation, leak), and their perceived invasiveness and negative impact on quality of life. Moreover, EUS-BD can be performed during same endoscopy session after failed ERCP, which avoids the need for repeated interventions and allows for timely biliary drainage in which bilirubin levels decrease more rapidly and permitting more rapid initiation of chemoradiation if needed [373,382]. EUS-BD also maintains bile within the GI tract to ensure proper digestion and absorption of nutrients.

**EUS-guided pancreatic duct interventions**

EUS-guided pancreatic duct (PD) interventions have recently gained increasing attention. EUS-guided PD intervention is divided into two types, antegrade and rendezvous techniques, following EUS-guided pancreaticography. During the antegrade technique, pancreaticoenterostomy is carried out by stent placement between the PD and the stomach, duodenum, or jejunum. Transenteric antegrade PD stenting is conducted by stent placement, advancing anteriorly into the PD through the pancreatic tract. The rendezvous technique is carried out by using a guidewire through the papilla or anastomotic site for retrograde stent insertion. Technical success (of stent placement) using these techniques is achieved in about 70% of patients with clinical success achieved in about two thirds of them [387,388]. Adverse events are not uncommon and include bleeding, hematoma formation, pancreatitis, abscess formation, pain necessitating hospital stay, and stent migration.

**EUS-guided drainage of peripancreatic fluid collections (PFC)**

Pancreatic fluid collections (PFCs) are categorized into acute fluid collections, pseudocysts, and walled-off pancreatic necrosis (WOPN). Acute collections lack a well-defined wall and usually require no intervention. However, well encapsulated and symptomatic collections warrant therapy. Indications for drainage of PFCs include pain, obstruction of the GI or biliary tract, infection, or fistula formation [389].

Although surgery is historically considered the standard technique for drainage of pancreatic pseudocysts, use of endoscopic methods is increasing. Varadarajulu and colleagues performed a single-center, open-label, randomized trial to compare endoscopic and open surgical cystgastrostomy for pancreatic pseudocyst drainage in 40 patients [390]. The primary end point was pseudocyst recurrence after a 24-month follow-up period. At the end of the follow-up period, none of the patients who received endoscopic therapy had a pseudocyst recurrence, compared with one patient treated surgically. There were no differences in treatment successes, complications, or re-interventions between the groups. However, the length of hospital stay was shorter for patients who underwent endoscopic cystgastrostomy (median, 2 days, vs. 6 days in the surgery group; \( P < 0.001 \)). Although there were no differences in physical component scores and mental health component scores (MCS) between groups at baseline on the Medical Outcomes Study 36-Item Short-Form General Survey questionnaire, longitudinal analysis showed significantly better physical component scores (\( P = 0.019 \)) and mental health component scores (\( P = 0.025 \)) for the endoscopy treatment group. The total mean cost was lower for patients managed by endoscopy than surgery (\$7011 vs. \$15 052; \( P = 0.003 \)). The authors concluded that there was no evidence that surgical cystgastrostomy is superior. The EUS-guided approach was associated with shorter hospital stays, better physical and mental health of patients, and lower cost.

One major limitation of an endoscopic (not EUS-guided) approach is that PFCs not causing a luminal compression cannot be treated endoscopically. This limitation is overcome with the performance of drainage procedures under EUS guidance [391], as long as the collection is within 1.5 cm from the GI tract. One randomized trial compared the rate of technical success between EUS and EGD for transmural drainage of pancreatic pseudocysts in 30 patients [392]. EUS had significantly higher success rate than EGD (100% vs. 33%; \( P < 0.001 \)). The authors recommended that EUS serve as the first-line treatment modality for endoscopic drainage of pancreatic pseudocysts given its high technical success rate.
We have described EUS-guided pseudocyst drainage as a one-step procedure using graded catheter and balloon dilation of the cystgastrostomy tract and a novel multiple wire insertion technique facilitated by a modified double lumen biliary cytology brush catheter [393,394]. Ten patients with 11 pseudocysts underwent EUS-guided pseudocyst drainage using this multiple wire insertion technique. Technical success, defined as successfully achieving access and drainage of pseudocysts, was achieved in all cases (100%) with no procedural complications. Clinical success was achieved in all cases with complete resolution of pseudocysts. The use of a modified double lumen biliary cytology brush catheter allowed for a simple and safe one-step EUS-guided drainage of pseudocysts [393,394].

Endoscopic therapy of WOPN is more technically challenging than standard transluminal drainage (Figure 146.16). Solid contents inside the cavity do not readily drain through small-caliber transluminal stents. This results in stent clogging and infection of sterile WOPN (as a result of contamination during endoscopic procedure). Other minimally invasive techniques for drainage of WOPN include endoscopic necrosectomy [395] or hybrid techniques (combination of laparoscopy, transcutaneous radiologic drainage, and/or endoscopy) [396]. Recently, a new EUS-based drainage technique of WOPN was described and entails creating multiple transluminal gateways to facilitate effective drainage of necrotic contents [397].

Recommendations for endoscopic management of patients with PFCs
It is preferable that patients with PFCs obtain MRI/MRCP prior to endoscopic therapy. MRCP may suggest pancreatic duct leak and need for ERCP. MRI (in contrast with CT) enables quantification of solid necrotic material inside the cyst. This can be later confirmed during EUS. If no solid material is identified (pseudocyst), then only conventional transmural drainage is required. If limited (<40%) percentage of cyst contents is solid, then multiple transluminal gateway technique is recommended.

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Figure 146.16 EUS-guided drainage of walled-off pancreatic necrosis (WOPN). (a) EUS image of WOPN prior to EUS guided drainage. Hyperechoic solid material (yellow arrow) is seen within the cyst. (b) Axial contrast enhanced CT shows a large intrapancreatic collection with near complete replacement of the pancreatic parenchyma measuring 11.7 cm. The collection has a large amount of debris (asterisk) with a thin sliver of fluid (arrow). (c) Axial T2 weighted MRI of abdomen demonstrates the presence of a collection measuring 11.6 cm that contains predominantly solid debris (asterisk) with small amount of fluid (arrow). (d) Axial contrast enhanced CT performed 2 months after stent placement demonstrates marked decrease in the size of the collection.
Alternatively, endoscopic necrosectomy or hybrid techniques could be performed in this setting but these techniques are associated with a non-trivial risk of morbidity and mortality [398]. However, these later approaches are mandatory for PFCs with extensive solid necrotic contents (>40%–50%). Placement of a nasocystic catheter with intermittent irrigation of the cyst cavity should be performed in patients with WOPN to ensure continuous irrigation and drainage. The irrigation catheter may be removed after resolution of infection and organ failure (if present), significant decrease in size of WOPN on repeat imaging, in association with absence of necrotic fluid on aspiration of drainage catheter. Subsequent imaging is usually obtained 6–8 weeks afterwards. If WOPN is resolved, transmural stents are removed by endoscopy. For patients with disconnected pancreatic ducts, the transmural stents are left in place indefinitely [399].

**EUS-guided celiac plexus neurolysis**

Celiac plexus neurolysis (CPN) involves chemical destruction of celiac ganglia and corresponding neural pathways by injecting dehydrated alcohol into the network of the celiac plexus. The result is moderate neuronal degeneration associated with residual fibrosis accomplished either transcutaneously under ultrasound, CT, or EUS guidance. The advantages of the EUS approach are the fine orientation of the needle above or lateral to the celiac trunk and the real-time performance of the procedure, under Doppler control of vessel interposition. In addition, the technique is easy, requiring only 2–3 minutes immediately after the staging or sampling of an inoperable pancreatic tumor. Better results can be expected owing to the better orientation of the needle, compared to the ultrasound or CT approach, and the real-time accomplishment of the procedure (Figure 146.17).

The EUS-guided technique consists of preprocedural hydration with 500 mL saline, followed by CPN performed with the patient in the left lateral position. After color doppler assessment of vessel-gut interposition, a therapeutic linear-array echo-endoscope is used and the puncture site is chosen. Proximity to the diaphragm should be avoided, because of the potential for immediate pain due to the spread of alcohol. The devices used are 22-guage, 19-guage needles, or fenestrated 20-guage needles designed for EUS-CPN (Cook Medical, Winston-Salem, NC, USA).

Different techniques can be implemented during EUS-CPN and include a single central injection, bilateral injection, and direct celiac ganglia injection. For central injection, which is easier to perform, the needle is advanced above the celiac trunk, in the space between the aorta and the origin of the celiac axis. If bilateral injection is chosen, the echoendoscope, situated above the celiac axis, is rotated to one side until the origin of the celiac axis is no longer seen, and half of the entire solution is injected; the procedure is then repeated on the opposite side. When ganglia are targeted, the echoendoscope is rotated clockwise and celiac ganglia are found above the celiac trunk, alongside the trunk, and below the trunk, just above the superior mesenteric artery takeoff.

Pain relief after EUS-CPN in patients with pancreatic cancer varies between 45% and 94% [400]. One metaanalyses showed a mean rate of pain alleviation of 80% but a much lower rate of complete pain response [401].

Many of the patients will still require the same dose of analgesic after EUS-CPN, which should be considered as an adjunct method to standard pain management. The postneurolytic residual pain could be related to nonvisceral pain, due to the invasion of the muscles or surrounding connective tissue, but factors concerning the technique used (type of technique, quantity of alcohol injected, timing of the procedure) have not been extensively studied.

One randomized controlled trial compared the central and bilateral techniques of EUS-CPN and found no difference in duration of pain relief (11 weeks vs. 14 weeks), complete pain relief (2/29 patients vs. 2/21 patients) or reduction in pain medications (9/29 patients vs. 7/21 patients) [402]. The technique of direct injection into the celiac ganglia has been used in only a few studies. One randomized controlled trial compared direct ganglia neurolysis with central neurolysis. The positive response rate at day seven and the complete response rate were higher in the ganglia neurolysis group (75.5% vs. 45.5% and 50% vs. 18.2%, respectively) [403].

**EUS-guided fiducial placement**

Patients with locally advanced pancreatic adenocarcinoma most often have tumor involvement of celiac axis or superior mesenteric artery. In these patients, chemotheraphy, conventional radiation therapy (RT) or a combination of both may positively influence overall survival and quality of life [404,405]. The goal is to attempt to downstage the tumor, improve local control, and offer palliation [406]. In recent years, improvements in RT, namely stereotactic body RT (SBRT), were possible.
because of advances in CT, MRI, and PET. SBRT delivers multiple beams of radiation with a high degree of accuracy, allowing the safe and effective delivery of RT to target sites [407,408]. However, treatment of extracranial lesions with SBRT requires placement of intratumoral radiographic markers (fiducials) to allow for image-guided RT (IGRT). With IGRT, it is possible to deliver high doses of RT therapy with submillimeter accuracy, sparing surrounding organs at risk [406].

Percutaneous radiographic marker placement is an established technique for the deployment of fiducials into pancreatic tumors [409]. However, this approach is invasive and carries a nontrivial morbidity risk with a relatively high rate of fiducial migration [409]. EUS-guided fiducial placement has been reported in recent years to be less-invasive and an effective means for fiducial placement in patients with inoperable pancreatic cancer [410–412]. EUS-guided fiducial placement is traditionally performed using 19-gauge or 22-gauge FNA needles [410,412,413].

Technique of EUS-guided placement of fiducials
Fiducials are placed using linear echoendoscopes and 19-gauge or 22-gauge needles. The FNA needle is backloaded with one fiducial marker. The stylet of the EUS needle is withdrawn about 2–3 cm and the fiducial is backloaded into the needle tip. The needle tip of the EUS needle is sealed with sterile bone wax to prevent unintended loss of the fiducial while advancing the needle through the therapeutic channel of the echoendoscope. The needle is then inserted into the target lesion under EUS guidance. The stylet of the EUS needle is advanced to maximal insertion, thus pushing the fiducial out of the needle and into the lesion (Figure 146.18). The EUS needle is then withdrawn from the echoendoscope and reloaded with a new fiducial, and the technique is repeated until the desired number of fiducials have been placed. Typically, two to four fiducials are placed to provide ample distance and angulation for IGRT. Fiducials are placed at the periphery of the tumor when possible.

EUS-guided angiography
Endoscopic management of GI bleeding is insufficient in about 10% of patients. The source of bleeding occasionally cannot be identified using conventional endoscopy. The initial experience with EUS to manage GI bleeding was described in a report that included five patients, four of whom had severe refractory bleeding that resulted from hemosuccus pancreaticus, a Dieulafoy’s lesion, duodenal ulceration, or GI stromal tumor (GIST) [414]. EUS-guided therapy was performed by injecting alcohol or cyanoacrylate (CYA). Power and pulse Doppler revealed complete cessation of blood flow and/or occlusion of the vessel of interest, thereby indicating a successful end point of angiography. None of the patients re-bled after EUS-guided therapy. A more recent study reported on EUS-guided sclerotherapy using CYA or polidocanol 2% to treat refractory GI bleeding in eight patients (varices, aneurysms, Dieulafoy’s) [415]. Procedures were successful in seven (87.5%) patients with immediate cessation of doppler signal at the end of procedures.

Figure 146.18 EUS-guided fiducial placement. (a) EUS image of a mass in the head of the pancreas. EUS-FNA confirmed pancreatic ductal adenocarcinoma. (b) EUS image showing FNA needle and a deployed hyperechoic fiducial (arrow)
catheter. Color Doppler is used to confirm absence of flow in the treated varix. Repeat injection of CYA and/or coils is performed for persistent flow. Medium or large esophageal varices are then treated by band ligation.

All (n = 30) included patients underwent successful EUS-guided transesophageal treatment of GFVs [416]. The mean number of GFVs treated was 1.3 per patient, and the mean volume of CYA injected was 1.4 mL per varix. Hemostasis of acute bleeding was 100%. Majority (96%) of patients attained GFV obliteration after a single treatment session. Rebleeding occurred in four patients, with none attributed to GFVs. There were no procedure-related complications and no symptoms or signs of CYA embolization.

This approach for treating bleeding due to GFV has multiple advantages (Box 146.1) and deserves further study to determine its efficacy and safety [417,418].

**Conclusion**

Interventional EUS has flourished during recent years and indications for its use are expanding. Interventional EUS procedures are technically demanding and frequently require skills in both endosonography and ERCP. Improvement in devices and accessories tailored specifically for interventional EUS are needed to expand the horizons of therapeutic EUS.

**Author disclosure**

Dr. Mouen A. Khashab, consultant for Boston Scientific and Olympus America, has received research support from Cook Medical.

References are available at www.yamadagastro.com/textbook

**Further reading**


CHAPTER 147
Computed tomography of the gastrointestinal tract

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Introduction
Since its initial introduction in the late 1970s, there have been many technical advances in computed tomography (CT) in terms of both scanner hardware and software. The latest generations of multidetector CT (MDCT) scanners have allowed dramatic improvements in both temporal and spatial resolution, making possible studies with minimal respiratory or motion artifacts [1]. The improvement in scanner speed has been immense, as the latest dual-source CT scanners can now complete a scan of the abdomen in less than 1 s, as opposed to roughly 10 s for the prior generation of 64-slice scanners. This improvement in temporal resolution, in addition to reducing artifacts, has also allowed more consistent acquisition of images at peak arterial enhancement, thereby improving the ability to diagnose hypervascular lesions such as pancreatic neuroendocrine tumors or hepatocellular carcinoma [2,3]. However, as important as hardware improvements have been, software improvements have been equally important, particularly the introduction of widely available three-dimensional (3D) post-processing software, which enables the radiologist to view the scan data in any imaging plane, as well as new CT applications such as virtual colonography and CT angiography.

In this chapter, we will review current state of the art CT imaging of the gastrointestinal tract, including the hepatobiliary tree, pancreas, and hollow viscera, as well as ancillary techniques such as 3D imaging and CT colonography.

The hollow viscera of the gastrointestinal tract

Techniques
Oral contrast
Identification of luminal gastrointestinal tract abnormalities, whether neoplastic or inflammatory, depends on the ability to adequately distend the bowel lumen and visualize the bowel wall, as well as distinguish the bowel from adjacent structures in the mesentery and peritoneum (a difficult task in certain cases when the bowel is collapsed) [4,5]. A variety of CT enteric contrast agents administered either orally and/or rectally, broadly categorized as positive agents, neutral agents, or negative agents can aid in accomplishing these goals [6–8].

Positive agents appear white on CT and usually consist of diluted (1.5%–2%) iodinated water-soluble contrast or diluted (2%) barium suspensions. These agents have been traditionally used for routine CT scans of the abdomen. Although positive agents are quite effective in discriminating the bowel from adjacent structures (such as mesenteric tumor implants or lymph nodes), high-density positive oral contrast is often associated

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with significant streak or beam-hardening artifacts, sometimes limiting evaluation of the bowel wall itself. As a result, in those situations where it is important to appreciate subtle changes in bowel wall thickness or enhancement (such as in Crohn’s disease), a positive contrast agent is usually not appropriate [9].

Neutral contrast agents appear gray on CT and usually have a density comparable to water. Currently used neutral agents include water, methylcellulose agents, and commercially available products such as Volumen (E-Z-Em; Lake Success, NY), which has a density value slightly greater than that of water [8]. Water is quite effective in distending the stomach and duodenum, particularly when ingested immediately prior to a scan, but is limited in its ability to distend the remainder of the small bowel due to its rapid absorption. As a result, while water is sometimes incorporated as a component of oral contrast administration regimens, it is usually not the only oral contrast agent utilized if the small bowel is the suspected site of pathology. Alternatively, Megibow and colleagues compared the neutral oral contrast agents Volumen and methylcellulose in 60 patients undergoing CT of the pancreas [8]. Volumen, which had an attenuation of 20 to 40 Hounsfield units (HU), resulted in superior distention of the bowel and demonstration of mural features and, as a result, Volumen is generally considered to be the most efficacious of all of the available neutral enteric contrast agents [10–14]. Overall, neutral contrast agents allow good distension of the bowel, without obscuring bowel wall thickening, enhancement, or density changes. Just as importantly, as 3D imaging has become a more widely used application in abdominal imaging, in contrast to positive agents, neutral contrast agents do not interfere with 3D postprocessing algorithms.

Finally, negative agents appear black on CT and typically consist of either gas granules administered orally to distend the stomach or insufflation of the colon with air or carbon dioxide for virtual colonoscopy. Other negative agents, such as oil-based products (peanut oil), are not used routinely in most practices [15].

**Intravenous contrast**

Intravenous (i.v.) contrast-enhanced images expand the diagnostic range of CT and have become essential for most clinical indications. Intravenous contrast should be used in every CT protocol with a few exceptions, that is patients with renal failure or a contrast allergy. Intravenous contrast enhancement can dramatically improve the visualization of pathological processes in virtually every facet of abdominal imaging, including the evaluation of the alimentary tract and the solid gastrointestinal organs. Not only is intravenous contrast essential in allowing the radiologist to recognize and differentiate normal structures from a pathological process, but once a pathological entity is recognized, intravenous contrast can significantly alter a differential diagnosis by highlighting attenuation differences or by accentuating vascularity, thereby facilitating the determination of histological type and neoplastic potential [16]. In many patients, the failure to utilize intravenous contrast may prevent the identification of a pathological process or neoplasm, as the lesion may not be distinguishable from adjacent normal structures.

Nonionic iodinated contrast agents are typically utilized, and the protocol for contrast administration will vary depending on the clinical indication. Different phases of contrast enhancement (i.e., arterial, venous, delayed, etc.) may be needed for different suspected diagnoses. For example, in a patient with suspected pancreatic cancer, it is important to acquire images in both the arterial and venous phases in order to ensure identification of the mass itself, as well as to appropriately stage the lesion with regards to mesenteric arterial and venous involvement [17,18]. Alternatively, in a patient with abdominal pain in the emergency room, a routine venous acquisition alone may be sufficient. The radiologist will tailor the CT protocol based on the provided clinical history and the clinical question and, as a result, two patients with slightly different clinical histories may undergo CT scans with significantly different CT protocols. Therefore, it is essential that the ordering physician provides appropriate clinical information in order for scans to be performed correctly.

**Scanning protocol**

Virtually every study performed on the latest generation of CT scanners is acquired with thin-collimation, typically with slice thicknesses as small as 0.5–0.75 mm. These isotropic datasets (i.e., identical resolutions in the x, y, and z axes) allow the creation of exquisitely detailed 3D reconstructions and multiplanar reformations (i.e., coronal and sagittal reformations), as well as the reconstruction of 3–5-mm slices for routine axial image review. While older-generation scanner technology often required active manipulation of scan parameters (such as tube current and tube potential) for individual patients, modern MDCT scanners have now automated much of the process, and the scanner software (such as “automated exposure control” or “automated tube potential selection”) can choose the appropriate mAs and kVp depending on the patient’s size and attenuation, as dictated by the scout image [1,9].

**Three-dimensional imaging**

For much of the history of CT, the radiologist has primarily relied on interpretation of the source axial images in order to make a diagnosis. However, such an overreliance on axial imaging is no longer sufficient or acceptable, and the radiologist must visualize a pathological process from multiple different perspectives, as well as understand the 3D relationship of structures, in order to make the most accurate diagnosis [19,20]. In order to visualize a dataset from alternative projections and perspectives, several different 3D techniques are available, including multiplanar reformations (MPR), volume rendering (VR), and maximum intensity projection (MIP). Multiplanar reconstructions are the simplest of these techniques to use, and allow the user to scroll through the dataset in any plane. These MPR images can be created quickly and
effortlessly directly at the CT scanner console following the conclusion of each case, and do not require any further post-processing or active editing by the radiologist. Most radiology practices across the country now utilize MPRs as part of their standard imaging protocols.

However, more advanced 3D visualization techniques (such as VR or MIP) require the radiologist to interactively manipulate the dataset using advanced reconstruction software at an independent workstation. Volume rendering, a 3D visualization technique, which assigns a unique color and transparency to each voxel in a dataset depending on its attenuation and relationship to other adjacent voxels, allows the brightness, opacity, window width, and window level to be adjusted in real time in order to accentuate certain tissue types or for selective viewing of the vasculature [20]. Although VR software was once labor intensive with high computational demands, the recent software packages are much easier to use and require less computational power. Maximum intensity projection is a 3D technique in which the brightest voxel is displayed along a ray, nicely illustrating high attenuation vasculature and providing detailed vascular maps [20]. The radiologist often utilizes a combination of these 3D tools to optimally display the relevant anatomy and pathology. In the last several years, specialized 3D software has also been developed for specific CT applications, including virtual colonography.

**Esophagus**

**Neoplasms**

For evaluation of a suspected or known esophageal mass, MDCT can play a valuable role in identifying the mass, assessing local extension, detecting local and regional lymphadenopathy, as well as identification of distant metastatic disease. Esophageal neoplasms can appear on CT as focal, asymmetric, soft tissue lesions arising from the wall or as discrete sites of focal wall thickening. However, these findings are nonspecific and can be seen with both benign and malignant tumors, as well as inflammatory conditions or esophagitis [21]. MDCT should not be relied upon for the primary diagnosis of an esophageal mass, particularly as a small or subtle lesion cannot be reliably distinguished from a collapsed esophagus [22] (Figure 147.1). Moreover, with regard to the primary lesion, MDCT provides no histological specificity; squamous cell carcinoma, adenocarcinoma, lymphoma, and metastatic disease to the esophagus can all have similar CT appearances. However, a primary esophageal leiomyoma should be considered when there is a prominent exophytic component to a mass, or alternatively, when confronted with an extremely well-circumscribed mass that appears to be primarily mural in origin [23].

As mentioned earlier, early superficial or small esophageal lesions may not be visible on MDCT and, therefore, MDCT should not be used to screen for esophageal cancer or as a primarily diagnostic tool [24]. Moreover, despite technical advances in CT scanners and 3D imaging software, MDCT cannot distinguish the individual layers of the esophageal wall and is not, therefore, an acceptable modality for T-staging of a lesion [24]. While MDCT can identify sizeable locoregional lymph nodes, endoscopic ultrasound (EUS) is likely more sensitive for identifying small periesophageal nodes. Once a primary tumor is identified, CT can also be helpful in evaluating local extension of the tumor, including involvement of the aorta, diaphragm, and tracheobronchial tree. Local extension can be extremely difficult to accurately diagnose, and involvement of these local structures must often be inferred based on the loss of a discrete fat plane between the tumor and the adjacent structure.

The real value of MDCT in patients with esophageal carcinoma is in the staging of distant metastatic disease, evaluating response to therapy, and identifying postsurgical complications. The most common sites of distant metastatic disease include mediastinal or upper abdominal lymph nodes (particularly periesophageal and gastrohepatic ligament lymph nodes), lung, liver, and adrenal glands. Several studies have suggested that PET may also serve as a valuable ancillary tool in the diagnosis of distant metastatic disease. Thus, Pfau and colleagues found that PET was able to identify more patients with metastatic disease than CT [24–26].

![Figure 147.1](a) Axial intravenous contrast-enhanced multidetector computed tomography (MDCT) image reveals a large circumferential esophageal mass (arrows), splaying the carina. An esophageal stent is in place (arrowhead). (b) Axial intravenous contrast-enhanced MDCT image demonstrates bulky mediastinal adenopathy (arrows). The esophageal stent is again noted (arrowhead).
Postsurgical complications after esophagectomy occur in up to 50% of patients, and MDCT can play an important role in their prompt diagnosis [27]. The most frequently noted complication seen on CT is an anastomotic leak, which may not always be detected by a standard contrast esophagography, particularly when the leak is small or slow [27]. In some cases, it may be beneficial to perform CT immediately after contrast esophagography to increase sensitivity in detecting small leaks that may be difficult to perceive at fluoroscopy. CT is also valuable in patients after esophageal stent placement to document patency and to detect potential complications [28].

Varices
Esophageal varices are easily detected with contrast-enhanced CT, and MDCT can easily detect both intraesophageal and extraesophageal varices, the latter of which can be underestimated by EUS [29]. Esophageal varices appear as thickening and scalloping of the esophageal wall, as well as enhancing vessels within the esophageal wall or in the adjacent soft tissues [30].

Esophagitis
While CT is neither sensitive nor specific for this diagnosis, esophagitis may produce thickening of the distal esophageal wall. CT does not aid in the differentiation of distal esophageal abnormalities and cannot distinguish carcinoma from severe esophagitis. CT may be useful in recognizing distal esophageal changes, and subsequently prompting endoscopic evaluation to determine a more specific etiology.

Achalasia
CT is not the imaging modality of choice in patients with suspected achalasia. However, CT is sometimes the first modality to suggest the diagnosis in patients imaged for evaluation of nonspecific symptoms, and can also be helpful in distinguishing achalasia from “pseudoachalasia” secondary to an obstructing tumor or mass. The CT appearance of achalasia can be dramatic, showing a markedly distended esophagus with retained fluid and food [31].

Stomach
While certainly not as sensitive or specific as upper endoscopy, MDCT can identify a number of gastric abnormalities, and can accurately assess the position of the stomach, the luminal contour, the thickness of the gastric wall, locoregional lymph nodes, peritoneal ligaments, and the surrounding viscera. When the stomach is distended adequately, the gastric wall should measure less than 5 mm. However, at the esophagogastric junction, the wall may normally be up to 1 cm thick, as a result of the scan plane and the orientation of the lower esophageal sphincter. Similarly, because of muscle orientation in the antrum, as well as antral contraction, the wall of the antrum may commonly exceed 5 mm in thickness, and can measure up to 13 mm and still be considered normal [32]. However, using absolute gastric wall measurements is not generally advisable, and it is usually more useful to qualitatively assess wall thickness in conjunction with other supportive imaging findings such as abnormal wall enhancement, wall irregularity, and ulceration. Moreover, simply measuring wall thickness is not always useful in distinguishing malignant from benign disease. In a study by Insko et al. the authors noted that a gastric wall thickness of 1 cm had a sensitivity of 100% for detecting malignant or potentially malignant lesions, but only had a specificity of 50% [33]. The authors found that focal eccentric enhancing wall thickening was always malignant in their patients, but was only present in a small percentage of individuals [33].

When MDCT is performed for a suspected gastric abnormality, adequate distension of the stomach and duodenum is critical, and patients should be instructed to rapidly ingest either water or Volumen immediately prior to undergoing the scan [6,34–36]. Positive oral contrast should be avoided, as streak and beam hardening artifacts may preclude subtle assessments of wall thickening and abnormal enhancement. Finally, several studies have confirmed the value of 3D imaging in the evaluation of the stomach and perigastric relationships [37].

Neoplasms
Gastric adenocarcinoma
Gastric adenocarcinoma can present with a number of discrete CT appearances, the most common of which is focal, irregular thickening of the gastric wall, sometimes with ulceration and necrosis (Figure 147.2). Other possible appearances include a discrete polypoid mass, as well as a scirrhous form (with or without ulceration) with diffuse infiltration of the gastric wall (i.e., linitis plastica). Scirrhous tumors can be difficult to diagnose as the degree of wall thickening is less than in the other forms of the malignancy, and this diagnosis is sometimes overlooked on MDCT, and in other cases is misdiagnosed as gastritis given its diffuse distribution [38].

MDCT is typically used for staging once the diagnosis has been made using endoscopy. Overall staging accuracy has been reported to be as high as 94%, with better results for advanced tumors than in early gastric cancers [39]. Studies have shown that EUS is more accurate than CT for determining depth of mural invasion and for local lymph node staging [39]. As already mentioned, CT does not yet possess the spatial resolution to distinguish the individual layers of the gastric wall and, consequently, superficial early gastric cancers may not be detected. Accordingly, MDCT is not an appropriate tool for T-staging of tumors [39,40].

Gastric cancer typically spreads along the perigastric peritoneal reflections through intramural lymphatics, via peritoneal seeding, and hematogenously. Lymphatic submucosal spread into the esophagus occurs in approximately 30% of patients with tumors in the gastric fundus. Extension into the serosa allows tumors access to the supporting mesenteries of the stomach, thereby providing pathways into the omentum, kidney, liver, pancreas, transverse colon, and spleen. Proximal lesions can
were visible on four-slice CT, suggesting that MDCT can be useful in screening symptomatic patients suspected of having GIST, using newer scanner and with careful attention paid to appropriately distending the stomach with water or Volumen immediately prior to the scan [46].

Lymphoma
Gastric lymphomas produce significantly greater wall thickening compared to gastric adenocarcinoma, although this finding is of limited value in generating a differential diagnosis in individual patients, particularly given that gauging the degree of thickening can be difficult in cases with poor gastric distension [41,42]. Like lymphoma elsewhere in the body, lymphoma of the stomach tends to minimally enhance and be relatively homogeneous, in contrast to the heterogeneous appearance typical for adenocarcinoma. In cases presenting with fold hypertrophy, there may be demonstrable clefts between the thickened folds extending through the wall into the extramural tumor [43]. Perhaps the most important differentiating feature is the presence of extensive lymphadenopathy, particularly lymph nodes distant from the gastric mass, a feature unusual in gastric adenocarcinoma.

Gastrointestinal stromal tumors
Gastrointestinal stromal tumors (GIST) are mesenchymal tumors that arise within the muscularis propria of the bowel wall. Approximately 60% of GISTs occur in the stomach, although they represent only 1%–3% of all gastric malignancies [44]. CT plays an important role in the detection and staging of these tumors, as CT can detect the tumor, assess for local spread, and identify distant metastases [45]. When small, GISTs are confined to the gastric wall, and usually appear as rounded, smoothly margined intramural masses (Figure 147.3) and, particularly when the stomach is well distended prior to the study, lesions as small as 1 cm can be reliably detected on MDCT [46]. In their series, Nishida et al. found that all GISTs over 2 cm extend into the diaphragm and the aorta. Again, these complex pathways of tumor spread are best appreciated when datasets are interpreted utilizing a combination of traditional axial imaging and 3D reconstructions.

Figure 147.3 Intravenous contrast-enhanced coronal multiplanar reconstruction, using water as oral contrast, demonstrates a 1.3-cm intramural gastric mass (arrows) compatible with a gastrointestinal stromal tumor. This was an incidental finding.
Inflammatory diseases
MDCT is not indicated for the primary evaluation of patients with suspected gastric inflammatory diseases. Nevertheless, because CT is so frequently ordered in patients with abdominal pain, it may be the first modality to suggest the presence of gastritis or peptic ulcer disease [47]. In patients with gastritis, MDCT may show focal or diffuse wall thickening, and the thickened wall may display some degree of low attenuation, reflecting intramural edema [48]. Although CT is not sensitive for the detection of ulcers, in rare instances they may be visualized, particularly when large, and in such cases a careful survey must be made for the presence of ectopic gas or fluid adjacent to the abnormal segment of the stomach, suggesting perforation [47]. In many of these cases where the stomach appears abnormally thickened, inflammatory and malignant gastric wall thickening cannot be accurately distinguished on MDCT, and endoscopy is usually indicated to exclude the presence of a malignancy.

Small intestine
The primary key to evaluation of the small bowel lies in adequate distension with orally administered contrast material [7]. CT enterography studies, designed specifically to interrogate the small bowel, should be performed utilizing a neutral contrast agent, most often Volumen, as positive oral contrast agents can obscure subtle sites of bowel wall thickening or abnormal bowel wall enhancement. There are a large number of CT enterography protocols in use across the country. The most common utilizes a total of 1350 mL of Volumen, with separate administrations of 450 mL at 60 min, 40 min, and 20 min prior to the study, followed by 500 mL of water immediately prior to the study. Such a protocol provides enough time for contrast to reach and distend the distal small bowel, but also distends the stomach and proximal bowel by the water ingested just prior to the scan. Medications, such as metoclopramide and glucagon, were once regularly administered, but have fallen out of favor across the country as they have little proven impact on image or scan quality. Many practices evaluate the small bowel with a single (portal venous) phase study, although the incorporation of dual-phase technique (arterial and venous) can have great advantages in identifying subtle sites of bowel wall abnormal enhancement or small hypervascular tumors [9,10,14,49].

Neoplasms
Early diagnosis of small bowel tumors continues to pose a significant challenge for both clinicians and radiologists. Not only are small bowel neoplasms relatively uncommon, but they represent less than 25% of all gastrointestinal neoplasms and less than 2% of all malignant tumors [50–53]. Moreover, small bowel tumors tend to be small initially and can be difficult to diagnose on MDCT, particularly if the diagnosis is not suspected prior to the scan [54]. While the diagnosis of these lesions was once contingent on contrast fluoroscopy studies, CT is now clearly the imaging modality of choice for these tumors, offering the added advantage of both visualizing the entire gastrointestinal tract as well as extraluminal structures such as lymph nodes [53]. However, MDCT’s efficacy is largely dependent on proper enterography technique and, more specifically, on achieving adequate distension of the small bowel so as to allow identification of a potential lesion.

Adenocarcinoma of the small intestine most often manifests as an “annular-constricting” lesion, with circumferential soft tissue attenuation, wall thickening, and irregular narrowing of the lumen, sometimes with associated proximal bowel obstruction [53]. Small bowel adenocarcinomas most frequently arise in the periampullary duodenum, but may occur anywhere along the mesenteric small bowel (Figure 147.4). Malignant lesions can also appear as exophytic or intramural masses with central necrosis and ulceration [55]. However, ulceration is not always well demonstrated on CT [56].

Four major patterns of small bowel lymphoma have been identified on radiographic studies [57]. First, lymphoma can appear as multiple nodules within the small bowel. Involvement of multiple sites along the small intestine aids in differentiation of lymphoma from adenocarcinoma and carcinoid tumor. Second, lymphoma can appear as a single dominant mass lesion of variable size, with these isolated lesions sometimes presenting due to small bowel intussusception. Third, lymphoma can be infiltrating and appear as focal wall thickening with destruction of normal small bowel folds. Unlike adenocarcinoma, small bowel lymphoma is considered to be a “soft” tumor, and is less likely to result in obstruction. In addition, as the tumor infiltrates the musculature of the wall, it can inhibit peristalsis and result in aneurysmal dilatation of the involved loop, as opposed to obstruction [57]. Fourth, small bowel lymphoma may appear as an exophytic mass, sometimes with ulceration. The presence of other manifestations of lymphoma elsewhere in the body, including extensive lymphadenopathy and splenomegaly may

Figure 147.4 Intravenous contrast-enhanced coronal volume-rendered image, using water as oral contrast, demonstrates a 2-cm lobulated mass (arrows) in the second portion of the duodenum. A common bile duct stent is in place (arrowhead). The patient underwent Whipple surgery and pathology revealed adenocarcinoma arising in a tubular adenoma.
be extremely helpful in arriving at the correct diagnosis [41]. Of note, acquired immunodeficiency syndrome (AIDS)-related lymphomas display two primary patterns on CT: single or multiple segments with homogeneous, circumferential wall thickening, or single or multiple cavitary lesions. The gross morphological features, distribution pattern, degree of wall thickening, and length of involvement are similar in AIDS-related and non-AIDS-related lymphomas [58].

Small bowel carcinoid tumors are neuroendocrine neoplasms. In their early stages, the tumors are small, confined to the bowel wall, and appear as enhancing intramural lesions, most often localized to the distal ileum in the right lower quadrant of the abdomen [59]. As the tumors grow, they can extend beyond the involved bowel wall, causing infiltration of the mesentery and desmoplastic reaction (Figure 147.5). At this stage, the MDCT appearance is characterized by radially oriented linear spiculations in the perienteric fat, with a discrete lymph node mass (frequently calcified) present centrally in the mesentery adjacent to the involved small bowel loop [60]. Bowel loops are usually drawn toward this central spiculated mass as a result of the desmoplastic reaction and scarring and, consequently, bowel obstructions and ischemic thickening of the involved loops (as a result of chronic lymphatic and venous obstruction) is common. In addition to MDCT, nuclear medicine techniques, utilizing 111 indium (or iodine 123)-labeled octreotide or iodine 131-labeled metaiodobenzylguanidine (MIBG) are useful tools to diagnose and localize carcinoid tumors and to identify their metastases. Retractile mesenteritis, a chronic inflammatory process of the mesentery, can produce a spiculated, calcified mesenteric mass that is virtually indistinguishable from a carcinoid tumor.

The fourth most common small bowel malignancy is GIST, which arises from smooth muscle cells within the wall of the GI tract and most commonly involves the stomach. Small bowel GIST tumors more commonly arise in the jejunum or ileum, as compared to the duodenum. It is usually not possible to distinguish benign from malignant GISTs radiographically unless obvious metastases are present. As with gastric GIST, small bowel lesions, when small, may go undetected on CT. As they enlarge, they typically become exophytic and often ulcerate, producing a characteristic appearance on MDCT [45]. These tumors can be bulky and large, and central necrosis or ulceration is quite common. Indeed, GIST tumors may become so large at presentation that it may be difficult to appreciate the site of origin. Tumor spread is usually through direct extension into adjacent organs or hematogenously to the liver. Liver metastasis can appear low-density or cystic, and may often become progressively more cystic following treatment with imatinib (Gleevec), rather than decreasing in size [45]. As a result, evaluating response to therapy in patients with GIST metastatic to the liver must entail a more complex determination of a liver lesion’s solid components, rather than simply relying on size measurements [61].

Metastatic disease

Metastatic disease to the small bowel can result from hematogenous spread or peritoneal seeding, each of which has a recognizable CT appearance. Hematogenous metastases are most commonly seen with melanoma, Kaposi sarcoma, and breast carcinoma, with these lesions typically presenting as discrete masses eccentrically arising from the bowel wall. Alternatively, tethering of the mesenteric border of individual bowel loops in the presence of peritoneal carcinomatosis is indicative of seeded metastases. In some cases, loops of bowel may appear abnormally clumped, tethered, and clustered together, often with the walls of these loops of bowel appearing abnormally thickened, usually suggesting serosal tumor implants in the setting of carcinomatosis. These patients may not be overtly obstructed per se, and their bowel may be normal in caliber and nondilated, but patients with this radiographic appearance often experience symptomatology that is akin to a small bowel obstruction. This constellation of findings is most commonly seen with metastatic ovarian, colon, breast, and lung carcinoma, as well as other malignancies with a predilection for peritoneal spread.
Nonneoplastic diseases

Crohn's disease

One of the earliest applications of CT in the alimentary tract was the evaluation of Crohn's disease [62]. Markedly expanded contrast and spatial resolution compared to plain film and fluoroscopy make CT ideal for identifying sites of both active inflammation as well as the stigmata of chronic inflammation [63]. In the setting of acute inflammation, the affected bowel wall displays variable degrees of mural thickening and submucosal edema and, particularly when dual-phase imaging is employed, the affected segments of bowel tend to show avid mucosal hyperenhancement, with engorgement of the adjacent vasa recta and mesenteric vasculature [64] (Figure 147.6). This increased vascularity associated with inflamed loops of bowel can be quite subtle, and can often be the first clue to a bout of active inflammation. Three-dimensional imaging, especially MIP reconstructions, is quite helpful in accentuating sites of early mesenteric hypervascularity that are difficult to appreciate on source axial imaging. Over time, as a result of multiple bouts of bowel-related inflammation, it is common for the affected segments of bowel to show prominent submucosal fat deposition, as well as fatty proliferation in the adjacent mesentry (i.e., “creeping fat”) with separation and displacement of bowel loops [9,65]. In a patient without a clear history, these findings strongly suggest a long period of bowel-related inflammation, although patients with diabetes or morbid obesity can also demonstrate similar CT features.

MDCT offers much more detail beyond simply illustrating inflamed loops of bowel. Given the propensity of Crohn's disease to result in fistulae or sinus tracks, MDCT can often accurately identify these fistulae, as well as associated fluid collections or abscesses. Fistulae occur not simply between loops of small or large bowel, but can involve the bladder as well, and the presence of gas within the bladder, or an inflamed bowel loop in close contiguity with focal thickening of the bladder wall, can be a strong clue to this diagnosis.

With advances in CT technology resulting in improved spatial and temporal resolutions, CT can provide useful information regarding disease activity in Crohn's patients. Bodily et al., retrospectively obtained quantitative information from CT scans of 96 patients with Crohn's disease, including measurements of small bowel mural attenuation and thickness. Mural attenuation correlated significantly with active Crohn's disease, although small bowel wall thickness by itself was not a significant factor [66]. In another study, of 143 patients, Colombel et al. found that endoscopic disease activity scores correlated significantly with CT bowel enhancement, “comb sign” (i.e., vascular enlargement of the vasa recta), and increased density in the mesenteric fat [67].

Small bowel obstruction

The CT findings of small bowel obstruction are contingent on three findings: (1) dilated loops of small bowel, typically over 3 cm in luminal diameter; (2) a discrete transition point at which dilated small bowel abruptly narrows; and (3) distal decompression of small bowel loops (with usually some degree of decompression of the large bowel as well) (Figures 147.7 and 147.8). MDCT is clearly superior to plain film radiography in detecting intestinal obstruction, determining the cause of obstruction, and identifying complications (such as perforation, ischemia, etc.) [68]. Studies have shown that CT sensitivities range from 90% to 95% in detecting obstruction, and that MDCT can establish the etiology of the obstruction in a majority of cases [69]. Perhaps the greatest advantage of CT in these patients is the ability to detect signs of bowel ischemia and strangulation, including bowel wall thickening and edema (ischemic signs), mesenteric inflammation, ascites, abnormal bowel wall hypoenhancement, pneumatosis, and portal venous gas [70]. While in the past it was relatively common practice for clinicians to utilize plain radiography as a screening examination for obstruction prior to utilizing MDCT, this is now generally unnecessary. In the setting of a suspected small bowel obstruction, MDCT should represent the first and most appropriate radiological study of choice, as it can change management by accelerating surgical treatment in obstructed patients with signs of ischemia or strangulation, resulting in improved outcomes [71,72]. The ability to view CT datasets in multiple planes (coronal and sagittal) has proven very important in many cases, as the exact site of transition may be difficult to detect on axial images. The use of MPRs for this indication has been shown to increase reader confidence [73].
Colon

Neoplasms

Malignant neoplasms

Thorough preoperative imaging in patients with colon cancer is essential in selecting appropriate operative therapy, incorporating neoadjuvant chemotherapy and, increasingly, deciding whether or not surgical resection of isolated liver or lung metastases might be appropriate [74]. These decisions are based on the anatomic location of the primary tumor(s) and the presence or absence of distant metastatic disease. Additionally, particularly in patients with rectal cancer, the degree of transmural extension of a tumor (i.e., T-stage), distance from the anal verge, distance between the tumor and circumferential resection margin, and the presence of bulky mesorectal lymph nodes can all have a major impact on the patient’s treatment options. EUS and MRI are superior to MDCT in the local staging of lesions (particularly in the rectum), but MDCT provides the best modality for the distant staging of colonic malignancies [75–82].

The detection of colorectal carcinoma with MDCT is highly contingent on the degree of colonic distention and adequacy of the preparation [83]. Routine MDCT (rather than a dedicated CT colonography protocol) is not a sensitive or specific option for colon cancer diagnosis, and all but the largest lesions will be overlooked. When visible, colon adenocarcinoma typically

![Figure 147.7](image1)

**Figure 147.7** Coronal multiplanar reconstruction from a noncontrast computed tomography demonstrates multiple dilated loops of small bowel, in keeping with a small bowel obstruction. Positive enteric contrast is identified in the left upper quadrant, without transit to the colon despite a relatively long delay.

![Figure 147.8](image2)

**Figure 147.8** (a) Intravenous contrast-enhanced coronal multiplanar reconstruction (MPR), using water as oral contrast, demonstrates moderate small bowel dilatation. The colon is decompressed (arrows). (b) Intravenous contrast-enhanced coronal MPR, using water as oral contrast, demonstrates multiple fistulae in the distal small bowel and colon (arrows). This was the source of the small bowel obstruction in this patient with Crohn’s disease.
Computed tomography of the gastrointestinal tract

CHAPTER 147

appears as a either a discrete soft tissue mass (with irregular, ill-defined margins) replacing the bowel, or, alternatively, as a site of eccentric irregular wall thickening (Figure 147.9) [83].

Transmural invasion is suggested when a tumor is clearly seen to extend beyond the colon wall into the surrounding mesenteric or mesorectal fat. However, the limitations of MDCT in local staging, particularly in the rectum, should not be underestimated; MDCT cannot reliably distinguish T/T2 tumors from T3 tumors that have extended beyond the muscularis propria into the mesorectal fat, nor can it reliably identify tumors that involve the mesorectal fascia and circumferential resection margin [76–82]. However, once a tumor has already been identified on colonoscopy, MDCT can be very useful in identifying acute complications that require urgent clinical or surgical attention, such as perforation, obstruction, and ischemia, all of which can be clinically silent but greatly impact long-term survival.

MDCT also plays a primary role in evaluating recurrent or distant metastatic disease after either abdominoperineal resection or colonic resection. CT is capable of demonstrating locally recurrent pelvic masses, lymphadenopathy, and liver metastases. Locally recurrent rectal cancer appears as a discrete irregularly shaped soft tissue mass in the presacral space, and can usually be differentiated accurately from normal postsurgical scarring and fibrosis in this location, which tends to appear as smooth, linear thickening, rather than as a discrete mass [84].

**CT colonography (virtual colonoscopy)**

The ability of multidetector CT to acquire a continuous volumetric data set three-dimensionally allowed the application of rendering techniques that result in a display of the luminal (mucosal) surface of the colon, an application known as CT colonography or “virtual colonoscopy” [85] (Figure 147.10). This method was first introduced in the mid 1990s, but was initially limited by slow scanner speeds, relatively thick 3–5 mm slice collimation, and the lack of easy to use software. Today, faster scanner speeds, thin section collimation, increasingly sophisticated 3D rendering software, and improved patient preparation protocols together allow these studies to be performed with a high degree of accuracy.

Like a traditional optical colonoscopy, the study requires adequate bowel cleansing, which can be achieved with any of a number of traditional colonoscopy agents, such as polyethylene glycol. For CT colonography, the patients also drinks special tagging agents comprised of dilute barium suspensions and an iodinated liquid. The tagging agents mix with any residual solid and liquid stool within the colon, which then appear white, easily allowing the radiologist to distinguish fecal material from soft tissue polyps. Studies are typically performed in both the

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**Figure 147.9** Axial intravenous and oral contrast-enhanced multidetector computed tomography demonstrates a subtle mass (arrow) in the right colon. Colonoscopy and biopsy revealed adenocarcinoma.

**Figure 147.10** (a) Axial prone image from virtual colonoscopy demonstrates an 8-mm polyp (arrow) in the right colon. (b) Endoluminal fly-through view from virtual colonoscopy shows the 8-mm polyp (arrow).
prone and supine positions to improve visualization of polyps along the dependent and antidependent surfaces of the colon, and images are also typically acquired before and after the removal of a rectal tube, maximizing sensitivity for subtle rectal lesions. Sophisticated 3D rendering software is now widely available from a variety of manufacturers, which allows time-efficient review of the datasets using a combination of multiplanar reconstructions and endoluminal “fly-through” views that simulate conventional optical colonoscopy. As a result, while these studies were once very time-consuming to interpret, expert readers can now review a study in 15–20 min.

The largest study of virtual colonography in a screening population was published by Pickhardt in 2003 [86]. This study included 1233 symptomatic adults who underwent both CT colonography and conventional colonoscopy in the same day. For adenomas >10 mm, the sensitivity using virtual colonoscopy was 94%, as compared with 88% for conventional optical colonoscopy, with a per patient sensitivity for virtual colonography of 96% [86]. A smaller screening virtual colonography study of 615 patients was subsequently published with disappointing results [87]. This study by Cotton et al. showed less than ideal results for virtual colonography, but included relatively inexperienced radiologists as readers, limiting the results of the study [87]. It is clear that virtual colonography requires training, and the American College of Radiology has recommended training of at least 50 cases for radiologists prior to interpreting cases in daily practice.

Results of the multicenter ACRIN national CT colonography trial, which was completed in late 2006, included over 2600 patients from 15 institutions. Inexperienced readers (who had read less than 50 cases in practice) were required to undergo training and pass a competency test before joining the study. All scans were performed on either 16 or 64-slice scanners, such that the data analysis was more reflective of modern multidetector CT technology. This study incorporated a number of techniques that have now become standard practice in most centers, including oral contrast tagging, automated CO₂ delivery for colonic distension, and the utilization of both 2D and 3D interpretation [88]. The ACRIN study found that CT colonography was able to identify lesions measuring 10 mm or greater in 90% of patients, with significantly lower sensitivity for smaller lesions [89]. Since the ACRIN study, a number of other studies have also supported the utility of CT colonography, which is now an accepted (and reimbursed) diagnostic test as a primary screening modality for patients at low and moderate risk of colorectal cancer, in patients at risk for complication during colonoscopy, patients who underwent prior incomplete optical colonoscopy, and as a follow-up to either prior CT colonography or prior optical colonography with polyp removal [88].

Nonneoplastic diseases

**Diverticulitis**

MDCT is the primary, and in most instances the only necessary, diagnostic test to diagnose diverticulitis [90,91] (Figure 147.11). Not only is MDCT useful for diagnosing diverticulitis, it is also helpful for identifying major complications, including the presence of a fluid collection, abscess, or large perforation (with free fluid and extensive ectopic gas) [92]. The diagnosis of diverticulitis is contingent on identifying thickened, inflamed colon in a segment with multiple diverticula and, in particular, focally inflamed divertica. MDCT is also excellent in diagnosing diverticulitis as a cause of fistulae arising from the colon, particularly fistulae involving the urinary bladder or the vagina [93]. In some cases a direct track between the involved segment of the colon and the bladder/vagina may be identified, although secondary signs can also be helpful, including ectopic gas within or adjacent to the bladder or vagina, or the loss of a fat plane between the involved structures.
The most important limitation of MDCT is the inability to assess the underlying colonic mucosa and, accordingly, a perforated neoplasm can be mistaken for diverticulitis in as many as 10% of patients [94]. As a result, it is often beneficial for the patient to undergo colonoscopy following the resolution of active symptoms and inflammation, particularly in those cases where the inflamed colon appears especially mass like or focally thickened [95]. Routine colonoscopy follow-up is probably not necessary in every case of suspected diverticulitis, although it is likely advisable in cases with significant wall thickening over 15 mm, the presence of a peridiverticular abscess, or the presence of suspicious extracolonic findings (such as suspicious liver lesions) [96]. While the distinction between a malignancy and diverticulitis may not always be simple on MDCT, colon cancers are more likely to result in locoregional lymphadenopathy, while diverticulitis is more likely to result in adjacent free fluid and thickening of the adjacent sigmoid mesocolon [97,98].

Appendicitis
CT is unequivocally the primary imaging modality in patients suspected of acute appendicitis, and patients now rarely undergo appendectomy without first being scanned [99]. Multiple outcome-based studies have documented a significant impact upon negative appendectomy rates in patients who have undergone CT imaging prior to surgery and, accordingly, there is little argument that patients should not, except in the most emergent circumstances, undergo surgery for suspected appendicitis without preoperative imaging [100–104]. MDCT theoretically has a comparable accuracy to ultrasound, and some have argued that the addition of ultrasound (prior to MDCT) might result in significant cost savings over simply beginning with a CT scan in all patients. Nevertheless, the negative predictive value of MDCT is significantly higher than ultrasound (as the appendix may not be adequately visualized on ultrasound for any number of technical or patient factors), and that ultrasound is highly user dependent and limited in its efficacy in larger patients [105]. As a result, local expertise, body habitus (thinner patients for ultrasound and larger patients for CT), and patient age (children should usually be first scanned with ultrasound before attempting CT because of radiation dose concerns and their thinner body habitus) should dictate the use of either CT or ultrasound.

The diagnosis of appendicitis is dependent on visualizing an abnormal, inflamed appendix (Figure 147.12). The collapsed normal appendix usually measures ≤6 mm in cross section; when distended, the appendix can measure up to 10 mm in diameter in normal patients [106]. A dilated appendix, as an isolated finding, can be suspicious, but is not diagnostic of acute appendicitis given that there is some degree of variation in the normal diameter of the appendix. More important defining criteria include a dilated, thick-walled appendix, which often demonstrates prominent mucosal enhancement on contrast-enhanced images [107,108]. Periappendiceal inflammation and fat-stranding are also important associated imaging findings, although there are rare cases in which periappendiceal inflammatory changes are not perceptible or are minimal on MDCT [109], even when the appendix is found to be gangrenous at surgery. Other important ancillary findings are the presence of a calcified appendicolith and the distension of the appendix with fluid. Although it is possible to recognize the findings of acute appendicitis on noncontrast studies [110], utilization of intravenous contrast [111] is critical in patients referred for evaluation of right lower quadrant pain. However, the added value of enteric contrast is more debatable, as several studies have suggested that enteric contrast does not make a significant difference in the accuracy of diagnosis, even in patients who are relatively thin and its use may cause delay in waiting for contrast to transit to the cecum [112–115].

Colitis
While MDCT is usually not necessary in patients in whom infectious colitis is strongly suspected, MDCT not uncommonly makes the diagnosis in these patients when they present with nonspecific symptoms or generalized abdominal pain [116]. The diagnosis of colitis on MDCT is contingent upon the presence of mural wall thickening, submucosal edema, mucosal hyperenhancement, and pericolonic fat stranding and inflammatory change. The degree of wall thickening, the extent of colonic mucosal enhancement, the distribution of bowel involvement, and associated mesenteric and small bowel disease are all important features to consider when seeking to differentiate infectious colitis from inflammatory bowel disease or ischemic colitis.

For example, patients with Clostridium difficile colitis (the most common infectious colitis to be identified on MDCT)
most often present with thickening of the entire colon (i.e., “pancolitis”), a distribution not common with other forms of ischemic or inflammatory colitis (Figure 147.13). Alternatively, ulcerative colitis typically begins at the level of the rectum and extends proximally, while Crohn’s colitis will often be associated with small bowel involvement (particularly the terminal ileum). Finally, ischemic colitis often involves a watershed distribution, with preferential involvement of the hepatic and splenic flexures, locations with a more tenuous blood supply.

**Solid organs of the gastrointestinal tract**

**Liver**

**Techniques**

Hepatic parenchymal enhancement following the injection of intravenous contrast is characterized by three distinct phases: an arterial phase (typically between 25 and 40 s), a portal venous phase (between 60 and 70 s), and a delayed phase (usually 2–4 min). The arterial phase is most useful in detecting primary hypervascular liver lesions (i.e., focal nodular hyperplasia [FNH], adenoma, hemangioma, etc.), hypervascular liver metastases, and hepatocellular carcinoma (HCC), and should be included in the MDCT protocol anytime a hepatic mass is suspected. The hepatic artery preferentially supplies all primary hepatic lesions, and it is during this phase that hypervascular lesions most avidly enhance and are most conspicuous, particularly because the background liver parenchyma has not yet reached peak enhancement and is still relatively hypodense. Given the speed of the most recent generation of MDCT scanners, images can be preferentially acquired during the early arterial phase (25–30 s) or the late arterial phase (30–40 s). The early arterial phase has its greatest utility as an angiographic phase for arterial vascular imaging, and can produce exquisite images of the central mesenteric vasculature and beautiful vascular maps, which can be quite useful to the surgeon or interventional radiologist prior to a surgery or procedure. The late arterial phase has been shown be superior to the early arterial phase for identification of hypervascular hepatocellular carcinomas [3,117–120].

Peak hepatic parenchymal enhancement is achieved in the portal venous phase, which is a necessary component of any evaluation of the liver [2]. Peak enhancement is maintained for approximately 30 s and then slowly decays over time. For most hypovascular liver tumors, including hypovascular metastases, the portal venous phase is the most important phase for lesion identification because this is the time when there is a maximal difference in attenuation between the normal-enhancing liver parenchyma and the poorly-enhancing hypovascular tumor. Delayed scanning during the equilibrium phase usually results in lesions being less conspicuous and is therefore unnecessary when imaging for hypovascular metastases. However, an equilibrium or delayed-phase acquisition is used at some institutions in conjunction with an arterial-phase acquisition for HCC imaging, as not only will HCCs “wash-out” in the delayed phase (i.e., become hypoattenuating to the liver parenchyma), but a small percentage of HCCs are not hypervascular on the arterial phase, and only visible on the delayed phase as areas of isolated wash-out. While unenhanced scans were once included in many liver protocols to differentiate intrinsically hyperdense regenerative and dysplastic nodules with internal copper and manganese content from truly enhancing lesions (such as HCC), the inclusion of noncontrast images is probably not necessary in the vast majority of cases.

With the latest generation of dual-source MDCT scanners, images of the entire abdomen (including the liver) can be acquired in less than 1 s, eliminating all respiratory and motion artifact. Even with older-generation scanners, the liver can be scanned in under 15 s using 16-slice MDCT or less than 5 s using 64-slice MDCT. This rapidity of scanning allows studies to be acquired consistently at peak arterial enhancement, improving vascular maps, as well increasing sensitivity for HCC. Following the arterial phase acquisition, the liver can be immediately rescanned to capture peak parenchymal enhancement during the portal vein phase [121]. In patients with cirrhosis or a suspected hepatic mass, dual-phase protocols (i.e., arterial and portal venous scans) are usually chosen (with a delayed phase included depending on the institution’s preference), while imaging patients with a known underlying hypovascular tumor typically requires only the portal venous phase [122–124]. In order to achieve the best results, and maximize enhancement in the arterial-phase images, contrast must be power injected at a rapid rate exceeding 4 mL/s. High infusion rates have been shown to increase both visualization of small hepatic arterial branches and conspicuity of HCC [120,125,126].
Diffuse diseases

Fatty infiltration
Fatty infiltration of the liver can be either diffuse or focal in its distribution. While typically not difficult to diagnose when diffuse, focal or geographic areas of fatty infiltration (or fatty sparing) can be easily confused with other pathological processes, such as a discrete mass, infarct, or infection. Steatosis lowers the CT attenuation of the liver, which should normally be roughly 10 HU greater in attenuation than the spleen on a noncontrast study [127]. Fatty infiltration of the liver is most reliably appreciated on noncontrast studies (where the liver attenuation is less than 10 HU greater than the spleen), but can be more difficult to diagnose accurately once i.v. contrast has been administered. Accordingly, measurement of the liver on unenhanced CT scans has been shown to be best for prediction of pathological fat content [128]. In most cases, the diagnosis of steatosis should not be made on arterial phase studies, as the attenuation of the spleen and liver are too heterogeneous and variable to allow accurate comparison. If the diagnosis must be made on contrast-enhanced images, portal venous-phase images should be preferentially utilized, and the liver should measure at least 25 HU lower than the spleen.

Focal fat deposition can be confused with a space-occupying lesion or other focal hepatic pathology. However, unlike a true pathological process, focal fat or focal fatty sparing should not displace or distort adjacent vessels and should not have any appreciable mass effect. Moreover, focal fat regularly tends to occur in certain classic locations, including adjacent to the falciform ligament, the undersurface of the medial left hepatic lobe, abutting the gallbladder fossa, and along the course of vessels and fissures [129]. When this distinction cannot be reliably made, the presence of focal fat can be proven by utilizing “chemical shift” MRI [130,131].

Cirrhosis
Cirrhosis is, fundamentally, a pathological diagnosis and, therefore, it is common, particularly in the earliest cases of cirrhosis, for a patient to be given the diagnosis of cirrhosis based on a biopsy result, even though the CT appearance of the liver may be relatively normal. However, characteristic CT features are usually identifiable in patients with advanced cirrhosis. The most specific sign of cirrhosis is capsular nodularity, with the outer surface of the liver appearing nodular and irregular, usually first apparent along the undersurface of the liver. Over time, the right lobe and medial segment of the left lobe often become atrophic, while the lateral segment of the left lobe and caudate lobe are characteristically enlarged [132–134] (Figure 147.14). Additionally, as a result of this nodularity and distortion of the underlying hepatic architecture, there is often widening of the intrahepatic fissures, porta hepatis, and gallbladder fossa as the liver retracts and shrinks. Associated changes of portal hypertension can often support the diagnosis of cirrhosis, including varices and portosystemic venous collaterals, the first of which is usually a recanalized paraumbilical vein, followed by perigastric, perisplenic, and paraesophageal varices. Enhancement of the cirrhotic liver is similar to normal liver during the arterial phase, but may be slightly less dense and more heterogeneous during the portal phase, likely on the basis of hepatic fibrosis and steatosis [135]. As mentioned earlier, a normal-appearing liver on CT should not be used to exclude the diagnosis of cirrhosis, as underlying hepatic fibrosis may still be severe on liver biopsy.

Other systemic diseases
Iron deposition and hemochromatosis, whether primary or secondary, will typically increase the attenuation of the liver and spleen on CT scans, a finding which can also be seen as the sequelae of chronic usage of certain medications (particularly amiodarone), certain glycogen storage diseases, and following gold therapy for rheumatoid arthritis [136]. While MRI is a more sensitive and specific modality for these diagnoses, the presence of a hyperdense liver (in comparison to the spleen and paraspinal musculature) should strongly suggest the presence of one of these underlying problems. Interestingly, despite high serum copper levels, the liver does not usually appear particularly hyperdense on MDCT in patients with Wilson disease [137].

Masses
Cysts
Cysts appear as homogeneous, low-attenuation (0–10 HU) masses with a smooth, sharp margin and without a perceptible wall. Cysts measuring under 1 cm in size can be problematic, particularly in patients with cancer, because of artifactually higher attenuation measurements from volume averaging, and accordingly such small hypodensities are often referred to as “too small to characterize” because of the radiologist’s inability to characterize such small lesions as benign cysts with a high degree of certainty. Comparison with prior studies may be
helpful in such cases [138], and MRI can be more specific for confirming that a small lesion is a cyst as opposed to a solid mass [139]. Many studies have found that such too small to characterize hypodensities are extremely common, and are overwhelmingly benign, even in the presence of a known underlying malignancy [140]. In most cases, even in a patient with an underlying malignancy, such small lesions can be safely followed over time to establish stability.

**Benign neoplasms**

Hepatic hemangioma is the most common tumor of the liver. Taking advantage of the improved contrast and temporal sensitivity of MDCT, hemangioma may be accurately and definitively diagnosed in over 90% of cases by MDCT, without the need for a confirmatory MRI [141]. On noncontrast studies, hemangiomas are typically hypoattenuating relative to normal liver, with a density similar to that of unenhanced blood vessels. After i.v. contrast administration, hemangiomas usually demonstrate peripheral globular enhancement and a centripetal fill-in pattern over sequential arterial, venous, and delayed-phase imaging (Figure 147.15). The enhancing areas have attenuation values identical to that of the aorta. Globular enhancement, isodense with the aorta, is 67% sensitive and 100% specific in differentiating cavernous hemangiomas and hepatic metastases. When this classic enhancement pattern is demonstrated, no further workup or confirmatory imaging is needed. However, hemangiomas can have atypical CT appearances, which can cause confusion, particularly in patients with a known underlying malignancy [142,143]. For example, small hemangiomas can be hypoattenuating, especially on early-phase scans, and may demonstrate no identifiable enhancement. Alternatively, due to arterioportal shunting, hemangiomas can show rapid enhancement, so-called “flash-filling” hemangiomas, which can mimic a hepatocellular carcinoma or hypervascular metastasis [142]. In the most confusing cases, where the distinction will impact patient management, the diagnosis of a hemangioma can be confirmed on MRI.

Hepatic adenomas and focal nodular hyperplasia (FNH) are vascular lesions that can present with a variety of CT appearances that are often indistinguishable, unless there is hemorrhage (indicating an adenoma). Both lesions are usually hypervascular in the hepatic arterial phase of enhancement, rapidly becoming isodense or slightly hypodense as peak portal enhancement is achieved. However, most adenomas are relatively heterogeneous (especially when larger than 3 cm in size), while FNHs are almost always homogeneously hypervascular and virtually invisible on the venous-phase images. The identification of a central, stellate, low-density “scar” is helpful in the diagnosis of FNH, but is seen only in a minority of patients and can rarely be present in an adenoma as well [144] (Figure 147.16). The introduction of MDCT has resulted in better visualization of the angioarchitecture of these lesions, which is useful for diagnosis, as FNH will typically demonstrate a unique paucity on internal neovascularity, while adenomas will often demonstrate a profusion of neovascularity internally [145]. CT angiography evaluation of FNH can reveal the presence of large feeding arteries and draining veins and help to better visualize the pseudocapsule and central scar [145]. While hepatic adenomas can be quite variable in their appearance (making the distinction from a HCC or metastasis difficult in the absence of an appropriate history of oral contraceptive or steroid use), FNHs almost always have a consistent appearance: homogeneously hypervascular on the arterial-phase images, invisible or isodense to the hepatic parenchyma on the venous and delayed

![Figure 147.15](image1.jpg) **Figure 147.15** Intravenous contrast-enhanced axial multidetector computed tomography demonstrates a 2.5-cm mass (arrows) in the right lobe of the liver with peripheral nodular enhancement, characteristic of a hemangioma.

![Figure 147.16](image2.jpg) **Figure 147.16** Axial intravenous contrast-enhanced multidetector computed tomography during portal venous phase of enhancement demonstrates a large mass in the right lobe of the liver (arrows), with a central scar (arrowhead). This is a typical computed tomography appearance of focal nodular hyperplasia.
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Malignant neoplasms

Hepatocellular carcinoma can present with a range of appearances, including as a discrete solitary dominant mass, multiple discrete lesions measuring over 1 cm (multifocal HCC), or as a diffuse, infiltrating process where discrete, measurable lesions cannot be identified (diffuse infiltrative HCC).

If noncontrast images are included in the MDCT protocol, HCC typically appears either hypodense or isodense to the normal liver, although smaller lesions can be nearly impossible to visualize without intravenous contrast. Following the administration of contrast, HCC is characterized by its tendency for hypervascularity and avid enhancement on the arterial-phase images [148,149] (Figure 147.17). However, while most HCCs are hypervascular, this can vary depending on a lesion’s histology, with most (93%) moderately or poorly differentiated lesions demonstrating hypervascularity during the arterial phase, as opposed to 44% of well-differentiated HCCs [149]. As a result, diagnosis of well-differentiated HCCs is more dependent on a careful appraisal of the venous or delayed images. In general, smaller lesions tend to be relatively homogenously hypervascular, while larger lesions tend to more heterogeneous, with a propensity for intratumoral necrosis, hemorrhage, and fat.

During the portal venous and delayed phases, regardless of histology, HCCs tend to become hypodense to the normal hepatic parenchyma (i.e., wash-out), a key diagnostic feature of HCC [150]. Additional possible imaging features of HCC include the presence of a fibrous capsule (which can often show delayed enhancement), fibrous septa, and an internal mosaic appearance [151]. The mosaic pattern is the result of the variable tissue composition of HCC, with enhancing nodular foci within the mass thought to indicate viable tumor cells, while lower-attenuation areas represent necrosis, fibrosis, or hemorrhage [152].

In general, when imaging a patient for suspected HCC, the inclusion of arterial-phase imaging should now be considered the standard of care. Miller et al. [153] reported detecting HCC in only 68% of cirrhotic patients with tumor, with the incorporation of arterial-phase imaging improving the detection of HCC tumor nodules over portal venous-phase imaging alone [154]. Correlation with subsequent transplant specimens has shown that arterial-phase imaging for detecting HCC in cirrhotic patients is a significant improvement over conventional portal venous contrast imaging. However, even with the inclusion of arterial-phase imaging and multiphase protocols, sensitivity for small lesions remains low (47%–57% for those ≤1 cm) [155]. The addition of a delayed phase (after portal venous) has been shown to significantly increase sensitivity for lesions ≤2 cm in cirrhotic patients, particularly for well-differentiated lesions [149]. Nonetheless, despite the combination of arterial, portal, and delayed acquisitions, MDCT scanning prospective and retrospective sensitivity for detection of HCC lesions in patients with cirrhosis has been reported to be 64% and 73%, respectively, and false positives resulted in disease overestimation [155].

When evaluating patients with HCC, assessment of the portal venous system is particularly critical, as the presence of portal vein thrombus, whether bland or malignant, can have a dramatic impact on a patient’s ultimate treatment. Bland thrombus will typically appear low in attenuation, with no appreciable enhancement on either the arterial or venous-phase images. It is critical to differentiate bland from tumor thrombus, as tumor thrombus generally precludes patients from any surgical treatment, including transplantation or surgical resection. Depending on the extent of the thrombus, a patient with bland thrombus may still be a transplant candidate. Tumor thrombus will generally expand and fill the vein,
will demonstrate some degree of internal enhancement on the arterial and venous-phase images, and may be hypervascular with tiny tumor vessels feeding the tumor thrombus on the arterial-phase images (i.e., “thread and streak” sign).

Liver metastases can demonstrate a variety of different CT appearances depending on the histology of the primary tumor. The majority of malignancies are hypovascular in nature and, accordingly, will appear hypodense compared to the adjacent enhanced liver parenchyma, although it is common for hypovascular liver lesions to show a rim of hyperenhancement or a surrounding perfusion abnormality on the arterial-phase images. The most common liver metastases with this appearance include breast, colon, lung, pancreas, and other gastrointestinal malignancies, all of which are considered hypovascular malignancies. In general, when imaging patients with one of these hypovascular malignancies, a single portal venous phase protocol is sufficient, and a dual-phase study is not necessary. Hypervascular metastatic lesions, including renal cell carcinoma, islet cell tumors, and thyroid carcinoma, tend to be avidly enhancing on the arterial-phase images and can be quite difficult to visualize on the portal venous phase [124,156]. Accordingly, when imaging a patient with one of these hypervascular malignancies, the inclusion of arterial-phase images is critical.

Abscesses
The diagnosis of a pyogenic hepatic abscess can, in the majority of cases, be made with a high degree of confidence based on a combination of the MDCT appearance of a lesion and clinical history [157]. MDCT is the screening procedure of choice in patients with a suspected pyogenic liver abscess, with detection rates as high as 97%. The MDCT imaging features of a pyogenic abscess tend to be relatively consistent, with lesions usually appearing as a hypodense, multiloculated cystic masses with thick, enhancing walls, as well as extensive edema and hypodensity in the surrounding liver parenchyma. Liver abscesses are very often multiple, although the multiple abscesses are often localized to one quadrant of the liver, with a clustered distribution. Gas within these collections is seen in approximately 20% of cases, and the presence of ectopic gas within a cystic liver lesion, in the absence of prior intervention, should be strongly suggestive of a liver abscess or an infected collection. Hepatic abscesses usually are of higher density than a simple cyst, but overlap in densities can make it difficult to differentiate a simple cyst from an abscess if these other supporting imaging features are not taken into account [158]. In some instances, the distinction between a liver metastasis and an abscess may be difficult, and in such situations (particularly in patients with a known underlying malignancy), the patient’s clinical history should play a primary role in distinguishing the two lesion types. In some cases, aspiration may be necessary to differentiate the entities.

Fungal abscesses usually present on MDCT as multiple, small, low-density, nonenhancing lesions spread throughout the liver, and similar lesions may also be seen in the spleen as well. Although MDCT is sensitive for detecting these lesions, active disease can elude CT visualization, as discrete lesions may not always be apparent [159]. The most common causative organism is Candida albicans, although biopsy is the only way to establish a specific etiological diagnosis. When confronted with many small lesions in the liver or spleen, patient history is once again critical, as these patients are very often immunocompromised and critically ill.

Amebic abscesses appear radiographically similar to pyogenic lesions, usually as low-density, multiloculated, thick-walled cystic lesions with surrounding parenchymal edema. Amebic abscesses are usually solitary, but 20% of patients demonstrate multiple lesions [160]. Echinococcal cysts (i.e., hydatid cysts) also appear as low-density cysts, often with internal septations and multiple daughter or inclusion cysts, creating the appearance of a “cyst within a cyst.” In the more chronic setting, as these lesions heal, serpiginous calcification may be seen in the cyst wall or associated with its septations.

Vascular diseases
A variety of hepatic disorders are related to obstruction of arterial or venous flow, and whereas older generation scanner had neither the spatial or temporal resolution to adequately evaluate the hepatic vasculature (either intrahepatic or extrahepatic branches), the newest generations of MDCT scanners, particularly in conjunction with 3D imaging, allow a comprehensive evaluation of the hepatic vasculature.

Portal vein
Portal vein thrombosis can be detected on MDCT by visualizing clot within the portal vein, sometimes accompanied by peripheral enhancement from opacification and thickening of the vas ovasorium (Figure 147.14). When such thrombus is occlusive, or nearly occlusive, extensive collateral formation in the porta hepatis is termed cavernous transformation and is readily visible on MDCT. While cavernous transformation has traditionally been thought to represent the sequelae of chronic thrombosis, these collaterals can develop in a relatively short period of time. Portal vein thrombus, particularly when involving intrahepatic branches, can result in prominent perfusion abnormalities in the involved segments of the liver, including hypoperfusion, presumably from diminished blood flow through the portal system, or alternatively, hyperperfusion, likely secondary to compensatory hyperemia from the segmental hepatic artery branches. In some cases, portal vein thrombus can result in slow flow peripherally in the liver, resulting in paradoxical hyperenhancement in the liver periphery. These varied perfusion changes can be seen not only when caused by a primary vascular abnormality with intrinsic thrombosis, but also with secondary tumoral obstruction of the portal venous system, such as with HCC. As already noted it is important to distinguish bland thrombus, which should be nonenhancing and low in density, from malignant tumor thrombus, which is often expansile, enhancing, and directly contiguous with a primary neoplasm (such as
hepatocellular carcinoma, cholangiocarcinoma, or a neuroendocrine tumor).

Zonal perfusion abnormalities may be also be seen in radiation hepatitis and, in the acute setting, the radiated segments of the liver will often demonstrate bizarre patterns of hyperenhancement, particularly on the arterial-phase images, sometimes with heterogeneous lower density on the venous-phase images as a result of edema. In the chronic phase, the irradiated liver will often demonstrate geographic areas of steatosis and volume loss/atrophy [161].

Hepatic veins
The most important abnormality of the hepatic venous system encountered in practice is Budd–Chiari syndrome, and MDCT remains the single best radiological modality for diagnosis. While primary Budd–Chiari is most common in the developing world (as a result of webs or congenital stenoses in the inferior vena cava [IVC] or hepatic veins), the vast majority of cases in the developed world are secondary, usually in patients with hypercoagulability, underlying malignancies, or other predisposing conditions. Budd–Chiari can result from thrombosis or narrowing at any level of hepatic venous outflow, including the hepatic veins, IVC, or even the hepatic venules.

While Doppler ultrasound does offer some benefits for this diagnosis, including its lack of ionizing radiation, consistent ability to visualize the hepatic veins and intrahepatic IVC, and its ability to obtain spectral Doppler waveforms from the hepatic veins, it is quite limited in its ability to visualize the extrhepatic IVC. MDCT can consistently visualize the entirety of the hepatic venous system and the intrahepatic/extrhepatic IVC, particularly when multiphase protocols with arterial, venous, and delayed images are included, as well as diagnose a large number of extravascular abnormalities, which might explain the patient’s symptoms, including malignancy [162].

In the acute setting, Budd–Chiari can have quite striking findings, including hepatosplenomegaly and ascites as a result of acute hepatic dysfunction and failure. After the injection of i.v. contrast, the liver parenchyma demonstrates a characteristic mottled enhancement pattern, with a “flip-flop” pattern of enhancement on multiphase imaging. Initially, in the arterial-phase images, the greatest contrast enhancement is seen in the caudate lobe and the peribronchial regions of the left lobe, but a reversal of this pattern is seen on the venous and delayed images, findings that are thought to be secondary to the unique venous drainage of the caudate lobe [162,163]. In some cases, particularly when good venous and delayed images are acquired, thrombus can be directly visualized within the IVC or hepatic veins, whereas in some cases the hepatic veins are not well seen and their nonvisualization may be the clue to the diagnosis. Interestingly, a similar mottled enhancement pattern is present in patients with chronic passive congestion, regardless of etiology, likely reflecting the fact that both Budd–Chiari and passive congestion arise due to impairment of hepatic venous outflow [164].

Chronic Budd–Chiari does not demonstrate the same unique pattern of multiphase enhancement but, rather, the liver exhibits generally heterogeneous enhancement with gradual hypertrophy of the caudate lobe (as a result of its unique, and preserved, venous drainage), while the entire periphery of the liver gradually atrophies over time [165]. It is common for patients with chronic Budd–Chiari to demonstrate large hypervascular regenerative nodules, thought to be secondary to the chronic distortion of the hepatic vasculature, and these hypervascular lesions can mimic HCC or hypervascular metastases if the patient’s history is not recognized [162,163,165,166].

Hepatic arteries
MDCT and CT angiography can be very useful in the evaluation of the hepatic vasculature, as MDCT can visualize both the intrahepatic and common hepatic arteries with a high degree of detail. Not only can MDCT provide detailed vascular maps displaying hepatic arterial anatomy and anatomic variants in both liver donors and recipients, 3D rendering software allows the presentation of this information in a form that is most useful for the surgeon. While ultrasound has traditionally been the primary modality utilized for the identification of hepatic arterial complications after a transplant, MDCT now has sufficient resolution to visualize these complications, include stenosis, occlusion, or pseudoaneurysms of the hepatic artery [167].

Pancreas
Technique
Proper MDCT technique is critical when performing a pancreatic protocol MDCT. Studies should be performed with dual-phase technique (i.e., arterial and venous phases) in order to maximize lesion conspicuity (including both hypovascular lesions such as pancreatic adenocarcinomas and hypervascular lesions such as pancreatic neuroendocrine tumors), identify distant metastatic disease, and evaluate involvement of both the arterial and venous central mesenteric vasculature [168].

Arterial-phase imaging (typically acquired between 25–30 s after i.v. contrast injection) is an essential part of a quality pancreatic protocol CT, providing the best chance of identifying vascular tumors (such as pancreatic neuroendocrine tumors and metastatic renal cell carcinoma), allowing detection of tumoral involvement of the central mesenteric arteries, as well as providing detailed vascular maps, which may be helpful to surgeons in the operating room. Portal venous-phase images (typically acquired between 60–70 s after i.v. contrast injection) are superior for the detection of hypovascular tumors such as pancreatic adenocarcinoma, detection of metastatic disease to the liver, as well as tumoral involvement of the central mesenteric venous vasculature. The pancreatic phase, typically acquired at roughly 40 s after i.v. contrast injection, is theoretically the best phase for identifying pancreatic adenocarcinoma, but is not routinely acquired in most centers given that the portal venous phase is nearly equivalent for identifying pancreatic adenocarcinoma [18,169–172].
Anatomic variants

_**Pancreas divisum**_ is the most common congenital anomaly of the pancreas. Although this anomaly most often goes unrecognized on CT scans, the pancreatic head can appear enlarged and simulate a mass lesion. Occasionally, the dorsal duct can be visualized on MDCT emptying into the accessory duct, confirming the diagnosis. MDCT is a more effective means of making this diagnosis than is commonly thought. In a study of 77 patients comparing four-slice MDCT and endoscopic retrograde cholangiopancreatography (ERCP), pancreatic ductal anatomy was visualized adequately in 95% of patients. ERCP detected pancreatic divisum in 10 patients, nine of which were also identified on MDCT, and there were a total of three false-positive diagnoses on MDCT [173]. The most recent generation of MDCT scanners, with improved spatial and temporal resolutions, almost certainly allow more reliable visualization of aberrant pancreatic ductal anatomy, and likely allow better performance than that reported on older studies. However, magnetic resonance cholangiopancreatography (MRCP) may still be a more sensitive noninvasive method for diagnosis [174].

_Agenesis of the dorsal pancreatic duct_ is identified on MDCT by visualizing only the head of the pancreas without a body or tail portion. The condition is often confused with a mass in the head of the pancreas with distal pancreatic atrophy [175].

_Annular pancreas_ is an embryological anomaly formed by the ventral anlage of the pancreas as the duodenum rotates, mainly due to hypertrophy of the left ventral bud. Annular pancreas can be divided into three types: type I, divisional annular pancreas; type II, branch annular pancreas; and type III, main duct annular pancreas. Final diagnosis is based on the evidence of ERCP combined with CT. The CT diagnosis is suggested by visualizing a collar of pancreatic tissue surrounding the descending duodenum [176] (Figure 147.18).

Neoplasms

**Adenocarcinoma**

Pancreatic adenocarcinoma most typically appears as a hypovascular, ill-defined, poorly marginated focal mass arising from the pancreas, which is usually difficult to define on noncontrast images and hypodense to the pancreas after intravenous contrast administration [177] (Figure 147.19). Identification of these lesions can often be aided by the utilization of dual-phase technique (arterial and venous phases). Although these lesions are usually best visualized on the venous-phase images, there are rare instances when pancreatic cancers are more conspicuous on the arterial-phase images [18,171,178]. With improvements in CT resolution, faster contrast administration, and the widespread availability of 3D imaging, it is now possible to detect even smaller tumors, as studies using MDCT and 3D imaging have demonstrated sensitivities for pancreatic cancer in the 95% range [2,179].

However, small tumors, particularly those smaller than 2 cm, may still be difficult to detect. Bronstein et al. found that the sensitivity of triple-phase helical MDCT for the detection of pancreatic masses less than 2 cm was only 77% [170]. It is thought that 5%–10% of pancreatic tumors are essentially isodense to the pancreas on all phases of contrast, making their detection much more difficult [180]. In such cases, even if the mass itself is not well visualized on MDCT, the presence of secondary findings strongly suggests the presence of an underlying tumor. These include segmental pancreatic duct dilatation with abrupt cut-off, upstream pancreatic atrophy, biliary...
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subtle peritoneal spread [189,190]. These numbers are a marked improvement from the earliest generation of CT scanners, which yielded accuracy rates in the range of 44%–73%, and it is quite likely that these rates might be even better with the latest generation of scanner technology [191,192].

The key to evaluation of the peripancreatic vasculature is high-resolution, thin-collimation scans performed using dual-phase technique, with the acquisition of both arterial and venous phases [193,194]. The ability to visualize the celiac axis, SMA, SMV and portal vein in 3D with a combination of MPR, MIP and volume rendering is essential for detecting subtle degrees of tumoral vascular involvement.

In addition to assessing potential vascular encasement, CT can also identify adenopathy in patients with pancreatic cancer. Radiologists usually rely on nodal measurements to identify potentially malignant nodes, and perhaps arbitrarily, nodes are considered to be suspicious if they measure 10 mm or greater in the short axis. Unfortunately, this is not always accurate, as even tiny nodes can harbor malignancy and large nodes can simply be reactive.

In a study by Roche, 62 patients with pancreatic cancer underwent detailed nodal analysis [195]. When applying a greater than 10 mm size threshold to detected nodes, that study showed a sensitivity of only 14% in the identification of malignant nodes with a specificity of 85% [195]. This resulted in a positive predictive value of 17% and a negative predictive value of 82% [195]. Therefore, when determining resectability of ductal adenocarcinoma, CT is quite poor in the prediction of nodal involvement. Nevertheless, this is not clinically consequential, as the presence of suspicious peripancreatic lymph nodes in a patient thought otherwise to be resectable does not typically prevent attempted surgical resection, as locoregional nodes are inevitably sampled and resected at surgery. Only large, bulky locoregional nodes or, alternatively, distant lymphadenopathy, might alter the decision to operate [18].

obstruction, or even a unusual contour of the pancreas. Of these, ductal obstruction is the most important secondary sign, and the presence of a locally dilated pancreatic duct with abrupt cut-off, even in the absence of a discernible mass, must be assumed to represent a tumor until proven otherwise, and should prompt further evaluation with EUS or MRI [169,181,182].

In addition to detecting the primary pancreatic mass, MDCT now plays an essential role in preoperative staging, determining resectability, and identifying patients who are candidates for a curative resection. Unresectability is defined as the presence of arterial or venous encasement, hepatic (or other distant) metastases, or distant lymph node metastases [183] (Figure 147.20).

The utility of modern MDCT’s improved spatial resolution has been highlighted by recent trends in pancreatic cancer treatment, with a new category of “borderline” resectable disease that can still be treated surgically (following neoadjuvant chemoradiation) despite the presence of vascular involvement [184]. Accordingly, MDCT is now routinely used to assess subtle gradations of vascular involvement, as a patient with limited tumoral involvement of the celiac, superior mesenteric artery (SMA), or hepatic artery, or even short-segment occlusion of the portal–superior mesenteric vein (SMV) confluence (with technical options for reconstruction) might still potentially be a surgical candidate [18,169,172,184,185]. Unfortunately, at the time of initial diagnosis, 50% of patients have distant metastases to the liver or peritoneal surface, and more than 80% of the remaining patients have locally advanced tumors. Nevertheless, MDCT can identify the small group of patients who may benefit from an attempt at curative resection.

MDCT has been shown to have a high predictive value for unresectability (90%–100%) with a slightly lower predictive value for resectability (76%–90%) [179,186–188]. This is primarily due to MDCT’s inability to detect tiny liver metastases or subtle peritoneal spread [189,190]. These numbers are a marked improvement from the earliest generation of CT scanners, which yielded accuracy rates in the range of 44%–73%, and it is quite likely that these rates might be even better with the latest generation of scanner technology [191,192].

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Figure 147.20 (a) Intravenous contrast-enhanced coronal volume-rendered image demonstrates a 4-cm mass (arrow) in the head of the pancreas causing common bile duct obstruction. The gallbladder is also distended. Biopsy revealed pancreatic adenocarcinoma. (b) Coronal maximum intensity projection demonstrates encasement of the superior mesenteric vein (arrow) with resulting collaterals. The patient was deemed unresectable.
MDCT is the modality of choice in the detection of distant metastases, most commonly the liver and peritoneum. Liver metastases typically appear as low-density, infiltrative, poorly margined lesions on the portal venous-phase images. Unfortunately, while the sensitivity and specificity of MDCT for liver metastases over 1 cm in size are quite good, both sensitivity and specificity for smaller lesions are still problematic, even with modern MDCT scanners. The smallest metastases to the liver may not be apparent on MDCT, and even a detected, tiny liver metastasis may not be readily distinguishable from the small nonspecific low-density lesions in the liver thought to represent tiny cysts, hemangiomas, or bile duct hamartomas (so-called too small to characterize lesions). As previously noted, the presence of a few tiny lesions in the liver should not necessarily suggest the presence of metastases, and these tiny lesions can be safely followed over time, as the vast majority of these tiny hypodensities turn out to be benign. However, unfortunately, a few will eventually prove to be metastases and, conversely, small liver and peritoneal implants that are below the resolution of even the latest generation of MDCT scanners can still be seen at surgery [189].

**Neuroendocrine tumors**

Pancreatic neuroendocrine tumors produce and secrete hormones to a variable degree. Depending on their clinical presentation, these lesions can be classified as either **syndromic** or **nonsyndromic**. Syndromic neuroendocrine tumors have clinical evidence of pancreatic production and produce a recognizable endocrinopathy. These lesions include insulinomas, gastrinomas, glucagonomas, VIPomas, and somatostatinomas. Such neoplasms usually present at a relatively smaller size compared with nonsyndromic neoplasms, because of the symptoms produced by secretion of their associated hormone. Nonsyndromic neuroendocrine tumors represent roughly half of all lesions and present at a larger size than functioning tumors due to lack of a clinically apparent endocrinopathy, even though they still secrete hormones to a lesser degree [196].

MDCT plays an important role in the diagnosis and staging of both syndromic and nonsyndromic neuroendocrine tumors [197]. The vast majority of neuroendocrine tumors are avidly hypervascular and avidly enhancing, usually most conspicuous on the arterial-phase images (hyperenhancing relative to the pancreatic parenchyma), although a small percentage of lesions are more conspicuous on the venous-phase images. In general, syndromic neuroendocrine tumors are less than 3 cm in size at presentation and, accordingly, have a tendency to be more homogeneously hypervascular (Figure 147.21) [198]. As noted, nonsyndromic neuroendocrine tumors tend to be larger at presentation than syndromic tumors and are more likely to be cystic or necrotic [199–201]. Unlike pancreatic adenocarcinoma, most neuroendocrine tumors do not obstruct the pancreatic duct or result in upstream pancreatic atrophy, although a small number of these lesions may atypically obstruct the duct as a result of secretion of serotonin-based hormones [202].

Cystic neoplasm

Cystic lesions of the pancreas are being identified with increasing frequency, due in part to the dramatic improvements in CT image quality and spatial resolution over the past decade. As a result, the vast majority of these lesions are now discovered incidentally in patients being imaged for unrelated reasons [203]. While many of these cystic pancreatic neoplasms are either benign or nonaggressive lesions that do not require direct intervention, some are precursors of pancreatic malignancy and require either close follow-up or surgical resection. Challenges posed by pancreatic cystic neoplasms have prompted a large body of research and debate in both the radiology and surgical literature as to the appropriate management. However, it is clear that MDCT is important in primary diagnosis, follow-up, and risk stratification of these tumors [204–212].

The three most common, and important, cystic pancreatic neoplasms encountered in daily practice are **microcystic or serous cystadenomas**, **macrocystic or mucinous cystic neoplasms** (MCN), and **intraductal mucinous pancreatic neoplasms** (IPMN) [213–215]. Currently, the three most important diagnostic modalities used in the diagnosis and risk stratification of cystic pancreatic tumors are MRI, CT, and EUS, although MRI and EUS largely serve as diagnostic adjuncts once a lesion has already been identified and characterized using MDCT [204,215,216]. While there are certain instances where MDCT can offer a specific diagnosis based on lesion morphology, there are limits to the ability of both CT and MRI to accurately differentiate between the classes of cystic neoplasms, and moreover even within a lesion category, to predict the likelihood that a lesion will progress toward a frank malignancy [215,217,218].
Of the three primary types of pancreatic cystic neoplasms, IPMNs are by far the most commonly encountered in practice, and the vast majority of these cysts are identified incidentally. They can be subdivided into three major types, namely: (1) main-duct IPMNs, which involve the main pancreatic duct (usually manifesting as a dilated pancreatic duct with or without internal mural nodularity) and carry a high risk of malignancy (perhaps up to 60%); (2) side-branch IPMNs, which represent small cystic tumors arising within a pancreatic side-branch (usually manifesting as a cyst with a direct connection to the adjacent normal-sized pancreatic duct) and carry a lower risk of malignancy (less than 20%); and (3) mixed-type IPMNs, which have features of both side-branch and main-duct IPMNs and have a risk of malignancy comparable to main-duct IPMN. The diagnosis of a main-duct or mixed-type IPMN on MDCT is typically not difficult, as the main pancreatic duct is usually significantly dilated (usually segmentally or diffusely) without a discrete obstructing lesion, and these patients almost always undergo surgical resection. Side-branch IPMNs, on the other hand, can be more difficult from both a diagnostic and management perspective. If a direct communication between a pancreatic cyst and the adjacent pancreatic duct can be demonstrated on MDCT, then the diagnosis is usually straightforward (Figure 147.22). However, when this is not possible, the diagnosis may be dependent on EUS and cyst aspiration (which demonstrates frank mucin and elevated carcinoembryonic antigen [CEA] levels). Even if a cyst is confidently identified as a side-branch IPMN, the management is not necessarily always clear, as the rate of malignancy or significant dysplasia can vary widely, and not all IPMNs need to be surgically resected. While there is some debate in the literature, the current practice in most centers is based on the Sendai criteria, which suggest that an IPMN should be surgically resected if the cyst measures 3 cm or greater in maximum diameter, demonstrates any discrete mural nodularity on imaging, or if the main pancreatic duct is dilated over 1 cm. In practice, management is often based on a combination of findings from MDCT, MRI, and EUS/cyst aspiration. In daily practice, when confronted by an indeterminate pancreatic cystic lesion, it is statistically likely that one is dealing with a side-branch IPMN (see Chapter 86).

Microcystic serous cystadenomas classically present as a cystic mass with innumerable internal cysts interspersed within a dense fibrous honeycomb, often with a central enhancing scar and stellate calcification (approximately 30% of patients). These lesions are fundamentally hypervascular, and there is often internal and peripheral avidly enhancing soft tissue associated with these cystic neoplasms. When lesions exhibit a classic appearance, the diagnosis can be made with a high degree of confidence, although EUS with cyst aspiration may still be helpful as a confirmatory test, as serous cystadenomas typically demonstrate low CEA levels. When the diagnosis is clear, lesions can either be followed sequentially or surgically resected depending on the lesion’s size, patient symptoms, and sequential growth. Unfortunately, atypical imaging appearances are common, as up to 25% of serous cystadenomas appear as a unilocular cyst, while others can appear as homogenously enhancing hypervascular masses that mimic neuroendocrine tumors (i.e., serous adenomas) [215]. The diagnosis in these cases is either made based on EUS and cyst aspiration or, alternatively, only after surgical resection [207,211].

MCN most often presents as a macrocystic (≥2 cm) unilocular cyst, typically in the pancreatic tail. Peripheral soft tissue modularity, peripheral calcification (in <5% of lesions), solid components, and a thick wall are all imaging features that strongly suggest this diagnosis, particularly when found in the context of a cystic lesion in the pancreatic tail in a middle-aged female patient (the most common demographic group affected). EUS and cyst aspiration are almost always important in the evaluation for these lesions and, given that they are uniformly malignant or premalignant, all MCNs should be resected [181,219].

**Figure 147.22** (a) Axial intravenous contrast-enhanced multidetector computed tomography demonstrates a 1-cm cystic lesion (arrow) in the pancreatic neck. (b) Axial image also demonstrates pancreatic ductal dilatation (arrowheads). These finding are very suspicious for intraductal mucinous pancreatic neoplasm.
Pancreatitis

Acute pancreatitis

Acute pancreatitis can be broadly divided into two forms: (1) acute interstitial edematous pancreatitis and (2) acute necrotizing pancreatitis. Edematous pancreatitis is far more common, but less clinically severe, while necrotizing pancreatitis is far more severe, but much less common [220]. MDCT has now become virtually mandatory in patients suspected of acute pancreatitis, and is essential not only in making the diagnosis, but also in assessing disease severity, differentiating edematous and necrotizing forms of the disease, risk stratifying patients and predicting patient outcomes, diagnosing major complications (including fluid collections and vascular abnormalities), and in some patients identification of the cause of pancreatitis (e.g., gallstones, an underlying tumor, or autoimmune pancreatitis) [221–224].

MDCT has proven very effective in predicting which patients are likely to suffer poor clinical outcomes. The first CT-based grading system to assess severity was the Balthazar classification system, which graded patients with pancreatitis on a scale from A through E based on the CT appearance of the pancreas: normal-appearing pancreas (grade A), mild gland enlargement (grade B), severely enlarged gland with peripancreatic edema (grade C), or single (grade D) or multiple (grade E) fluid collections [225]. Pancreatic necrosis on CT, recognized by regional nonenhancement on contrast-enhanced CT scans, was included in the grading system as an additional important feature suggesting a worse prognosis; patients with greater than 30% parenchymal necrosis are presumed to have a particularly poor clinical outcome [226,227]. In the Balthazar system, the degree of parenchymal necrosis, combined with CT grading of the appearance of the gland and the presence or absence of fluid collections, has greater prognostic implication than either manifestation alone [228]. While the Balthazar system is still the most widely utilized CT grading system for pancreatitis, the most up-to-date grading system today is the Revised Atlanta classification system, which similarly assigns a severity grade based on a number of different CT imaging features, the presence of parenchymal necrosis, and complications. In general, regardless of which system is utilized, the greater the degree of pancreatic inflammation, necrosis, and complications (whether vascular or fluid collections) on a MDCT scan, the greater the risk of a poor patient outcome. However, it is possible for a patient to have pancreatitis based on biochemical markers (i.e., elevated lipase levels) but a normal CT scan (i.e., Balthazar A pancreatitis), the absence of a suggestive CT scan should not dissuade a clinician from making the diagnosis [229–232].

Detection of necrosis is one of the primary goals of performing an MDCT in suspected pancreatitis and, accordingly, it is essential that a CT scan performed for this purpose utilizes intravenous contrast as it is not possible to accurately gauge the presence or absence of necrosis on a noncontrast study. Pancreatic necrosis can be recognized as focal or diffuse areas of nonenhancement, liquefaction, or severe hypoenhancement in the pancreatic parenchyma. In general, patients with any significant degree of necrosis usually demonstrate severe inflammation and phlegmonous change in the retroperitoneum. Intravenous contrast is also critical for the identification of vascular complications, which are particularly common in severe pancreatitis. Pseudoaneurysm formation occurs in 2%–5% of patients, with the splenic artery and gastroduodenal artery particularly common sites of formation. Patients are also at risk for venous thrombosis, with the splenic vein the most common of the central mesenteric veins to be affected [233]. Intravenous contrast is essential for the accurate identification of peripancreatic fluid collections. In the acute setting, fluid collections surrounding the pancreas are usually termed either acute peripancreatic fluid collections (in cases of acute edematous pancreatitis) or postnecrotic fluid collections (in cases of necrotizing pancreatitis). As these collections mature over time and develop well-defined walls composed of granulation tissue, such collections are then termed either pseudocysts (in cases of acute edematous pancreatitis) or walled-off necrosis (in cases of necrotizing pancreatitis). The terminology is important, as different types of collections relative to the time course are often treated differently [234].

Chronic pancreatitis

MDCT reveals findings in over 90% of patients with documented chronic pancreatitis. In decreasing order of frequency, these findings include: beading and dilation of the main pancreatic duct, parenchymal atrophy, pancreatic calcifications, fluid collections, focal pancreatic enlargement, biliary ductal dilation, and alterations in the peripancreatic fat or fascia [235]. Focal mass-like chronic pancreatitis can be a significant diagnostic dilemma, as the development of a chronic fibrocalcific inflammatory mass can mimic the CT appearance of pancreatic adenocarcinoma and, consequently, can result in pancreati-coduodenectomy due to an inability to exclude neoplasm. In a series from the Mayo Clinic [236], 22 of 603 pancreati-coduodenectomies performed between 1956 and 1990 were secondary to chronic pancreatitis because of the presence of a mass and inability to exclude malignancy. When a patient with a pancreatic mass has a history of alcoholism and pancreatitis, as well as normal serum CA 19-9 levels, mass-forming pancreatitis should be considered in the differential diagnosis when confronted with a mass suspicious for pancreatic adenocarcinoma [237].

Biliary tract

MDCT is an excellent modality for the evaluation of both benign and malignant diseases of the biliary tree and, because of its use for general survey tool of the abdomen, varying forms of biliary disease are frequently encountered on abdominal CT examinations performed for unrelated reasons.

While MDCT was once considered inferior to ultrasound in its ability to identify normal intrahepatic and extrahepatic bile ducts, current MDCT scanners obviate those limitations. The biliary tree can be uniformly visualized in its entirety, in
contrast to ultrasound, which is often unable to identify normal-sized intrahepatic ducts and whose performance is heavily user dependent. Just as importantly, while ultrasound can visualize small portions of the extrahepatic duct, usually at the level of the porta hepatis, MDCT with 3D reconstruction and MPRs can delineate the entirety of the common hepatic duct and common bile duct in multiple planes, allowing the radiologist to appreciate not only a discrete obstructing mass, but also the morphology of the duct at any site of narrowing, including abrupt margins, abnormal hyperenhancement of the duct wall, and irregular thickening at the site of narrowing. The increased efficacy of MDCT in visualizing normal ducts makes it valuable for assessing normal-caliber ducts. Intrahepatic bile ducts are now visualized in nearly all patients, and should not be confused with ductal dilation [238]. In general, intrahepatic ductal dilation should be diagnosed if the intrahepatic ducts measure 3 mm or greater, or are larger than their portal venous branch counterpart. The extrahepatic bile ducts normally measure up to 6 mm, with an additional 1 mm added for each decade over the age of 60 [239]. The extrahepatic biliary tree normally dilates slightly in patients who have undergone cholecystectomy. When ducts appear borderline enlarged, and it is unclear whether they are truly dilated or at the upper limits of normal, it is best to recommend correlation with clinical and biochemical markers of biliary obstruction. When there is a high degree of suspicion for malignant obstruction of the ducts, MDCT is the clear examination of choice, as it allows the staging of extent of disease in a standard, reproducible fashion, with depiction of all regions surrounding the duct and distant sites as well.

**Congenital anomalies**

Congenital anomalies of the biliary tract are more typically diagnosed definitively with direct cholangiography or MRCP, although CT and ultrasound can suggest their presence. Congenital anomalies of the gallbladder are rare, consisting mostly of positional variants. Thus the gallbladder can be seen in the left abdomen or in suprahepatic, intrahepatic, and other unusual locations. CT can identify these anomalies if the gallbladder is not seen in its usual location at ultrasound, although none of these gallbladder variants has any clinical significance except when a gallbladder intervention is planned.

Congenital cystic diseases of the biliary tree, including choledochal cysts, choledochoceles [240], and Caroli disease, can often be diagnosed by demonstrating a dilated biliary tree with appropriate patterns of dilation. Choledochal cysts appear as focal dilations of the intrahepatic and/or extrahepatic bile ducts, which may be mild and simulate a dilated duct or may be as large as 15 cm in diameter [241].

**Gallbladder disease**

Ultrasound should be considered the modality of choice for evaluating the gallbladder in most patients. However, given that MDCT is the imaging modality of choice in patients with non-specific abdominal pain and that gallbladder abnormalities may be incidentally identified on MDCT examinations performed for unrelated reasons, a number of gallbladder abnormalities are first diagnosed by MDCT in these patients. In this context, thickening of the gallbladder wall, stones within the gallbladder or the extrahepatic duct, or calcifications within the gallbladder wall (e.g., porcelain gallbladder) may all be first identified by MDCT. However, MDCT only demonstrates gallstones in 74%–79% of patients with cholelithiasis, as stones that are isoattenuating with bile cannot be easily delineated, limiting MDCT’s utility as a primary diagnostic modality for many common gallbladder conditions [242,243].

**Neoplasms**

Gallbladder cancer carries a grim prognosis, with overall survival rates as low as 12%. The majority of these tumors are discovered only in their later stages, and unfortunately, patients with advanced-stage tumors tend to have a generally dismal prognosis. Long-term survivors of gallbladder cancer typically present with lower stage disease (usually T1 or T2 tumors). Not only do higher-stage tumors carry a poor prognosis, but tumors with a higher T-stage also necessitate more extensive radical resections (with their associated morbidity and mortality), compared to lower-stage tumors, which can, in some cases, be treated with a simple laparoscopic cholecystectomy [244–251].

While ultrasound is generally considered to be the best modality for assessment of the gallbladder, MDCT plays an important role in diagnosis given that many of these tumors, particularly in those cases where patients present with lower-stage malignancies, are found incidentally. Accuracy rates for MDCT have been reported to be as high as 92%, but diagnostic performance is largely dependent on the radiologist having a high index of suspicion. Subtle abnormalities of the gallbladder may be difficult to appreciate if only axial images are examined, as coronal and sagittal MPR images must be utilized to get a full view of gallbladder lesions [244–246,248–254].

Early-stage gallbladder cancer can present with subtle focal wall thickening, irregular circumferential wall thickening, or, rarely, with a small polypoid mass. While subtle wall thickening at the fundus may sometimes be attributed to adenomyomatosis, the loss of the normal fat plane between the gallbladder and the liver, a feature suggesting invasion of the liver parenchyma by a tumor, is an important clue to the presence of a malignancy. Gallbladder tumors in their later stages are usually more easily diagnosed, and will often present as a focal mass replacing the gallbladder and invading the liver parenchyma, and in such cases the gallbladder itself may no longer be clearly identifiable. MDCT can also play a role in identifying sites of spread, as gallbladder malignancies commonly metastasize to the liver, locoregional lymph nodes, and the peritoneum, with a unique predisposition towards invasion of adjacent organs including the liver and duodenum. Gallbladder cancer has a unique predisposition to present with bulky locoregional lymphadenopathy in the porta hepatis and retroperitoneum, and such findings...
should prompt a careful evaluation of the gallbladder to find the primary lesion [244–246,248–254].

Cholecystitis
The most common CT findings of cholecystitis are gallbladder wall thickening (>3 mm) and cholelithiasis [255]. However, these findings are neither specific nor sensitive, and can also be seen with gallbladder carcinoma, hyperplastic cholecystosis, and a number of benign causes (e.g., cirrhosis, congestive heart failure, renal failure, etc.). Other CT findings suggestive of the diagnosis include increased attenuation of the bile (>20 HU) and loss of clear definition of the gallbladder wall. Increased attenuation in the adjacent hepatic parenchyma, thought to represent reactive hyperemia as a result of the gallbladder inflammation, is a useful indicator of acute inflammation [256]. In more advanced disease, pericholecystic fat stranding can be a strong clue to the diagnosis. Air within the gallbladder wall or lumen in the absence of a history of prior enteric anastomosis or sphincterotomy is virtually pathognomonic of complicated cholecystitis [257]. A low-attenuation halo around the gallbladder may indicate edema or minimal pericholecystic fluid, and is a useful clue in differentiating cholecystitis from carcinoma on CT scans [258].

Bile duct diseases
Neoplasms
Cholangiocarcinoma, primary bile duct malignancy arising from the bile duct epithelium, typically can be divided into different forms depending on the appearance and location, including: (1) mass-forming intrahepatic cholangiocarcinoma, (2) periductal infiltrating cholangiocarcinoma, (3) intraductal cholangiocarcinoma, (4) hilar cholangiocarcinoma (so-called Klatskin tumor), and (5) extrahepatic cholangiocarcinoma [259]. Mass-forming cholangiocarcinomas arise within the liver itself as a solitary dominant mass, and are not typically difficult to identify, while periductal cholangiocarcinomas tend to be more difficult to identify, presenting as subtle wall thickening or soft tissue along the margins of the intrahepatic ducts. Intraductal cholangiocarcinoma is quite rare. It presents as a soft tissue mass arising from within the lumen of the duct and, consequently, can be quite difficult to appreciate if there is no significant proximal biliary dilatation. Hilar cholangiocarcinomas present near the porta hepatitis arising from the confluence of the ducts, producing obstruction of the main hepatic ducts and intrahepatic branches. Extrahepatic cholangiocarcinomas typically cause obstruction of the entire proximal biliary tree, and can manifest either as a discrete obstructing mass or, alternatively, as only subtle enhancement and thickening of the bile duct wall with surrounding stranding and induration.

Cholangiocarcinomas, regardless of their subtype, are hypovascular tumors and typically present as a hypodense lesion with minimal peripheral enhancement, including some hyperenhancement peripherally on arterial-phase images. They usually cause proximal biliary dilatation at the margins of the mass and capsular retraction as a result of scirrhus fibrotic nature of the tumors, and demonstrate increasing contrast enhancement on delayed images [260]. Retention of contrast within the tumor during delayed-phase imaging, thought to be secondary to the fibrotic scirrhus nature of the tumors, is a characteristic contrast CT feature of any subtype of cholangiocarcinoma. This feature is critical in arriving at a specific diagnosis based on imaging, and can be helpful in differentiating cholangiocarcinoma from HCC in cirrhotic patients [261,262]. Accordingly, if cholangiocarcinoma is suspected, a delayed phase should be included in the MDCT protocol. Particularly with the periductal infiltrating, intraductal, hilar, and extrahepatic forms of cholangiocarcinoma, where a discrete mass may be more difficult to appreciate, secondary signs may be very helpful in arriving at the diagnosis, including segmental or lobar biliary dilatation and hepatic parenchymal atrophy. Lobar or segmental biliary dilatation and parenchymal atrophy should always be considered to be secondary to an obstructing tumor until proven otherwise.

Inflammatory diseases
Acute infectious cholangitis is usually found in patients with underlying biliary tract obstruction and, accordingly, patients typically demonstrate dilated intrahepatic and extrahepatic bile ducts. Infrequently, suppurrative material and debris within the bile ducts may be seen on CT, although a more common imaging feature is thickening and enhancement of the bile ducts [239]. Rarely, gas may be identified within the biliary tree in cases of infection with gas-forming organisms. Acute suppurative cholangitis can result in frank liver abscesses and fluid collections.

The characteristic imaging features of primary and secondary sclerosing cholangitis, although more easily appreciated by either conventional cholangiography or MRCP, can also be demonstrated on MDCT [263]. Intrahepatic ductal stenoses, dilated peripheral ducts with no apparent connection to the central ducts, and irregular intrahepatic ductal dilatation with a beaded appearance are all characteristic CT findings. If there is active inflammation, thickening and hyperenhancement of the bile duct walls may be appreciated. Primary sclerosing cholangitis should be considered as a premalignant condition, with more than 15% of patients at risk of developing a cholangiocarcinoma [264]. As such, careful search for masses, delayed contrast enhancement, progressive biliary dilatation, and thickening of the bile duct wall is required, as any of these features may indicate the development of a biliary malignancy [265]. Of note, cytomegalovirus and Cryptosporidium can cause inflammation of the biliary tract in patients with AIDS, which result in changes on CT, ultrasound, and cholangiography similar to those of sclerosing cholangitis, with bile duct wall thickening, multiple strictures, and duct wall contrast enhancement [266].

Other less common causes of infection can also be diagnosed on MDCT images, including recurrent pyogenic cholangitis (RPC) (“oriental cholangiohepatitis”). RPC occurs almost
Computed tomography of the gastrointestinal tract

CHAPTER 147

Contrast images add little diagnostic value while increasing radiation exposure to the patient [272,276]. Technical adjustments may increase the conspicuity of stones and the overall utility of MDCT in assessment of patients with stone disease [277,278].

Peritoneum

Many neoplastic and nonneoplastic gastrointestinal diseases can have associated peritoneal findings, which can be quite subtle. Recognition of peritoneal abnormalities requires a systematic evaluation of the peritoneal structures based on a detailed understanding of the typical spread of disease processes within the abdominal cavity. The majority of ligaments and mesenteries in the abdomen are formed from remnants of the ventral and dorsal mesenteries, which suspend the primitive gut. The pelvic ligaments are mainly formed by reflections of peritoneum over the pelvic organs or structures. The mesenteries and ligaments form the boundaries of the peritoneal spaces. Accurate localization of fluid collections and detection of neoplasms requires an accurate understanding of the normal pathways of spread through adjacent ligaments and mesenteries [279]. For the purposes of radiological diagnosis, the peritoneal cavity is often arbitrarily considered to be an “end organ,” in that the response to a pathological process is similar regardless of the underlying etiology.

Neoplasms

While primary neoplasms such as mesothelioma can rarely arise from the peritoneum, the majority of peritoneal tumors reflect involvement of the peritoneum by metastases (i.e., peritoneal carcinomatosis). Peritoneal carcinomatosis can be associated with a variety of thoracoabdominal malignancies, but the most common tumors to metastasize to the peritoneum include ovarian cancer (and other gynecological malignancies), melanoma, gastric cancer, colon cancer, appendiceal cancer, exclusively in patients from Asia with chronic Clonorchis infection, and is usually manifested by marked segmental intrahepatic and extrahepatic bile duct dilation, sharp tapering of peripheral extrahepatic bile ducts with loss of arborization, giant ductal calculi, and intraductal debris.

Choledocholithiasis

The noninvasive diagnosis of common bile duct stone disease has been simplified with the development of MRCP, which has a sensitivity and specificity similar to ERCP, without the risks of the latter [267]. Reported sensitivities of CT for common duct stone detection vary from 45% to 97%. The highest sensitivity (97%) was reported using submillimeter multidetector CT, suggesting that the performance of up-to-date MDCT technology is likely better than previously thought for this indication [268–270]. Use thin collimation with multiplanar reformations undoubtedly improves stone detection rates [271]. However, even with submillimeter MDCT (0.75 and 0.625 mm), small stones can be missed, particularly when the stones are isodense to the bile (rather than hyperdense or calcified) or when soft tissue density stones are impacted at the ampulla [268,269,272–275].

Focusing on the source axial images alone is not sufficient for the detection of common duct stones given that the common hepatic duct and common bile duct do not primary run in the axial plane; MPRs and 3D postprocessing are critical for diagnosis [268,272] (Figure 147.23). Using MPRs and multiphase acquisitions, Kim et al. reported 97% sensitivity and 96% specificity for choledocholithiasis in 34 patients with stones confirmed by ERCP or PTC (percutaneous transhepatic cholangiography) [268].

There is little evidence that incorporation of noncontrast images into biliary protocols improves visualization of stones [276]. One study has shown that combining i.v. contrast-enhanced axial sections with MPRs results in diagnostic accuracy comparable to the use of combined pre- and postcontrast CT (both techniques 89% sensitive), suggesting that the non-contrast images add little diagnostic value while increasing radiation exposure to the patient [272,276]. Technical adjustments may increase the conspicuity of stones and the overall utility of MDCT in assessment of patients with stone disease [277,278].

Figure 147.23 (a) Axial intravenous contrast-enhanced multidetector computed tomography in a patient with obstructive jaundice shows a subtle filling defect in the common duct (arrow). (b) Coronal multiplanar reconstruction better demonstrates the stone (arrow) in the distal common bile duct.
pancreatic cancer, and other gastrointestinal malignancies. Lymphoma can also involve the peritoneum with a MDCT appearance, termed lymphomatosis, akin to other forms of carcinomatosis [280,281].

Peritoneal carcinomatosis can manifest several discrete forms, including a micronodular pattern (with tiny nodules measuring <5 mm studding the peritoneum and omentum), a nodular pattern (with more discrete nodular implants in the omentum measuring >5 mm), and “omental caking” (diffuse soft tissue infiltration of the omentum and mesentery). The micronodular pattern is the most difficult to diagnose on imaging, and often will present as only subtle induration and infiltration of the omentum, while the nodular and omental caking patterns are usually easier to appreciate on imaging. In the majority of cases, ascites fluid will be present, and the presence of subtle peritoneal thickening and enhancement along the margins of the ascites fluid serves as a strong clue to the presence of early carcinomatosis. Loculated pockets of ascites are quite common, particularly along the paracolic gutters. In some cases, when carcinomatosis involves the bowel and there is evidence of serosal tumor implants, the bowel wall may appear thickened and irregular (with or without obstruction), and loops of bowel may be clumped and clustered together as a result of encasement by serosal tumor. These patients often experience symptoms similar to bowel obstruction as the serosal implants may prevent normal bowel transit [190,282,283].

Unfortunately, even with advances in scanner technology and spatial resolution, MDCT’s sensitivity for carcinomatosis is still poor, with sensitivities as low as 7% for tumor implants under 1 cm in size, and overall sensitivities for carcinomatosis as low as 25%. Not only is it difficult to visualize tiny implants, anatomic relationships can obscure tiny tumor implants in certain locations, particularly under the diaphragms, along the liver surface, and the porta hepatitis [190,283]. Although the sensitivity of MDCT for carcinomatosis is limited, it is critical that the radiologist carefully inspect the omentum and major sites of peritoneal ligamentous attachment in order to increase sensitivity for detection of tiny tumor implants [284]. One study showed that the use of multiplanar reconstructions increases lesion detection rates in patients with ovarian cancer metastatic to the peritoneum, including lesions involving the infracolic omentum [285].

Pseudomyxoma peritonei is an uncommon form of peritoneal tumor implant, exhibiting many of the same characteristics as traditional carcinomatosis but with unique implants, which are often large, low in attenuation, cystic, and with calcifications along their borders (Figure 147.24). These tumor implants tend to occur at the margins of the peritoneum, and will often scallop the borders of the liver and spleen. When pseudomyxoma peritonei is suspected, careful attention should be given to the appendix or ovaries, as pseudomyxoma most often results from a perforated appendiceal mucocoele, cystadenoma, or cystadeno-carcinoma, or, alternatively, from dissemination of a primary mucinous neoplasm (usually from the ovary or GI tract).

Although rare, primary peritoneal tumors include mesothelioma, benign mesenteric cysts, stromal neoplasms, lymphoid neoplasms (such as Castleman disease), and desmoid tumors. Distinguishing primary and secondary neoplasms of the peritoneum may not be possible on imaging, particularly in cases with extensive tumor infiltration.

Nonneoplastic peritoneal diseases

Enteric inflammatory processes cause localized fat stranding within the adjacent mesenteric and intraperitoneal fat [286]. This does not necessarily suggest acute generalized peritonitis, and in cases with true generalized acute peritonitis, there is usually evidence of significant free fluid, peritoneal thickening, and peritoneal hyperenhancement. A large variety of intraabdominal pathologies give rise to secondary peritonitis, including appendicitis, bowel perforation, and diverticulitis. Some infectious causes of chronic peritonitis produce imaging findings that are essentially identical to peritoneal carcinomatosis, including retention of contrast during delayed-phase imaging, thought to be secondary to the fibrotic scirrhous nature of the tumors. Tuberculosis can result in extensive soft tissue infiltration of the peritoneum and omentum, along with ascites, peritoneal enhancement, and peritoneal thickening, findings which are indistinguishable from tumor spread [287]. In such cases, the distinction between a tumor and infection can be difficult, and other stigmata of tuberculosis (i.e., involvement of the spine, kidneys, lungs, etc.), as well as an appropriate clinical history with risk factors, may be necessary to establish the correct diagnosis.

In patients who present with acute abdominal pain, CT is useful to diagnose possible peritoneal abnormalities, including
Computed tomography of the gastrointestinal tract

CHAPTER 147

Hernias

MDCT is the best radiological modality to diagnose or characterize an abdominal wall hernia [296]. Although most hernias are diagnosed clinically, they may be occult, particularly in obese patients, or they can be a source of acute abdominal pain. A variety of abdominal wall hernias have been described, including lumbar, spigelian, obturator, and perineal. These hernias may cause bowel obstruction; complications of hernia-related bowel obstructions can include incarceration and strangulation (Figure 147.25). CT manifestations are similar to findings seen in a strangulated small bowel obstruction, with findings of ischemia as a result of strangulation of both the arterial and venous blood supply to the involved segments of bowel [297].

The CT appearance of internal hernias, when bowel protrudes through an opening or defect in the mesentery or peritoneum, have been well described [298]. Predisposing factors that cause a defect include surgery, trauma, inflammatory disease, or a congenital defect in the mesentery [299]. Of the six types of internal hernias that have been described, paraduodenal internal hernias are most common, followed by pericecal, transmesenteric, foramen of Winslow hernias, intersigmoid, and, least commonly, paravesical [298]. CT findings of a right paraduodenal hernia are encapsulation and clustering of small bowel loops in the right midabdomen with looping of arterial and venous jejunal branches behind the superior mesenteric artery. The findings of a left paraduodenal hernia, which are more common than right paraduodenal hernias, are less specific, but include clustering or encapsulation of small bowel loops at or above the level of the ligament of Treitz with intermittent dilation, depression of the duodenal–jejunal junction, and compression of the posterior gastric wall [300,301].

Traumatic diaphragmatic hernias may cause diagnostic difficulty, particularly as these hernias can be easily missed when the dataset is viewed in only the axial plane. The diagnosis is often contingent on using the coronal images to judge the relationship of abdominal structures relative to the diaphragm, as well as to determine whether or not the diaphragm is truly disrupted [302]. Of note, in one study using MDCT, the diagnosis was missed using subjective prospective interpretation in up to 50% of cases. While the diagnosis can be difficult, predefined criteria have been reported to increase sensitivity for detecting blunt diaphragmatic rupture to nearly 100% [303,304].

References are available at www.yamadagastro.com/textbook
Further readings


Magnetic resonance imaging

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Introduction

Magnetic resonance imaging (MRI) is a powerful imaging tool for the evaluation of disease processes of the abdomen. It has an established role as a primary diagnostic technique in abdominal imaging, with evidence showing MRI to have advantages over computed tomography (CT) with regard to diagnostic sensitivity and specificity for many pathological processes of solid organs, bile and pancreatic ducts, bowel, peritoneum, and retroperitoneum.

Since the development of MRI, applications for its use in the gastrointestinal tract have expanded rapidly. The evaluation of the abdomen by MRI was initially hampered somewhat because of artifacts associated with respiratory and bowel motion. However, the development of newer fast imaging techniques has overcome these motion effects, enabling examination of structures and organs that were previously not reliably imaged. These new techniques have improved the results of MRI of the abdomen, particularly when compared with CT.

MRI has certain advantages over CT. CT relies on the single variable of X-ray attenuation for tissue contrast. All image contrast with CT relies on attenuation, and vascularity of structures can be inferred by the changes in attenuation imparted by intravenous contrast agents. Basic differences that can be distinguished include air, calcification, bone, soft tissue, fat, and changes in soft-tissue attenuation imparted by intravenous contrast agents. However, MRI incorporates several parameters that can distinguish pathological tissues. These include T1, T2 (see following section), lipid content, the magnetic susceptibility imparted by metal ions such as iron in the liver, and specific characteristics of flowing blood. In addition, various types of contrast agents, some of them targeted receptor agents, have been developed for imaging the abdomen. Finally, newer techniques such as diffusion and perfusion imaging, are being developed for imaging the abdomen. Compared with CT, MRI has a range of tissue characteristics with which to build the image, and therefore has a greater potential for tissue characterization.

The risks of CT derive from the dose of radiation and from the risk of nephrotoxicity with intravenous contrast agents. The risks of radiation dose may be significant, particularly in younger patients. The probability of a radiation-induced cancer in a young adult undergoing CT of the abdomen and pelvis is about one in 2000 or greater. The current cost in the United States of this one-time radiation dose has been estimated at $30/mSv, or $300 per abdominal CT. These considerations have led one author to suggest that MRI in younger patients may be cost-effective compared with CT based on considerations of radiation risk alone. Costs associated with irradiation of unsuspected pregnancies have not been assessed.
CT of the abdomen routinely employs iodinated contrast agents for delineation of vascular anatomy, and to increase the tissue contrast between tumors and normal organs. Iodinated contrast agents pose three dangers to patients: anaphylactic reaction, renal nephrotoxicity, and osmotic load. Certain patients, such as those with diabetic nephropathy or renal insufficiency from any cause, are at increased risk from renal nephrotoxicity from iodinated contrast agents.

MR may be difficult to tolerate by those patients prone to claustrophobia. If this is severe, it may be treated with sedative or anxiolytic agents or when necessary general anesthesia. However, availability of newer widebore scanners has reduced the incidence of claustrophobic feelings for many patients. MR is contraindicated in individuals who have older type cardiac pacemakers, ferromagnetic metal aneurysm clips, cochlear implants, intrauterine metallic implants, or other metal implants where patient may suffer complications if they do undergo MRI scans, since the scanner may interfere with the proper functioning of the ferromagnetic device.

Allergy or an abnormal reaction to the contrast medium that may be used during some MRI procedures, although rare is another potential limitation of MR for those affected. The risk of anaphylactic reaction associated with currently available gadolinium agents is very low. These agents have no known cross-reactivity with the iodinated contrast agents used for CT, so these patients may be safely imaged with MR. Nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is a well-recognized but poorly understood syndrome characterized by progressive multiple-organ fibrosis [1,2]. The cutaneous manifestations, including hyperpigmentation and brawny induration of the skin, were first observed in 1997 but were not reported until 2000 [2]. A multiplicity of extracutaneous systemic manifestations, including visceral organ fibrosis and vascular thrombosis, has since been recognized [2] and described. NSF appears to occur exclusively in patients with renal impairment, and to our knowledge, no cases to date have been described in a patient with normal renal function. The association between NSF and gadolinium-based contrast agents (GBCAs) was first proposed in a 2006 study in which the investigators reported that five of nine patients with pathologically proven NSF had undergone contrast material–enhanced MRI examinations days to weeks before developing NSF [1].

Patients who are older than 60 years and those who are younger than 60 years with risk factors are screened by means of serum creatinine level measurement and estimated glomerular filtration rate (eGFR) calculation within 30 days before the MR study date. If the eGFR is found to be lower than 60 mL/min/m², an alternative imaging procedure should be considered. The availability of potentially renoprotective therapies, such as N-acetyl-L-cysteine, hydration, and sodium bicarbonate, may make iodinated contrast-enhanced CT a safer alternative to contrast-enhanced MR imaging for these patients. If contrast-enhanced MR examination remains the preferred diagnostic option, the decision to administer a GBCA will depend on the severity of renal disease. A patient at risk of NSF should receive a GBCA only when a risk–benefit assessment for that patient indicates that the benefit clearly outweighs the potential risk, or risks. In the United States, the US Food and Drug Administration (FDA) has requested the prescribing information of all GBCAs to be revised by adding a boxed warning, according to which the use of GBCAs in at-risk patients should be avoided unless the diagnostic information is essential and not available with unenhanced MRI. All unenhanced MRI sequences that may be helpful to make a diagnosis should be performed and the images should be evaluated by an experienced radiologist to ensure that the administration of a GBCA is still deemed necessary. If the use of a GBCA is still deemed necessary after unenhanced MRI, the lowest dose needed to reliably provide the diagnostic information being clinically sought should be used, and according to the boxed warning required by the FDA, the recommended doses should never be exceeded. However, the recommended doses for some agents can be up to 0.3 mmol/kg of body weight. It is recommended to not exceed the standard dose of 0.1 mmol/kg even if the GBCA to be used is approved for higher doses. The use of lower doses, when possible, is encouraged in Europe and Japan. Some GBCAs (gadodiamide, Omniscan; gadopentetate dimeglumine, Magnevist; gadoveresetamide, OptiMARK) are contraindicated for use in patients at risk of NSF [3,4]. Other GBCAs may be given to at-risk patients, but only if regarded clinically essential. The FDA did not mandate specific contraindications, but requested that the same boxed warning be added to the prescribing information of all five GBCAs sold in the United States (the three above plus gadobenate dimeglumine [MultiHance, Bracco] and gadoteridol [ProHance, Bracco] [1,2]. The usefulness of hemodialysis in the prevention of NSF is unknown. However, to enhance and speed up the GBCA elimination, it is recommended that patients on hemodialysis undergo a hemodialysis session no later than 2 hours after the administration of the GBCA. A second hemodialysis session should be considered within 24 hours of the first session. Patients at risk of NSF should be followed for 1 year after a contrast-enhanced MRI examination to identify any symptom or sign suggestive of NSF, and then evaluated accordingly. If a new diagnosis of NSF is made, it is recommended that the regulatory authorities should be immediately notified.

In this chapter, we explain some of the tissue characteristics and basic principles of imaging and discuss specific applications and techniques in MRI.

Basic principles (Table 148.1)

Differences in tissue contrast with CT are measured by Hounsfield units, which are a measure of X-ray attenuation. In MRI, the difference in tissue contrast (white, gray, black) depicted on the image is termed its signal intensity. High signal intensity refers to structures which are white on the image and low signal...
intensity to structures which are dark on the image. Unlike Hounsfield units in CT, signal intensity units are arbitrary and have no real meaning as absolute numbers.

The terms T1 and T2 refer to specific tissue properties that describe the way protons (mostly in water and lipids) behave after being excited by a radiofrequency pulse in a strong magnetic field. Each type of tissue will show a typical T1 and T2. When the image tissue contrast is based mostly on the differences in T1 between the tissues, the image is termed a T1-weighted image. T1 is termed the longitudinal relaxation rate and T2 the transverse relaxation rate or spin-relaxation rate. Structures or fluids that are bright on T1-weighted images have a short (lower) T1 because of greater longitudinal magnetization, and images which are dark have a long T1. Structures containing no water or fat, such as bone or air, also will appear black on a T1-weighted image.

Table 148.1 Terms used in magnetic resonance imaging.

<table>
<thead>
<tr>
<th>Term</th>
<th>Synonym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Longitudinal magnetization</td>
<td>Amplitude of magnetization (and potential signal intensity) that is oriented along the main magnetic field</td>
<td></td>
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<tr>
<td>Transverse magnetization</td>
<td>Amplitude of magnetization (and actual signal intensity) that is oriented perpendicular to the main magnetic field in the plane of the receiving coil</td>
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<tr>
<td><strong>Tissue characteristics</strong></td>
<td></td>
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<tr>
<td>T1</td>
<td>Longitudinal relaxation time or spin-lattice relaxation time</td>
<td>Measurement of the rate at which the longitudinal relaxation returns to the direction of the main magnetic field after perturbation by a radiofrequency pulse</td>
</tr>
<tr>
<td>T2</td>
<td>Transverse relaxation time or spin-spin relaxation time</td>
<td>Measurement of the rate at which spins dephase relative to each other in the transverse plane which cannot be refocused by a 180° refocusing pulse</td>
</tr>
<tr>
<td>Magnetic susceptibility</td>
<td></td>
<td>Local distortion of the magnetic field induced by paramagnetic compounds, metal, air-tissue interfaces, etc., which decrease the signal intensity</td>
</tr>
<tr>
<td>Chemical shift</td>
<td></td>
<td>Reference to the different resonant frequencies of certain compounds such as fat or silicone relative to water, which allows their selective saturation</td>
</tr>
<tr>
<td><strong>User-controlled parameters</strong></td>
<td></td>
<td></td>
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<tr>
<td>TE</td>
<td>Time to echo or echo time</td>
<td>Time interval between the alpha pulse (a 90° pulse in a spin echo pulse sequence) and the center of the received signal</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition time</td>
<td>Time interval between the phase-encoding steps</td>
</tr>
<tr>
<td>TI</td>
<td>Inversion time</td>
<td>Time interval between an inversion pulse in an inversion recovery sequence. The time interval between the inversion pulse and the TE</td>
</tr>
<tr>
<td>Pulse sequence</td>
<td>Sequence</td>
<td>Complex set of commands that control the magnetic resonance system, gradients and radiofrequency generator in a specific manner, to generate the received signal</td>
</tr>
<tr>
<td>In-phase image</td>
<td></td>
<td>Image in which fat and water in the image are in-phase with one another and therefore their signal intensity is additive in the image</td>
</tr>
<tr>
<td>Opposed-phase image</td>
<td></td>
<td>Image in which the fat and water signals are out of phase with one another and therefore subtractive or cancel in the image</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>Matrix</td>
<td>Number of frequency-encoded steps and phase-encoded steps, which determines the resolution of the image</td>
</tr>
<tr>
<td>Magnetic resonance angiography</td>
<td>MRA</td>
<td>Set of images, usually gradient echo images, which are designed to emphasize flow within blood vessels. These are displayed in a format via computer reconstructions to resemble conventional angiograms</td>
</tr>
<tr>
<td>Magnetic resonance cholangiopancreatography</td>
<td>MRCP</td>
<td>Set of images that are heavily T2-weighted and designed to demonstrate fluid within the biliary tree and pancreatic duct</td>
</tr>
<tr>
<td>Contrast agent</td>
<td></td>
<td>Chemical compound injected or ingested to change the tissue contrast on the magnetic resonance image</td>
</tr>
<tr>
<td>Paramagnetic (e.g., gadopentetate dimeglumine)</td>
<td></td>
<td>Chemical compound that alters the relaxation properties of water, generally shortening T1 (producing brighter signal intensity on T1-weighted images) more than T2</td>
</tr>
<tr>
<td>Superparamagnetic (e.g., iron oxides)</td>
<td>SPIO</td>
<td>Chemical compound that alters the relaxation properties of water, generally shortening T2 (producing low signal on T2-weighted sequences) more than T1</td>
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</table>
The specific parameters chosen to acquire the image determine whether an image is T1-weighted or T2-weighted or some other type of image. TE and TR refer to the echo time and repetition time, respectively, and are the parameters chosen by the operator to acquire a T1-weighted or T2-weighted image. The specific parameters chosen by the technician determine exactly what kind of image is obtained and are termed the pulse sequence. This sequence therefore describes a set of images covering a specific anatomical area, with identical imaging parameters such as TE, TR, and resolution. T1-weighted images have a short TE and a relatively short TR.

Images designed to show contrast based mostly on the T2 values of the tissues are called T2-weighted. Such images generally have a long TE and a long TR. Structures which are high signal intensity (white) on the T2-weighted image are generally fluid-containing structures such as cysts, intestinal contents, or gallbladder bile. Most tissues in the abdomen, such as liver, pancreas and intestinal wall, have low signal intensity (dark) on T2-weighted images. Structures which have a high fluid content or contain more fluid than normal tissues are brighter on the T2-weighted image. Examples are cysts and hemangiomas of the liver. Structures such as malignant tumors contain higher water content than normal tissues, and therefore show higher signal intensity than normal tissues. Because of their long repetition time (2–3 s), T2-weighted images usually take longer to acquire than T1-weighted images, and therefore are somewhat more susceptible to motion artifact. Within a strong magnetic field, protons (hydrogen atoms in water or lipid) have a physical property termed spin (angular momentum). These spins can be perturbed by a radiofrequency pulse at a specific frequency, the resonant frequency of the spin. After this excitation pulse or tip, the spins will emit a signal termed the free-induction decay (FID). This radiofrequency signal is the basis of the magnetic resonance signal.

Because it occurs soon after the initial radiofrequency pulse, the FID is not received normally. The FID rapidly decays in signal amplitude because of dephasing of the spins. This means the spins precess out of phase relative to each other because of small differences in the magnetic field strength in the tissues and therefore have no net signal. This effect of signal amplitude decay, because of dephasing, can be overcome by the application of the 180° pulse after the 90° pulse, in order to refocus the spins and bring the spins back into phase with a corresponding rapid increase in signal amplitude. This process is termed the spin echo and is used in spin echo sequences, which are the most frequently used sequences in MRI. Spin echo sequences can be T1-weighted, T2-weighted, or intermediate-weighted. Intermediate-weighted images use a short TE and a long TR, and are sometimes called proton density-weighted images. They generally have limited usefulness for abdominal imaging.

The signal from the spin echo is localized in space within the body by applying magnetic field gradients. These gradients change the resonant frequency and phase of the spins linearly across the body so that the source of the radio signal can be localized. These gradients are termed the frequency-encoding and phase-encoding gradients. A map of the location of the signal and the strength of the signal strength linearly across the body is the image. The complex radio signal received by the receiver coil from the body is decoded into the spatial location of the signals and the strength of the signals by a mathematic algorithm called the Fourier transform.

Another way of refocusing the signal after the 90° pulse is by the application of bipolar gradients, which are gradients that are switched on in one direction and then switched on rapidly in the opposite direction. This will cause refocusing of the FID signal in a manner that is appropriate for spatial localization of the signal. These sequences are termed gradient refocused echoes or gradient echo (GRE) sequences. The advantage of GRE sequences is that they are acquired very rapidly, allowing acquisition within a breath-hold period. GRE images designed specifically to image blood flow are termed magnetic resonance angiography (MRA) sequences, because flowing blood appears bright on these sequences. The resonant frequencies of water differ from the protons in lipid molecules, such as adipose tissue or fat. Because of this difference in resonant frequencies, these two populations of protons in the body can be imaged separately, sometimes termed chemical shift imaging. The most frequently used method is the application of a radiofrequency pulse which saturates the signal selectively from fat or water. If this is performed at the resonant frequency of fat, it is called a fat saturation sequence, or fat saturation image.

On GRE images, fat and water may be out of phase with one another and thus cancel their signal. Whether the fat and water spins are out of phase with one another depends on the TE. If fat and water are out of phase relative to each other, small volumes of tissue containing both fat and water (such as fatty infiltrated liver) will cancel their signal and appear dark on the image. This type of image is called an opposed-phase image. In contrast, an in-phase image shows the lipid and water protons in the image as bright. In-phase and opposed-phase images are very sensitive to the presence of small amount of lipid in tissues. These sequences are used to detect fatty liver and the lipid that commonly occurs in adrenal adenomas.

MRA refers to a family of pulse sequences that image flow within blood vessels. These pulse sequences take advantage of the fact that flowing blood is bright (high signal intensity) on certain GRE sequences. Blood flowing into a slice being imaged is fully unsaturated (i.e., has greater longitudinal magnetization) because it has not experienced prior excitation pulses. This effect renders the blood flowing into the slice as very high signal intensity on the image. Blood flowing through the slice shows less signal intensity because it experiences the excitation pulses.
used to acquire the data for the image. If thin slices are obtained continuously, preferably with the blood vessel of interest in cross-section, the resulting data can be reconstructed into a dataset representing the entire volume of tissue and then projected into images which resemble conventional angiograms. The principle described here is called “time-of-flight MRA.”

There are other forms of MRA that rely on different physical principles, such as phase contrast angiography, bolus tracking, black blood techniques, and three-dimensional gadolinium-enhanced MRA. Description of these techniques is beyond the scope of this chapter. However, these techniques have in common the principle of imaging flowing blood, while not necessarily imaging the vascular structures themselves. They are all susceptible to certain artifacts that give the impression of occluded or stenotic vessels, such as slowly flowing blood and turbulent flow, and artifacts from adjacent structures such as metallic surgical clips. The basic goal of these sequences is to increase the contrast between the vessel and surrounding structures dramatically. Thus, the vessels are selectively displayed with markedly higher signal intensity than surrounding stationary tissue. A magnetic resonance technique that simulates MRA but which differs in principle is magnetic resonance cholangiopancreatography (MRCP). The goal of MRCP is to selectively image fluid within the biliary tree and pancreatic duct. Very heavily T2-weighted images are used to achieve this effect. With the very long TEs used for these heavily T2-weighted images, virtually all solid tissue has low signal (dark on the image). By virtue of its long T2, fluid within the biliary tree, gallbladder, and pancreatic duct retain signal intensity and therefore appears bright on the image. Like MRA, multiple projections in a manner similar to conventional cholangiography or endoscopic retrograde cholangiopancreatography (ERCP) can be obtained.

Current pulse sequences for imaging the liver are designed for very fast acquisition of images so that motion artifacts are limited or absent. These very fast images generally require improved (high performance) gradient systems. For T1-weighted images, fast GRE sequences are used. T1-weighted images that acquire the whole liver as a volume (three-dimensional imaging) can be used for dynamic perfusion studies, or MRA studies, or both. For T2-weighted images, subsecond pulse sequences have been developed so that motion-free images are obtained, whether or not the patient is holding their breath. These sequences are called HASTE (half-Fourier acquisition single-shot turbo spin echo), EXPRESS, or single-shot fast spin echo (FSE) sequences, depending on the manufacturer of the system. Echo planar imaging is not a new development but has been relatively recently adapted to average clinical scanners with improved gradient systems and can also acquire subsecond images.

Injected contrast agents identify vascular structures and areas of abnormality within organs by differences in their vascularity. Contrast agents for use during MRI are available and have similar functions to iodinated contrast agents used in CT. The most frequently used agent in MRI is gadopentetate dimeglu-
Benign lesions

Cysts

Benign lesions of the liver are common in the adult, and cysts represent the most common benign lesion. Pathology typically shows a wall comprising a single layer of epithelial cells. Etiologies are mostly idiopathic, but cysts may be seen in association with developmental disorders such as polycystic kidney disease or von Hippel–Lindau disease, infections including Echinococcus, or hemorrhage. Cysts appear uniform and high in signal intensity on T2-weighted images and low in signal intensity on T1-weighted images, with well-defined margins (Figure 148.1) and no evidence of enhancement on gadolinium-enhanced spoiled gradient echo (SGE) images [6,7]. Benign cysts may appear slightly complicated with lobulation of borders and septations, and may have elevated signal on SGE T1-weighted images, typically in association with protein or related to prior hemorrhage. As complexity becomes more prominent, other possibilities include biliary cystadenoma (Figure 148.2), biliary cystadenocarcinoma, and mucinous cystadenocarcinoma of ovarian or other origin, usually bowel or pancreas. These tumors typically show perilesional gadolinium enhancement. These lesions may also have internal septations and enhancing mural nodules. These lesions will also increase in size on follow-up imaging.

Bile duct hamartomas

These lesions are relatively common, occurring in 3% of the population, and comprise irregular branching bile-dilated bile ducts. Bile duct hamartomas are frequently peripheral, multiple, and less than 1 cm in size. These lesions have features identical to cysts on T2- and unenhanced T1-weighted images, with the exception of demonstrating a peripheral thin and uniform rim of gadolinium enhancement (Figure 148.3). Metastases show perilesional enhancement, and hypervascular tumors show central enhancement on arterial phase [7,8].

Abscess

Pyogenic abscesses are associated with sepsis, recent bowel surgery, diverticulitis, Crohn’s disease, and appendicitis. Fungal microabscesses are more common in immunocompromised patients. Typically, abscesses (Figure 148.4) have high central increased signal and intermediate peripheral rim on T2-weighted images. The central portion is low on T1-weighted images and does not enhance on postcontrast images [9]. The peripheral rim shows persistent late enhancement without centripetal progression of enhancement [10]. There is indistinct perilesional enhancement on the early phase because of hyperemia [11].

Hemangiomas

Hemangiomas are the most common benign liver neoplasm, are multiple in up to 70% of patients, and are found with highest incidence in young adult women. Histology shows a series of vascular lakes and channels, with larger lesions developing areas of thrombosis and fibrosis. Imaging shows moderately elevated signal on single-shot T2-weighted images, typically less intense than demonstrated by simple cysts, and low signal on T1-weighted images [6,12]. Enhanced images show peripheral interrupted nodules on the arterial phase (Figure 148.5), and this finding is pathognomonic for this pathology. Venous and delayed phases may show progressive enlargement and coalescence of the peripheral nodules with variable degrees of central filling [6,13]. Smaller lesions generally fill more quickly, and larger lesions are progressively more likely to show slower central filling. Giant hemangiomas, usually larger than 5–10 cm, typically develop central areas that fail to fill in on delayed enhanced images, and may show central cystic areas that are as bright as simple fluid, such as cerebrospinal fluid, with well-defined margins and no enhancement. Small (<1 cm) lesions may fill quickly and be difficult to delineate from other arterial-phase enhancing neoplasms, such as a small hepatocellular carcinoma (HCC) or hypervascular metastases [14]. In such cases,
Figure 148.1 Simple hepatic cyst. (a) Axial T2 image, (b) axial T1 image, (c) postcontrast three-dimensional GRE image, and (d) magnetic resonance cholangiopancreatography (MRCP) demonstrate high T2 signal lesion (arrow on a and d) and low T1 signal nonenhancing lesion (arrow on b and c) consistent with simple hepatic cyst.

Figure 148.2 Biliary cystadenoma. Axial T2 image (a) and corresponding axial three-dimensional gradient echo (GRE) images of the liver (b) before and (c) after contrast demonstrate large cystic lesion in the left and right lobes of the liver with internal enhancing septations that was surgically proven to be biliary cystadenoma.
ducts that can form an unencapsulated mass with abnormally structured vessels and bile ducts. These lesions may appear iso- to mildly hyperintense on T2-weighted images, and isointense to mildly hypointense on T1-weighted images (Figure 148.5). An important, and unique, characteristic of FNH is the formation of a central fibrovascular core, which may produce a high signal on T2-weighted images [6,7,12,16]. On gadolinium-enhanced imaging the fibrovascular core may demonstrate slowly progressive enhancement, with no perceived enhancement on arterial phase, and becoming maximally conspicuous on delayed-phase images [16,17]. This is in contrast to the bulk of the mass surrounding the core that typically enhances uniformly and intensely in the arterial phase, and which becomes isointense or slightly hyperintense to surrounding liver on venous and delayed phases. Small lesions (less than 1–2 cm) may appear more uniform in enhancement and a fibrovascular core may not be perceived. Other distinguishing features on gadolinium-enhanced imaging from other arterial-phase enhancing tumors include the lack of capsule enhancement, as is observed with adenomas and HCC [16–19]. Fibrolamellar HCCs are typically large, greater than 10 cm at presentation, but may share features of FNH with the exception that the central scar of fibrolamellar tumors is typically lower than surrounding tumor on T2-weighted images and shows radiating enhancing bands on postgadolinium images [16,20]. Alternative contrast

Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is most commonly seen in young adult women and seems to represent a hamartomatous lesion with a disorganized growth pattern of hepatocytes and

Figure 148.3 Bile duct hamartomas. Axial T2 image (a) and corresponding axial three-dimensional gradient echo (GRE) images of the liver (b) before and (c) after contrast demonstrate scattered, less than 1 cm cysts (arrows) in the liver with thin peripheral rim of enhancement consistent with biliary hamartomas.

the distinguishing features can be found on venous and delayed images, where the other hypervascular neoplasms typically show washout whereas hemangiomas may demonstrate persistent enhancement with signal above that of the adjacent liver parenchyma. Metastases have been described as enhancing progressively from outside-in; however, the pattern of enhancement does not show peripheral interrupted nodules with coalescence, as is typical of hemangiomas [15,16]. An optimally timed arterial-phase enhanced image typically provides the most critical diagnostic information [16].

Figure 148.4 Hepatic abscess. (a) Axial T2 image and (b) postcontrast three-dimensional gradient echo (GRE) image of the liver demonstrate large, peripheral, enhancing, thick-walled abscess (arrow).
oral contraceptives, and rarely with exogenous anabolic steroids, galactosemia, and glycogen storage disease type Ia. Spontaneous hemorrhage may occur in larger masses, typically greater than 4–5 cm in diameter, and can result in presentation with abdominal pain, with a risk of extrahepatic extension and intraperitoneal bleeding. Hepatic adenomas comprise sheets of hepatocytes and form a pseudocapsule related to compression of adjacent hepatic parenchyma; however, in contrast to FNH, they do not form bile ducts. T2-weighted images show isointense to slightly hyperintense signal and T1-weighted images show mildly hypointense to mildly hyperintense signal (Figure 148.6) [5].

**Figure 148.5** Hepatic hemangioma (arrow) and focal nodular hyperplasia (arrowhead). (a) Long echo time (TE)(180 ms) and (b) fat-suppressed intermediate TE (80 ms) axial T2-weighted images of the liver demonstrate a high T2 signal lesion (arrow) adjacent to the inferior vena cava. Of note, a second lesion (arrowhead) is also seen on b but not on a. Three-dimensional gradient echo (GRE) images (c) before contrast, (d) during arterial phase, and (e) delayed post contrast demonstrate peripheral enhancement of the paracaval lesion (arrow) with progressive delayed enhancement consistent with a hemangioma. The second lesion (arrowhead) enhances avidly in the arterial phase and becomes isointense to hepatic parenchyma on delayed imaging, consistent with focal nodular hyperplasia.

**Adenomas**

Adenomas are benign neoplasms of epithelial origin, with predominant incidence in young women. They are associated with oral contraceptives, and rarely with exogenous anabolic steroids, galactosemia, and glycogen storage disease type Ia. Spontaneous hemorrhage may occur in larger masses, typically greater than 4–5 cm in diameter, and can result in presentation with abdominal pain, with a risk of extrahepatic extension and intraperitoneal bleeding. Hepatic adenomas comprise sheets of hepatocytes and form a pseudocapsule related to compression of adjacent hepatic parenchyma; however, in contrast to FNH, they do not form bile ducts. T2-weighted images show isointense to slightly hyperintense signal and T1-weighted images show mildly hypointense to mildly hyperintense signal (Figure 148.6) [5].

Opposed-phase SGE T1-weighted images
demonstrate signal drop related to lipid accumulation in approximately half of adenomas [21]. Blood products may result in irregular foci of mixed high or low signal on T1- and T2-weighted images. Gadolinium enhancement is maximal during arterial phase and seen as an arterial-phase blush with rapid fading in the venous and delayed phases to hypointensity or isointensity to adjacent liver, with development of a persistent enhancing rim related to the pseudocapsule [5,19]. An enhancing scar is observed in a small subset, but such a scar does not produce high signal on T2-weighted images as seen in FNH. Although most features of adenoma mimic HCC, HCC is usually associated with a background of chronic liver disease and evidence of cirrhosis [5,19]. However, in patients with HCC risk factors where the liver is normal and tumor markers are negative, differentiation may be difficult. The presence of portal venous involvement helps differentiate HCC, and the presence of blood products helps differentiate adenoma. Hepatic adenomatosis is a rare entity that involves numerous adenomas scattered throughout the liver, which have malignant potential [22].

**Malignant lesions**

Primary HCC is the most common primary liver malignancy and usually occurs in the setting of cirrhosis [23]. These tumors are thought to arise from premalignant dysplastic nodules, and dysplastic nodules are thought to progressively dedifferentiate from low- to high-grade histology [24]. HCC occurs as a solitary lesion in 50% of cases, is multifocal in 40%, and diffuse in 10%. HCC is typically greater than 2 cm in diameter, in contrast to dysplastic nodules, which are typically less than 2 cm [23]. Imaging features are variable, but the pattern of elevated signal on T2-weighted images and diminished signal on T1-weighted images increases the likelihood of HCC as compared with dysplastic nodules (Figure 148.7) [5]. However, in the setting of cirrhosis highly specific imaging features for HCC are reliably found on gadolinium-enhanced SGE images, which show irregular marked arterial-phase enhancement with rapidly diminished enhancement on venous and delayed-phase images, and development of a peripheral enhancing rim resulting from a pseudocapsule [23]. High-grade dysplastic nodules may show enhancement, but do not develop a pseudocapsule [25]. Diffuse HCC shows inhomogenous T2- and T1-weighted signal, with inhomogeneous enhancement that has regions that washout, while other regions persist, and typically can be shown to have portal vein arterial-phase enhancing tumor thrombosis [25].

**Hypovascular metastases**

Most common malignant hepatic tumors can be further classified as hypovascular or hypervascular based on imaging features. Hypovascular metastases are the most common and usually arise from colonic adenocarcinoma. These tumors tend to have mixed arterial and portal venous supply, and usually develop central necrosis presumably because of poor vascular perfusion to the center of enlarging tumors [26]. Hypovascular metastases may have variable appearance on T2-weighted
Magnetic resonance imaging CHAPTER 148

Diffusion-weighted (DW) MR imaging has evolved into a mature functional MR imaging technique for many brain imaging applications [30]. DW MR imaging is an MR imaging technique that derives its image contrast on the basis of differences in the mobility of protons (primarily associated with water) between tissues. In tissues that are highly cellular (e.g. tumor tissues), the tortuosity of the extracellular space and the higher density of hydrophobic cellular membranes restrict the apparent diffusion of water protons [28]. In such an environment, water diffusion is said to be relatively “restricted.” By contrast, in cystic or necrotic tissues, the apparent diffusion of water protons is relatively “free.” Thus, DW MR imaging is unique in its ability to provide information that reflects tissue cellularity and the integrity of cellular membranes [28,29].

Diffusion imaging of the liver
Since the first brain diffusion imaging in 1986 and the widespread application for stroke detection in the early 1990s [27–29], diffusion-weighted (DW) MR imaging has evolved into a mature functional MR imaging technique for many brain imaging applications [30]. DW MR imaging is an MR imaging technique that derives its image contrast on the basis of differences in the mobility of protons (primarily associated with water) between tissues. In tissues that are highly cellular (e.g. tumor tissues), the tortuosity of the extracellular space and the higher density of hydrophobic cellular membranes restrict the apparent diffusion of water protons [28]. In such an environment, water diffusion is said to be relatively “ restricted.” By contrast, in cystic or necrotic tissues, the apparent diffusion of water protons is relatively “free.” Thus, DW MR imaging is unique in its ability to provide information that reflects tissue cellularity and the integrity of cellular membranes [28,29].

With recent advances in technology, DW MR imaging has the potential for standard clinical use in the abdomen, particularly in the liver. DW MR imaging is an attractive technique for multiple reasons: it can potentially add useful qualitative and quantitative information to conventional imaging sequences; it is quick (performed within a breath hold) and can be easily incorporated into existing protocols; and it is a nonenhanced technique (performed without the use of gadolinium-based contrast media), thus easy to repeat, and useful in patients with...
diffusion (high signal intensity) on higher b value (≥500 sec/mm²) images and lower apparent diffusion coefficient (ADC) values [27–29]. By contrast, cystic or necrotic tissues will show a greater degree of signal attenuation on higher b value diffusion images and return higher ADC values. However, the signal intensity observed on the diffusion image is dependent on the tissue T2-relaxation time, which is a possible confounding factor [28]. This means that a lesion may appear to show restricted diffusion on DW MR images because of the long T2-relaxation time rather than the limited mobility of the water protons (T2 shine-through). This phenomenon can be observed in the normal gallbladder, cystic lesions, and hemangiomas. The presence of T2 shine-through is recognized by correlating high-b-value images with the ADC map. Areas demonstrating substantial T2 shine-through rather than restricted diffusion will show high diffusivity on the ADC.
Magnetic resonance imaging  

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Including the evaluation of perfusion by gadolinium enhancement pattern within a treated malignant mass [33]. Demonstration of decreased vascularity after therapy, reflected by reduced enhancement, reduced intermediate T2 signal, and necrosis, has been associated with tumor response (Figure 148.10) [34,35].

Diffuse liver diseases
MRI of the liver can also be used for the evaluation of diffuse liver diseases, including abnormal lipid metabolism, iron deposition disease, and perfusion abnormalities related to inflammation, fibrosis, vascular occlusion, or infarction and hemorrhage [36].

Fatty liver
Lipid accumulation in hepatocytes can occur as a result of impaired liver function secondary to a variety of etiologies. In

Figure 148.9 Hypervascular hepatic metastases. Axial T2 image (a) and three-dimensional gradient echo (GRE) images (b) before contrast, (c) during arterial phase, and (d) during portal venous phase demonstrate multiple arterial enhancing lesions (arrowheads) in this patient with melanoma metastases. Note increased signal on precontrast T1-weighted images in lesion in the lateral segment of the left lobe of liver (arrow) secondary to melanin or hemorrhage.

map and high ADC values. For this reason, diffusion images should be interpreted concurrently with the ADC map and all other available morphologic imaging to prevent misinterpretation [29].

Posttherapeutic imaging
Cross-sectional imaging has largely relied on anatomical depiction of disease, including tumors. There is a large subset of patients with malignancy being treated by nonsurgical approaches, including chemotherapy and radiation, where the ability to follow tumor response is valuable [31]. Current methods have mostly relied on anatomical depiction of tumor and measurement of tumor size to evaluate tumor response [31]. This is believed to require a relatively long follow-up period in most applications, and other measures of tumor response sensitive to cellular and vascular reactions may be more useful [32]. A multitude of approaches are being evaluated using MRI [33], including the evaluation of perfusion by gadolinium enhancement pattern within a treated malignant mass [33].

Demonstration of decreased vascularity after therapy, reflected by reduced enhancement, reduced intermediate T2 signal, and necrosis, has been associated with tumor response (Figure 148.10) [34,35].
must include evaluation for the presence of fatty infiltration, which is considered a contraindication to transplantation when severe and can lead to failure of the transplant. Abnormal lipid accumulation in liver can be detected on MRI, by comparing liver signal on SGE images acquired in-phase and out-of-phase [39,40]. Protons in a voxel containing 100% fat process 220–230 Hz slower than a voxel comprising 100% water at 1.5 T. That means every 4.4 ms the fat protons migrate 360° and regain in-phase orientation relative to water protons, whereas at 2.2 ms, or at half this time, the fat and water protons are 180° out-of-phase [37]. Current generation MRI systems have incorporated dual echo breath-hold SGE sequences that can acquire two sets of k-space filled to obtain two sets of images, one set in-phase, the other out-of-phase, with spatially matched slices. Liver containing lipid results in image voxels with a physical mixture of water and lipid, which when imaged out-of-phase results in phase cancellation and diminished signal (Figure 148.11) [36,37]. The spleen does not accumulate fat, and can be used as a control against which liver signal can be assessed as a ratio to test for relative diminishment in liver signal on out-of-phase images. Splenic signals can change as a result of iron deposition, and use of kidney or skeletal muscle within the image may be more reliable for assessment of relative liver signal changes between in-phase and out-of-phase images. Fat accumulation in the liver can be diffuse, diffuse with focal sparing, or focal. Typical regions affected by focal fatty accumulation occur around the falciform ligament, gallbladder fossa, and inferior vena cava [38]. One possible explanation is that these are areas of liver prone to irritation or stimulation, resulting in local changes in carbohydrate–lipid metabolism. Contrast-enhanced CT and standard ultrasound are relatively nonspecific and less sensitive for assessment of fatty liver, and can confuse irregularly accumulated lipid with a mass [38]. Fatty liver can lead to reduced CT density, and diminish contrast between a low-density mass and adjacent liver, making the mass less conspicuous.

Iron deposition disease
Iron accumulates within the liver by two basic mechanisms: accumulation within hepatocytes through normal metabolic chelation mechanisms; or uptake within the phagocytic Kupffer cells, which are part of the reticuloendothelial system. Serum iron and transferrin saturation are poorly correlated with the degree of iron overload. Hepatocytes chelate the iron that accumulates within the cytosol. Pancreas also has chelation mechanisms within acinar cells, and can accumulate excess intracellular iron. Iron accumulation can occur in most tissues to some degree, typically after hepatic stores have reached high levels. Important examples include the pituitary and heart, where this can result in impaired pituitary function and fatal cardiac arrhythmias and congestive heart failure. Patients presenting with a first-time diagnosis of primary hemochromatosis with the combined findings of elevated liver and cardiac iron deposition, and congestive heart failure, have a poor prognosis with a
within liver sinusoids and in splenic tissue. In contrast to primary hemochromatosis, the pancreas does not typically accumulate iron. The clinical significance of primary hemochromatosis includes the observation that many patients develop cirrhosis and approximately 25% of patients develop HCC.

The presence of iron deposition within the liver may be detected by MRI of the liver \[41\]. Liver biopsy has been used for biochemical determination of iron overload and has been used as the basis for therapy management in patients treated by periodic phlebotomy and iron chelation therapy; however, this method has bleeding risks associated with the invasive procedure, and is susceptible to sampling error in patients with heterogeneous iron deposition in the liver. The sensitivity of CT is insufficient, with a minimum threshold for liver iron more than five times above the normal liver iron load, particularly in cases with fatty liver. MRI is sensitive to iron concentration in the liver because of the para-magnetic properties of iron, resulting in T2 or T2* effects that diminish the signal intensity on both single-shot breath-hold T2 images and breath-hold T1-weighted multiecho SGE images (Figure 148.12) \[41\]. Quantitative assessment of liver iron concentration based on MRI has been demonstrated using both SGE and spin echo sequences, relying on measurements of T2* and T2 decay. Coronal breath-hold T2-weighted single-shot FSE images, which should be obtained as part of a routine abdominal MRI examination, are very useful for rapid visual evaluation, providing slices that include liver, psoas muscle, and spleen within the same image \[42\]. Normally, liver signal intensity is near the midpoint between the lower signal intensity of muscle and the higher signal intensity of spleen. In iron overload disease, the liver signal intensity becomes as low as or lower than skeletal muscle. In secondary iron overload, spleen similarly becomes dark. In cases where there is bone marrow abnormality, such as in myelofibrosis, normal high-signal marrow fat becomes replaced with low-signal cellular marrow hypertrophy and sclerosis \[42\]. Chronic iron overload can lead to cirrhosis and increased risk for HCC, complications that can be assessed on MRI. For more sensitive and potentially quantitative noninvasive measurement of liver iron, T2* and T2 decay rate measurements can be performed. T2* decay is a measure of how quickly protons lose phase coherence without use of refocusing pulses, and T2 decay is a measure of proton-dephasing rates after application of refocusing pulses, measuring only dephasing effects that are not correctable \[43\]. Generally, the T2* decay rate is more sensitive to lower levels of intracellular iron accumulation \[41\]. Intracellular iron accumulation can cause localized magnetic field distortion that leads to susceptibility effects, which result in more rapid loss of phase-dependent signal \[41\].

One method used to detect this effect is based on multi-echo GRE imaging to measure T2* decay, whereas a spin echo single-shot or echo-planar technique with increasing echo times may be used for T2 decay measurements \[41\]. When performing imaging dedicated to iron measurement, a series of GRE images
are acquired with increasing increments of TE [44]. As TE lengths, the proton dephasing leads to progressively increased loss of signal intensity, and this process has been shown to be proportionately increased in relation to intracellular liver iron concentration. When performing a dedicated T2* analysis of liver iron, TEs may be selected to correspond to in-phase echoes to avoid potential out-of-phase effects from fat, a potentially spurious effect in the setting of fatty liver infiltration [41]. At minimum, routine imaging of the abdomen and liver should include a dual-echo SGE acquisition that can be used in conjunction with the coronal single-shot T2. The longer second echo image (TE 4.4 ms) should show darkening of the liver compared with the shorter echo image (TE 2.2 ms) in the setting of elevated liver iron concentration (Figures 148.12 and 148.13) [41]. The sensitivity to liver iron may be improved on SGE imaging by increasing the echo time to include, for example, echoes at 8.8 ms and 13.2 ms. If only routine shortest possible dual-echo out-of-phase (TE 2.2 ms), and in-phase (TE 4.4 ms) imaging is used, then the relative sensitivity of the single-shot spin echo technique is more sensitive. With this approach, demonstration of low liver signal on single-shot spin echo alone indicates a relatively lower liver iron concentration, and demonstration of low liver signal on both single-shot spin echo and on the longer dual-echo SGE indicates relatively higher liver iron burden. Others have shown that liver iron concentration may be calculated and that noninvasive measurement of tissue iron concentration may be feasible [44]. This represents the only noninvasive technique available for liver iron quantitation, and could be used for example for following hemochromatosis patients on therapy, minimizing the need for liver biopsy [44,45].

**Acute hepatitis**

Inflammatory liver disease can result from a large number of etiologies, including idiopathic, drug induced, viral, alcoholic, and gallstone bile duct obstruction. It has been noted that MRI may be sensitive to acute hepatitis [46]. On MRI, the most sensitive images are the postgadolinium breath-hold SGE images acquired during arterial phase. It has been reported that this abnormal enhancement becomes more marked and can persist into the venous and delayed phases as the severity of disease increases, and can resolve in cases when hepatitis resolves. Furthermore, the arterial-phase timing critically determines sensitivity to mild acute hepatitis. By performing SGE imaging every 5 s after administration of gadolinium in a patient with mild acute hepatitis, irregular liver enhancement is detectable only during the time when the portal veins are filling with contrast, and the hepatic veins are still unenhanced. In mild hepatitis, images acquired before portal venous filling are too early, and liver images acquired when the hepatic veins are filled are too late. For most patients, optimal timing falls between 18 s and 22 s after initiation of the gadolinium injection into an antecubital vein, administered at 2 mL/s, followed by a 20-mL saline wash-in bolus. No other imaging technique has been shown to be sensitive for detection of acute hepatitis. MRI could be used as a diagnostic aid in patients with equivocal liver enzyme elevation and nonspecific symptoms, and in patients presenting with fatty infiltration. The reasons for heterogeneous liver enhancement in acute hepatitis have not been fully determined. It may be that the areas of relative arterial-phase hyperenhancement represent regions of abnormality [47]. Periportal inflammation may differentially compress the lower pressure portal vein intrahepatic branches, leading to preferential segmental hepatic arterial perfusion. Alternatively, inflammation may lead to altered vascular regulatory effects, with vasodilation and increased hepatic arterial flow to the
involved regions. Pathological correlation is challenging given that histopathological correlation lacks the ability to determine pathophysiological \textit{in-vivo} processes involved in hemodynamics, an advantage inherent to contrast-enhanced imaging.

Findings suggestive of acute hepatitis (seen as irregular arterial-phase gadolinium enhancement) in the setting of fatty liver (seen as signal drop on opposed-phase GRE images) are consistent with steatohepatitis and raise the possible diagnosis of alcoholic steatohepatitis or nonalcoholic acute steatohepatitis. Nonalcoholic acute steatohepatitis is a recognized disease entity thought to represent a hepatitis that is directly related to excess intracellular fat accumulation within hepatocytes [47,48]. MRI has greater sensitivity and specificity for detection of fatty liver, and is the only imaging test sensitive for milder cases of hepatitis as compared with CT or ultrasound. Multiple causes of transient hepatic perfusion abnormalities have been described; however, in cases presenting clinically with right upper quadrant pain and abnormal liver arterial-phase perfusion, acute hepatitis should be the major diagnostic consideration [47]. It may be argued that patients with right upper quadrant abdominal symptoms should be preferentially examined by MRI rather than CT. MRI has potential advantages with regard to contrast sensitivity, and can provide excellent temporal resolution because of the small contrast volume used, in combination with the acquisition of contrast data for the entire liver over approximately 4–5 s, usually in the center of a two-dimensional T1-weighted GRE sequence using interleaved phase acquisition. The safety profile of gadolinium agents and nonionizing radiation imaging for a multiphase examination are also attractive characteristics of MRI.

**Chronic hepatitis and cirrhosis**

Cirrhosis is a major complication of chronic hepatitis. In Western nations, alcohol-induced hepatitis used to be the most common etiology, but viral hepatitis is now the most common cause. Globally, viral hepatitis is the most common association with chronic hepatitis, cirrhosis, and HCC. Fibrosis associated with cirrhosis is reflected in progressive enhancement on delayed MRI, resulting from leakage of gadolinium contrast agent from the intravascular into the interstitial space within the fibrotic regions [49]. The typical patterns of cirrhosis include fine reticular and coarse linear bands, with these fibrotic bands outlining foci of regenerative nodules. If active hepatitis is also present, the fibrotic tissue bands may have edema, and appear high in signal on T2-weighted images, and the liver tissue may develop irregular patchy areas of enhancement seen mostly on arterial-phase images [49]. Regenerative nodules occur in the setting of cirrhosis, and represent relatively more normal hepatic parenchyma that derives its major blood supply from the portal venous system [50]. These nodules maximally enhance during portal venous-phase postgadolinium SGE images, and are usually less than 1 cm in diameter. These nodules can accumulate iron, and appear low in signal on both SGE T1- and single-shot FSE T2-weighted images, with little
corresponding to abnormalities of portal venous, hepatic fibrosis, hepatic venous, or mixed disease. Images optimal for visualizing changes related to portal hypertension are obtained on equilibrium-phase SGE images with fat suppression. In early or mild portal hypertension images show dilation of the portal vein, and possibly splenic vein. In more severe and chronic cases, the portal vein can occlude and become thin or not visualized, with development of multiple smaller-caliber collaterals seen within the porta hepatis, gastrohepatic ligament, paraesophageal region, and with demonstration of splenorenal connections. A patent periumbilical vein can be seen as a vessel, sometimes massive, extending from the left portal vein anteriorly along the falciform ligament toward the anterior abdominal wall umbilical region. Ascites is commonly seen in combination with more advanced portal hypertension as simple uniform high-signal T2-weighted fluid in the free intraperitoneal space.

Dysplastic nodules are premalignant and are believed to have the potential to develop progressively higher grades of dysplasia, and finally transform into HCC [50]. Dysplastic nodules are typically larger than regenerative nodules, and grow over a period of weeks or months [49,50]. These lesions can show overlap with HCC, with mildly elevated T1-weighted signal and low T2-weighted signal. Features that help distinguish HCC include increased T2-weighted signal, transient marked arterial-phase postgadolinium enhancement, capsular peripheral rim enhancement on venous- and equilibrium-phase images, relative washout on delayed images, and size greater than 2–3 cm. It may be that higher-grade dysplastic nodules overlap more with the HCC features; however, this distinction may be of small clinical significance because higher-grade dysplasia has the potential to transform to HCC rapidly (Figure 148.14). HCC frequently invades vessels and a small subset may contain fat.

Portal hypertension results from obstruction at presinusoidal, sinusoidal, postsinusoidal, or a combination of these sites, corresponding to abnormalities of portal venous, hepatic fibrosis, hepatic venous, or mixed disease. Images optimal for visualizing changes related to portal hypertension are obtained on equilibrium-phase SGE images with fat suppression. In early or mild portal hypertension images show dilation of the portal vein, and possibly splenic vein. In more severe and chronic cases, the portal vein can occlude and become thin or not visualized, with development of multiple smaller-caliber collaterals seen within the porta hepatis, so-called cavernous transformation. Furthermore, portosystemic collaterals can be seen as increased number and size of retroperitoneal vessels in the region of the splenic hilum, gastrohepatic ligament, paraesophageal region, and with demonstration of splenorenal venous connections. A patent periumbilical vein can be seen as a vessel, sometimes massive, extending from the left portal vein anteriorly along the falciform ligament toward the anterior abdominal wall umbilical region. Ascites is commonly seen in combination with more advanced portal hypertension as simple uniform high-signal T2-weighted fluid in the free intraperitoneal space.

**Figure 148.14** Hepatic cirrhosis with hepatocellular carcinoma. (a) Hepatocellular carcinoma lesion is hypointense to liver on precontrast, fat-suppressed, three-dimensional gradient echo (GRE) image (b), and enhances avidly during arterial phase on fat-suppressed, three-dimensional GRE image (c). Lesion washes out faster than adjacent liver parenchyma in hepatic venous phase three-dimensional GRE fat suppressed image. (d) Axial, fat-suppressed, intermediate T2-weighted image demonstrates cirrhotic liver with nodular contour. Lesion (arrow) in the left lobe of liver shows increased signal on intermediate T2-weighted image relative to adjacent liver parenchyma.
Biliary tree

MRI has become a valuable imaging tool for the pancreas and biliary tree. Applications in this area have been aided greatly by developments in MRA and MRCP, which allow selective visualization of the vascular structures and biliary and pancreatic ducts. MRCP is useful for the detection of biliary obstruction, calculi, and normal variants of biliary anatomy that have surgical importance [51]. The bile ducts appear as high signal intensity with this technique. Calculi appear as low signal intensity filling defects. Unlike CT, where the attenuation of calculi is variable and may approximate that of surrounding soft tissue, calculi identified by MRI are almost universally low signal intensity on T2-weighted images. MRCP has been shown to be accurate for the detection of calculi in the common bile duct [51].

Cholangiocarcinoma

Because of its ability to image bile ducts, vascular structures, and soft tissue of the hepatic parenchyma in one examination, MRI is useful for the detection of cholangiocarcinoma [52]. Cholangiocarcinoma shows a characteristic pattern of enhancement on dynamic-enhanced images. Classically it shows little uptake of contrast on the arterial and portal phases and increased enhancement on delayed images [52,53]. With hilar cholangiocarcinomas (Klatskin tumors), MRCP can show the multiple obstructed ductal segments. Unlike percutaneous transhepatic cholangiography, which requires separate injection of the different ductal segments if they are completely obstructed, MRCP visualizes all the obstructive ductal segments simultaneously [31]. Therefore, MRCP can assist in treatment planning for these tumors [31].

Pancreas

Developments in faster imaging systems with improved contrast resolution continue to enhance the role of MRI in imaging pancreatic abnormalities with equivocal features on CT. In addition, MRCP is accepted as a noninvasive and accurate method of imaging the pancreatic duct and is now considered an important imaging technique for the diagnosis of chronic pancreatitis. Endoscopic ultrasound (EUS) and positron emission tomography (PET) have emerged as important complementary modalities for imaging of pancreatic abnormalities.

MRI of the pancreas is optimally performed with a high-performance gradient system (1.5T) using phased-array torso coil to improve the signal-to-noise ratio with a smaller field of view and thin-slice profile [54]. Breath-hold GRE or FSE sequences are most commonly used. Moderately T2-weighted FSE and single-shot FSE (HASTE) sequences, followed by T1-weighted in-phase GRE and T1-weighted opposed-phase GRE images are included in the MRI protocol. To evaluate cystic lesions of the pancreas or pancreatic ducts in patients with chronic pancreatitis, coronal and axial MRCP with single-shot FSE or HASTE are obtained. For gadolinium-DTPA-enhanced MRI (0.1 mmol/kg body weight), triple phase, breath-hold, fat-suppressed, three-dimensional, fast SGE sequences are acquired. Fat-suppressed, high-resolution, T1-weighted images acquired 10 minutes after administration of mangafodipir trisodium (5 mol/kg, in a slow bolus over 1–2 min) are useful for lesion detection in equivocal cases. The basis for utilization of mangafodipir is that normal pancreatic parenchyma enhances following mangafodipir administration and becomes hyperintense on T1-weighted images, whereas tumors do not enhance. Use of mangafodipir for tumor detection is usually reserved for equivocal cases and differentiation from benign inflammatory masses of the pancreas.

MRCP with single breath-hold, thick (2–5 cm) section can provide excellent selective display of the whole extrahepatic biliary tract and pancreatic duct with no respiratory artifacts and few susceptibility artifacts. Some authors have stressed the value of secretin administration in improving pancreatic ductal details in MRCP. Exogenous administration of secretin stimulates secretion of pancreatic juice, notably fluid and bicarbonate, which consequently increases the volume of stationary fluid in the pancreatic ducts. Secretin (1 mL per 10 kg body weight) administration 10–15 minutes prior to MRCP improves pancreatic duct and side-branch delineation and permits evaluation of pancreatic flow dynamics and assessment of pancreatic exocrine function.

Normal anatomy and variants

On MRI, the normal pancreas has signal intensity similar to that of the liver. It has relatively high signal intensity compared with the liver on in-phase T1-weighted images. In opposed-phase T1 images, a hypointense rim surrounding the pancreas is observed due to etching artifact. On fat-suppressed images, the relative signal intensity of pancreas increases, thus facilitating detection of pathological conditions with decreased signal intensity. Being a highly vascular organ, the pancreas shows intense contrast enhancement in the arterial phase followed by rapid washout of contrast agent (Figure 148.15). This makes optimum arterial-phase imaging crucial for accurate detection of most focal pancreatic lesions, which usually enhance less than the normal parenchyma and hence are rendered more conspicuous.

The head and neck regions of pancreas reveal lateral contour anomalies in up to 35% of individuals, the most common of which is discrete lobulation of pancreatic tissue lateral to the gastroduodenal or anterior superior pancreaticoduodenal artery. Pancreas divisum results from failure of fusion of ventral and dorsal pancreatic buds [55]. In this anomaly, the dorsal pancreatic duct drains the neck, body, and tail regions through the minor papilla of duodenum, whereas the ventral pancreatic duct drains the head and uncinate process through the major papilla (Figure 148.16) [51]. Obstruction of the dorsal duct is associated with an increased incidence of pancreatitis. Bret and colleagues have reported an accuracy of 100% for MRCP in the
defined as focal or diffuse areas of nonviable parenchyma typically associated with peripancreatic fat necrosis. Acute fluid collections occur in about 50% of patients in the early course of the disease and contain enzyme-rich pancreatic juice. Encapsulated collections of pancreatic fluid called pseudocysts evolve from the persistent peripancreatic or intrahepatic fluid collections. Peripancreatic abscesses represent circumscribed pus collections that occur in areas of limited necrosis with secondary infections. The frequency of development of sepsis increases with time after onset of symptoms of pancreatitis. Infected necrosis is associated with high mortality and represents infected pancreatic or peripancreatic necrotic tissue.

CT is the imaging modality of choice for diagnosis and staging of suspected acute pancreatitis, follow-up evaluations, and guidance for percutaneous and surgical intervention. Some experimental and human studies have raised concerns about possible aggravation of pancreatic injury with the use of...
capillary blush in mild pancreatitis. More severe cases of pancreatitis are associated with variable diminution of signal intensity on T1-weighted fat-suppressed images and immediate postgadolinium GRE images (Figure 148.17) [3]. Nonenhancing pancreatic parenchyma suggests the possibility of necrosis or suppuration. MRI is at least as sensitive as CT in depiction of necrosis and peripancreatic fluid collections and is superior to CT in demonstration of the internal consistency and drain-ability of these collections. Some authors have recommended that predrainage MRI should be performed in patients with pancreatic collections to differentiate pancreatic abscess from pancreatic necrosis, which is not usually amenable to percutaneous management [56].

### Chronic pancreatitis

Chronic pancreatitis is an irreversible inflammatory disease of the pancreas characterized by replacement of glandular acini, ducts, and blood vessels by fibrous tissue that causes ductal strictures, obstruction, and dilatation leading to parenchymal atrophy and stone formation. Early changes of chronic pancreatitis are difficult to recognize with CT. MRI and MRCP have become widely accepted as the primary imaging modalities for the diagnosis of chronic pancreatitis [4]. Findings with MRI and MRCP include atrophy of the gland, changes in signal intensity of pancreatic parenchyma with reduced signal on T1-weighted images, irregular dilatation of the pancreatic duct, pancreatic calcification, and chronic pseudocysts [57]. Pancreatic parenchyma shows decreased signal intensity on T1-weighted fat-suppressed images attributed to fibrosis and reduced concentration of soluble proteins. On T2-weighted images, the signal intensity of the pancreas may be normal because of the presence of fibrosis with variable degrees of inflammation and residual pancreatic tissue (Figure 148.18) [57]. Differentiation between pseudotumorous lesions in cases of chronic pancreatitis and pancreatic carcinoma may be difficult due to similar mild contrast enhancement of focal lesions. However, MRI with mangafodipir may improve the detection rate and characterization of focal pancreatic lesions because of better delineation of the abnormal area. MRCP demonstrates pseudocyst in or near the pancreas and ductal abnormalities, including segmental dilatation, narrowing, ductal filling defects representing calculi, or mucinous casts in pancreatic ducts [58]. In some instances, the ductal communication of pseudocyst can be demonstrated with MRCP, which can frequently be difficult with ERCP. Studies have reported significant increase in pancreatic duct visibility after secretin injection ($P < 0.05$) [59]. These authors have also reported significantly higher fluid filling of the duodenum in healthy persons and in those with pancreas divisum compared with those with chronic pancreatitis or pancreatic tumors [59]. Focal pancreatitis has been reported to occur in 20% of patients and typically involves the pancreatic head. It often simulates pancreatic malignancy, and differentiation, though critical, is often difficult. Although signal intensity of chronic pancreatitis is decreased compared with the normal normal pancreatic parenchyma shows high signal intensity on T1-weighted fat-suppressed images and possesses a uniform

![Figure 148.16](image.png) (a) Axial T2-weighted image and (b) magnetic resonance cholangiopancreatography (MRCP) demonstrate pancreas divisum with primary draining pancreatic duct of Santorini (arrow) crossing the common bile duct (arrowhead) to empty via the minor ampulla.
PART 5 Diagnostic and therapeutic modalities in gastroenterology

with pancreatic exocrine dysfunction. In addition, pancreatic calcification and cystic and macrocystic pancreas may be seen on MRI.

Trauma
CT plays an important role in the detection and management of pancreatic trauma. Following injury, MRCP may show the duct disruption and associated fluid collections. MRCP offers a useful alternative to invasive ERCP in assessing delayed complications secondary to pancreatic duct injury [61].

Neoplasms

Adenocarcinoma
Pancreatic adenocarcinoma is the fourth most common tumor in the United States. About 90% of pancreatic tumors are ductal adenocarcinomas. Neuroendocrine tumors and acinar cell carcinomas constitute about 2%–5% of all pancreatic tumors. The major aims of imaging pancreatic malignancies are detection and staging, which determine the appropriate management options and ultimate prognosis of the disease. Most commonly, adenocarcinoma appears as a mass distorting the contour of the gland with associated findings such as dilated pancreatic duct...
and common bile duct, atrophy of the gland, vascular invasion, and metastases to regional nodes, liver, and peritoneal cavity. On MRI, T1-weighted spin-echo images with and without fat suppression and immediate postgadolinium SGE images have been found to be superior to spiral CT for detecting small lesions. Because of their scirrhous character from dense fibrotic tissue, pancreatic adeno-carcinomas are generally slightly hypointense relative to the pancreas on T2-weighted images but are difficult to visualize unless there is substantial necrosis [62]. Being relatively hypovascular, ductal adenocarcinomas enhance to a lesser extent than normal pancreatic tissue on early postcontrast images. Hence, they appear distinctly hypointense to the maximally enhanced pancreas during the arterial phase of dynamic contrast enhancement (Figure 148.19) [63]. A thin rim of greater enhancing pancreatic tissue is commonly observed in patients with pancreatic cancers and may help to establish the focal nature of the disease process. Normal pancreatic tissue becomes hyperintense on T1-weighted images after intravenous administration of the tissue-specific contrast agent mangafodipir trisodium [64–66]. Because pancreatic adenocarcinomas do not take up manganese, they are well delineated in the background of enhanced normal pancreatic parenchyma on T1-weighted fat-suppressed images. T1-weighted spin-echo imaging has been reported to be superior to dynamic contrast-enhanced CT for the determination of vascular encasement. Gadolinium-enhanced T1-weighted SGE is extremely useful for evaluating arterial and venous patency. Three-dimensional, contrast-enhanced dynamic MRA with fat suppression exquisite delineates vascular encasement or occlusion for the determination of nonresectability and regional vascular anatomy. MRCP features of pancreatic head adenocarcinoma include encasement and obstruction of the pancreatic duct or bile duct. Dilatation of biliary and pancreatic ducts (double-duct sign) occurs in 77% of cases of pancreatic head carcinoma, biliary duct dilatation occurs alone in 9%, and pancreatic duct dilatation in 12%. MRCP readily demonstrates this double-duct pattern of obstruction, strongly suggesting a pancreatic or ampullary carcinoma. When performed in conjunction with abdominal MRI, MRCP is useful in detecting pancreatic malignancies and in
establishing resectability and preventing unnecessary preoperative ERCP. In addition, MRCP is helpful in planning percutaneous biliary drainage and radiation therapy. Metastases to peripancreatic and paraaortic lymph nodes and the lymph nodes in mesenteric and celiac chains can be well depicted on T2-weighted, fat-suppressed, spin-echo images and gadolinium-enhanced, T1-weighted, fat-suppressed images. However, detection of small peripancreatic lymph nodes can be difficult on MRI. Gadolinium-enhanced MRI has greater accuracy for detection and characterization of liver metastasis compared with helical CT. MRI is more sensitive than helical CT in the detection of subcentimeter-sized liver metastases and visualization of peritoneal implants [63]. In patients with a focal pancreatic lesion there is a significant increase in contrast-to-noise ratio with mangafodipir-enhanced MRI without and with fat saturation [64]. Qualitative image analysis has also demonstrated a significant improvement of mangafodipir-enhanced fat-suppressed MRI in delineating pancreatic parenchyma \((P < 0.01)\) and pancreatic tumors \((P < 0.01)\). Romijn and colleagues have reported that MRI following mangafodipir trisodium administration provides better delineation of pancreatic tumors but does not significantly improve the detection rate and staging accuracy of focal pancreatic lesions over MRI without this contrast medium [65].

**Neuroendocrine tumors**

Pancreatic neuroendocrine tumors or islet cell tumors are believed to originate from the neuroendocrine cells of the pancreas [30,67]. They are uncommon, slow-growing pancreatic or peripancreatic masses that either result in symptomatic hormonal overproduction (functional) or show no clinical findings of hormone secretion (nonfunctional). On MRI islet tumors are well depicted, being hypointense relative to normal high-signal pancreatic parenchyma on pre contrast T1-weighted images and typically hypervascular following contrast enhancement (Figure 148.20) [30,67]. On fat-suppressed T2-weighted images, tumors may be high signal compared with adjacent pancreatic parenchyma. Lesions with increased fibrous component may be T2 hypointense or isointense to pancreas [30,67].

**Cystic tumors**

The differential diagnosis of cystic pancreatic lesions includes both congenital true cysts and acquired cysts. Congenital cysts include simple cysts, cysts associated with poly cystic disease of pancreas, or other disorders. Acquired cysts include pseudocysts, hydatid cysts, retention cysts, angiomatous cysts, and cystic neoplasms, that is serous cystadenoma, mucinous cystadenoma, mucinous cystadenocarcinoma, papillary cystic neoplasm, intraductal papillary mucinous neoplasm [IPMN], ductal adenocarcinoma with cystic necrosis, teratomatous cysts, cystic choriocarcinoma, and neuroendocrine cystic tumors of pancreas [68].

The most common types of cystic neoplasms of the pancreas are serous and mucinous tumors and IPMN [69]. Serous tumors
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Magnetic resonance imaging

shot, echo-train, spin-echo sequences. Cyst components are typically smaller than 1.5 cm. Tumor septa usually enhance minimally on early and late postgadolinium images. Delayed enhancement of the central scar may occasionally be observed. Mucinous cystic neoplasms are most often located in the body or tail of the pancreas and have a strong female predilection [70]. These lesions are unilocular or have larger internal (>1.5 cm) cystic components and have malignant potential. Mucinous cystadenoma and cystadenocarcinoma do not demonstrate a central scar.

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Figure 148.20 Pancreatic islet cell tumor. (a) Axial T2 image demonstrates high-T2 signal lesion in the body (arrow). Three-dimensional gradient echo (GRE) images (b) before contrast and (c) during arterial phase show prominent enhancement in the arterial phase characteristic of an islet cell tumor (arrow).

Figure 148.21 Pancreatic mucinous cystadenocarcinoma. (a) Axial T2 image demonstrates septated cystic lesion (arrow) in the tail of the pancreas with (b) internal nodular enhancement (arrowhead) consistent with mucinous cystadenocarcinoma.

are benign and typically contain more than six cysts that are smaller than 20 mm and which have a central stellate scar. These tumors usually occur between the ages of 34 and 88 years and have a strong female predilection. Accurate radiological diagnosis and differentiation from mucinous cystic tumors are crucial to avoid aggressive surgical intervention in the case of an asymptomatic serous cystadenoma, which has low malignant potential [69]. On MRI, serous cystadenoma appears as a well-defined lesion that does not show invasion of fat or adjacent organs. On T2-weighted images, the small cysts and intervening septations may look like a cluster of small grape-like hyperintense cysts, best depicted on breathing-independent, single-shot, echo-train, spin-echo sequences. Cyst components are typically smaller than 1.5 cm. Tumor septa usually enhance minimally on early and late postgadolinium images. Delayed enhancement of the central scar may occasionally be observed. Mucinous cystic neoplasms are most often located in the body or tail of the pancreas and have a strong female predilection [70]. These lesions are unilocular or have larger internal (>1.5 cm) cystic components and have malignant potential. Mucinous cystadenoma and cystadenocarcinoma do not demonstrate a central scar.
Lymphoma
Pancreatic lymphoma is almost invariably of the non-Hodgkin B-cell type and may be associated with concomitant infection with a retrovirus or Epstein–Barr virus (Burkitt lymphoma). It is usually associated with peripancreatic and retroperitoneal lymphadenopathy or splenic, hepatic, renal, and epidural space lesions. Presence of intact fat planes between the nodes and the pancreas, and anterior displacement of the pancreas help to distinguish peripancreatic lymphadenopathy from a primary neoplasm [75]. Diffuse pancreatic enlargement often noted in pancreatic lymphoma may be due to diffuse pancreatic tumor, tumor-induced pancreatitis, or pancreatitis associated with tumor lysis from chemotherapy. MRI demonstrates diffuse or focal pancreatic enlargement that is isointense to normal pancreatic parenchyma on T1- and T2-weighted images. Contrary to the enhancement of the normal pancreas after mangafodipir administration, these lesions do not show any uptake of mangafodipir [76].

Pancreatic metastases
The most common primary tumors that metastasize to the pancreas are from the lung, breast, kidney, and melanoma. There are three different patterns of pancreatic involvement, namely localized, multifocal, or diffuse enlargement. Pancreatic metastases should be suspected in the presence of multiple pancreatic masses in a patient with another known primary carcinoma. On MRI most pancreatic metastases appear hypointense on T1-weighted images and hyperintense on T2-weighted images [77]. The majority of metastases are hypointense to a background of high-signal pancreas on T1-weighted fat-suppressed images. Contrast-enhanced MRI may be useful in the evaluation of pancreatic metastases by showing features such as increased vascularity in the presence of a hypervascular primary malignancy [77].
Gallbladder

Magnetic resonance sequences used to evaluate the gallbladder are similar to other imaging protocols used in the abdomen, including axial T1-weighted breath-hold GRE chemical shift sequences, T2-weighted sequences, MRCP, and contrast-enhanced T1-weighted sequences. Both T2-weighted and MRCP sequences are essential in the evaluation of the gallbladder and surrounding structures. Gallstones are low signal intensity against the higher signal intensity of bile. Gallbladder wall edema and pericholecystic fluid are hyper-intense on both sequences because of their fluid content. Contrast-enhanced, breath-hold, fat-suppressed, T1-weighted sequences are used to evaluate the gallbladder and adjacent hepatic parenchyma. Dynamic gadolinium-enhanced MRI may also play a role in differentiating benign and malignant gallbladder masses based on early and delayed enhancement patterns [78]. Hepatocyte-specific T1-shortening agents such as mangafodipir trisodium have biliary excretion and can provide temporal information on hepatobiliary excretion (Figure 148.24). Lack of excretion into the gallbladder lumen implies cystic duct obstruction, which in conjunction with additional findings may be used to diagnose acute cholecystitis. The normal gallbladder contents show high signal intensity on T2- and heavily T2-weighted images (MRCP) because of static fluid content of bile. The T1-weighted signal intensity of bile varies depending on patient's fasting status, bile viscosity, and bile salt concentration. In the fasting state, 90% of water is removed from the bile with a resultant increase in concentration of phospholipids, cholesterol and bile salts. Concentrated bile can therefore be hyperintense to liver and fat on T1-weighted images due to T1 shortening [78].

Acute cholecystitis occurs when the outflow of bile is prevented by occlusion of the cystic duct, often by a gallstone impacted in the gallbladder neck or cystic duct. Although not used as a screening test for acute cholecystitis, MRI may be used for diagnosis in certain patients with a confusing clinical presentation or equivocal sonographic or cholescintigraphic findings. The presence of cholelithiasis, pericholecystic fluid in the absence of ascites, gallbladder thickening (<3 mm), and gallbladder edema on T2-weighted images suggest a diagnosis of acute cholecystitis. Gallbladder thickening and pericholecystic fluid in themselves are nonspecific findings and can also occur in the setting of hypoalbuminemia, hepatitis, chronic cholecystitis, cirrhosis, and renal disease. Contrast-enhanced MRI can help confirm a diagnosis of acute cholecystitis by showing hyperemia (>80% enhancement) of the gallbladder wall and transient hyperenhancement of the adjacent hepatic parenchyma (Figure 148.25) [79]. Pericholecystic enhancement is present in more than 70% of patients with acute cholecystitis and may extend into the medial segment of the left hepatic lobe. Pericholecystic enhancement is secondary to increased hepatic arterial flow in response to local inflammation of the gallbladder. The finding of segmental absence of mucosal enhancement on contrast-enhanced MRI suggests a diagnosis of complicating gangrene in patients with suspected acute cholecystitis [79,80]. Chronic cholecystitis can present as a small and irregularly shaped gallbladder with a thickened gallbladder wall. Fibrosis in the gallbladder wall shows delayed enhancement. The degree of wall enhancement is significantly lower than that present in acute cholecystitis [79].

Gallbladder adenomyomatosis is characterized by overgrowth of mucosa, hypertrophy of the muscularis layer, and
extension of mucosa into the thickened gallbladder wall, forming intramural diverticula known as Rokitansky–Aschoff sinuses. Adenomyomatosis is found incidentally in 20% of patients who have cholecystectomy. There are three subtypes: localized (usually in the gallbladder fundus), diffuse, and segmental (segmental stricture composed of a thickened wall that divides the gallbladder lumen into separate interconnecting compartments) [81]. The MRI diagnosis of adenomyomatosis is based on the demonstration of Rokitansky–Aschoff sinuses. The thickened gallbladder wall appears hypointense on T2-weighted images, while the intramural diverticula are revealed as discrete, linearly arranged, smoothly marginated, intramural cyst-like structures that are isointense to bile on T2-weighted images and MRCP. The appearance of the intramural cysts in a circumferential distribution has been described as the “pearl necklace” sign.

Gallbladder polyps are elevated lesions of the mucosal surface of the gallbladder wall and are often incidental findings on imaging evaluation of the abdomen. The majority of resected polyps are cholesterol polyps that have no malignant potential. Polyp size is a significant predictor of malignant potential, with a 40%–88% prevalence of malignancy in polyps larger than 10 mm. On MRI, polyps are discrete wall-based lesions that contrast against the high T2 signal of the adjacent bile. They enhance following contrast administration, best appreciated on fat-suppressed T1-weighted images. They are distinguished from stones because of their fixation to the gallbladder wall and their enhancement. Size greater than 10 mm, solitary polyp, age greater than 60 years, sessile morphology, coexistence of gallstones, and rapid growth increase the risk of polyps being malignant.

Gallbladder carcinoma is a rare but aggressive malignancy. It predominantly affects females (3:1 over males) and gallstones are present in 90% of patients with gallbladder cancer. Symptoms occur with advanced disease include anorexia, weight loss, jaundice, and abdominal pain. The most common mode of spread is direct invasion into the liver. Tumor can also directly invade the duodenum, colon, and pancreas. On MRI, the primary gallbladder cancer is hypointense to liver on T1-weighted images and slightly hyperintense to liver on T2-weighted images [82]. T2-weighted and MRCP images typically depict gallstones surrounded by a tumor mass. Direct liver invasion, when present, is typically an ill-defined mass in the adjacent hepatic parenchyma contiguous with the gallbladder mass (Figure 148.26). Dynamic contrast-enhanced MRI can demonstrate the margin of tumor extension, facilitating accurate staging. The identification of regional lymph nodes larger than 10 mm with ring-like or heterogeneous enhancement suggests lymphatic spread.

The gallbladder is very rarely the site of involvement by other malignancies. Metastatic breast or metastatic melanoma can occasionally involve the gallbladder, the latter being more frequent [83]. Primary non-Hodgkin lymphoma of the gallbladder is also very rare and has a very poor prognosis. This presents with diffuse thickening of the gallbladder wall with moderate enhancement.

**Magnetic resonance cholangiopancreatography (MRCP)**

In the initial evaluation of biliary and pancreatic disorders, MRCP has replaced the use of diagnostic ERCP at many institutions. This technique uses MRI to visualize stationary or slow-moving fluid, such as bile, displaying them as high signal intensity. Heavily T2-weighted sequences are generally used for MRCP with the single-shot, echo-train, spin-echo technique achieving the most widespread use. Because of the heavy T2 weighting of this sequence, signals from the fluid in the biliary system and pancreatic duct are hyperintense, whereas the signal of background tissue is rendered hypointense, enabling excellent depiction of the biliary system and pancreatic duct (see Figure 148.25). Acute cholecystitis. (a) Coronal T2 and (b) axial postcontrast images demonstrate thickening of the gallbladder wall (arrowheads) and mild pericholecystic edema consistent with acute cholecystitis.
be reviewed. However, it is not possible with these images to evaluate periductal structures, such as tumors, which may cause narrowing or obstruction of the ducts. Also, fluids with relatively short TE, such as concentrated bile or mucinous fluid, may produce very little signal with long effective TE sequences and obscure small bile ducts or mucinous lesions. To overcome those drawbacks of MRCP with long effective TE, an intermediate effective TE (80–100 ms) can be used. This produces images where not only all fluid including concentrated bile and mucinous fluid is bright, but also periductal structures are well depicted. This combination of MRCP with intermediate effective TE and ERCP-like images gives detailed evaluation of both intraductal and periductal structures. Studies show that MRCP is comparable with or more useful than other techniques, such as ultrasound, CT, and ERCP, for studying choledocholithiasis, malignant obstruction of the biliary or pancreatic ducts, congenital anomalies, and chronic pancreatitis [84]. MRCP is noninvasive and safe because it does not require anesthesia or injection of intraductal or intravenous contrast agent. Using current MRI systems, high-quality images can be obtained consistently. MRCP is also useful in patients after incomplete or unsuccessful ERCP. In some patients, such as those who have undergone surgery with biliary enteric anastomosis or Billroth II, it may not be possible to perform ERCP because of the anatomy, so MRCP is the modality of choice for evaluating these postsurgical patients. Unlike ERCP, MRCP produces images of the ducts in their natural state, because it does not involve distention of the ducts by injected contrast medium. ERCP cannot evaluate extra-ductal structures directly, whereas MRCP can be combined with conventional MRI for the evaluation of extraductal disease, such as tumors [59]. ERCP has advantages over MRCP, including the ability to perform direct therapeutic interventional procedures concurrently with diagnostic imaging. ERCP is generally a safe procedure, but is still associated with morbidity and even mortality. Also, technical failures occur in 5% to 10% of cases because of unsuccessful cannulation of the common bile duct (CBD) or pancreatic duct.

Benign cystic disease
MRCP is effective and comparable with ERCP for the evaluation of congenital cystic lesions of the bile duct. Also, the combination of MRCP and gadolinium-enhanced T1-weighted images is useful for diagnosing associated findings, such as gallstone disease and cancer. MRCP has been demonstrated to be effective in evaluating choledochal cyst (Figure 148.27), choledochocele, and Caroli disease.

**Congenital variants of the biliary system**
Anatomical variants of the cystic duct have received much attention because of the higher risk of complications during cholecystectomy. In one study, MRCP accurately demonstrated a range of variants, such as low cystic duct insertion, medial cystic duct insertion, parallel course of the cystic and hepatic ducts, and aberrant right hepatic duct [55].
dominant pancreatic duct running anteriorly to the CBD and draining into the minor papilla (see Figure 148.16). A study that evaluated 108 patients who underwent both ERCP and MRCP demonstrated exact correlation between the two techniques for the depiction and exclusion of pancreas divisum [55].

### Cholelithiasis
The primary imaging modality for cholelithiasis is sonography. However, MRCP is highly sensitive and accurate in diagnosing cholelithiasis and can outperform ultrasound and CT. The most reliable approach for detecting gallstones is with the use of single-shot T2-weighted sequences [85].

### Choledocholithiasis
Accurate diagnosis of stones in the biliary ducts is crucial because their presence is a difficult challenge for cholecystectomy. Ultrasound and CT show relatively low sensitivity and accuracy for the diagnosis of bile duct stones. ERCP is considered the gold standard procedure for the evaluation of the biliary system and has a major advantage over other imaging modalities because it can be used to perform therapeutic interventions and diagnosis [85]. However, the rate of failed ERCP is 5%–20% and there is risk of major complications, or death. MRCP has been shown to be an excellent method for detecting bile duct stones [86]. It is superior to CT or ultrasound and comparable or superior to ERCP in detecting bile duct stones. On thin-slice source images, stones appear as signal-void lesions, with stones as small as 2 mm being detected in dilated and nondilated ducts (Figure 148.28). On thick-slab images, large or medium-sized stones in normal-caliber ducts are easily detectable, but small stones that are completely surrounded by fluid may be obscured and difficult to detect because of volume-averaging effects [87]. There are several pitfalls and mimickers of stones with MRCP. Intraductal air bubbles (pneumobilia) may mimic the appearance of stones (Figure 148.29) [85,87]. An important differentiating feature from stones is that air bubble filling defects lie on the nondependent portion of the bile duct against the wall on axial images. Blood clots may appear indistinguishable from bile duct stones [88]. Other pitfalls that may mimic bile duct stones include tortuosity of the bile duct running in and out of the imaging plane, merging of the cystic duct into the CBD when observed en face on coronal images, which may result in a round hypo-intense focus, metallic clips, and extraductal compression from the right hepatic or gastroduodenal artery, which may result in a signal-void focus (Figure 148.30).

Correct diagnosis can usually be achieved by careful attention to the exact location of these foci and interpretation of thick-slab MRCP or MIP-reconstructed images in conjunction with the thin-slice source images [88].

### Primary sclerosing cholangitis
Primary sclerosing cholangitis is characterized by chronic fibrosing inflammation of the biliary system of unknown etiology.
The diagnosis of primary sclerosing cholangitis is made by cholangiographic findings supported by histological analysis of liver biopsies. Primary sclerosing cholangitis is characterized by multiple irregular strictures and saccular dilatations of the intrahepatic and extrahepatic bile ducts, producing a beaded appearance. The conventional imaging modality for the diagnosis of primary sclerosing cholangitis is ERCP. However, complications from ERCP may result in progression of cholestasis in patients with primary sclerosing cholangitis. MRCP has been shown to be useful for the diagnosis and follow-up of primary sclerosing cholangitis [89]. A study evaluating MRCP in patients with primary sclerosing cholangitis demonstrated a sensitivity of 85%–88% and specificity of 92%–97% [89]. However, diagnostic challenges remain. Subtle changes of mild primary sclerosing cholangitis may be difficult to detect by current MRI techniques, and cirrhosis may cause distortion of the intrahepatic bile ducts and mimic primary sclerosing cholangitis [90]. MRCP does provide visualization of bile ducts proximal to even severe stenoses, which may not be evaluable by ERCP. The characteristic feature of “beading” reflects intrahepatic ductal dilation with areas of dilation and stenosis (Figure 148.31).

**Postsurgical biliary complications**
The most common postsurgical biliary complication is benign biliary stricture. MRCP can visualize the biliary tree distal and
proximal to a high-grade stricture or complete obstruction. However, the bile ducts distal to a stenosis may be collapsed and nonvisualized on maximum intensity projection (MIP)-reconstructed images, leading to overestimation of the stricture. Thin-section source images must be used to evaluate the extent of high-grade stenoses, because even small amounts of fluid in collapsed ducts can be depicted on these images. Other postsurgical biliary complications include retained bile duct stones, biliary leak, and biliary fistula. These conditions can be evaluated effectively by MRCP. In patients with biliary-enteric anastomoses, it may be difficult or impossible to perform ERCP. On the other hand, MRCP is very effective in evaluating the anatomy of the anastomosis, strictures of the anastomosis, strictures of the biliary ducts, and biliary stones proximal to the anastomosis in up to 100% of patients. Thin-section source images should be examined thoroughly because the biliary-enteric anastomosis and stones may be obscured on thick-slab and MIP-reconstructed images by the high signal intensity of surrounding bile and bowel fluid. Also, metallic surgical clips and pneumobilia can also produce artifacts that should not be mistaken as stones or strictures.

**Chronic pancreatitis**

On ERCP, typical findings of chronic pancreatitis include dilatation, narrowing or stricture, or irregularity of the pancreatic duct. Prominent dilatation of side branches is a feature of chronic pancreatitis that helps distinguish this entity from obstructed pancreatic duct caused by pancreatic cancer (see Figure 148.18). A study evaluating 30 patients with chronic pancreatitis undergoing ERCP and MRCP demonstrated sensitivity and specificity of 91% and 92%, respectively, and excellent correlation between ERCP and MRCP was reported.

**Cholangiocarcinoma**

Cholangiocarcinoma can be classified into three types according to anatomical location: peripheral type, originating from
Peripheral bile ducts in the liver; hilar type (Klatskin tumor), originating from the confluence of the right and left hepatic ducts; and extrahepatic type, originating from the main hepatic ducts, common hepatic duct, or CBD. Ductal obstruction is observed in all patients with Klatskin tumor and extrahepatic cholangiocarcinoma. Evaluation of the level of obstruction is important for treatment. In a study evaluating malignant perihilar biliary obstruction in 40 patients including 26 Klatskin tumors, MRCP was as effective as ERCP in detecting the presence and the level of biliary obstruction (40 of 40 cases on MRCP and 38 of 38 cases on ERCP). On MRI, cholangiocarcinoma is poorly defined with low to intermediate signal on T2-weighted images and demonstrates delayed enhancement following contrast (Figure 148.32). ERCP may result in sepsis caused by failure to drain contrast from an obstructed biliary duct with stagnant bile colonized by bacteria; additionally, ERCP may be unable to provide sufficient biliary opacification to adequately evaluate the region of narrowing. However, MRCP can demonstrate the bile duct proximal to the obstructing site safely and efficiently. T1-weighted fat-suppressed SGE acquired 2–5 min after gadolinium administration is the most consistent technique for demonstrating cholangiocarcinoma, which appears as moderately enhancing tissue (Figure 148.32).

**Pancreatic cancer**

Typical pancreatographic features of pancreatic cancer include irregular narrowing or obstruction of the main pancreatic duct and dilatation proximal to the lesion. Pancreatic head tumors also result in obstruction of the CBD. MRCP is able to evaluate the pancreatic duct proximal to an obstructing site that ERCP may be unable to demonstrate. In a study evaluating 124 patients with suspicion of pancreatic cancer, MRCP was as effective as ERCP for the detection of the pancreatic cancer, with sensitivity and specificity of 84% and 97% respectively for MRCP, and 70% and 94% respectively for ERCP. As with other malignant tumors, when pancreatic ductal adenocarcinoma is suspected clinically routine MRI sequences are also performed. T1-weighted SGE acquired immediately after gadolinium administration is the most consistent technique for demonstrating pancreatic cancer (see Figure 148.32).

Another advance in MRCP is the use of contrast agents that are hepatocyte-selective and eliminated, at least in part, by the biliary system. With these agents and faster acquisition with thin-section, three-dimensional, T1-weighted images of the biliary system, demonstration of smaller intrahepatic biliary branches is feasible. This approach may facilitate detection of functional obstruction or bile duct leak or injury.

**Intestine**

MRI has had an increasing role in evaluating the bowel compared with CT and conventional barium studies. Traditionally motion of the bowel, caused by either respiratory motion or peristalsis, degraded the magnetic resonance images. Newer techniques such as single-shot FSE and three-dimensional volumetric gradient echo imaging have reduced these problems to some extent. Antiperistaltic agents are also helpful for reducing bowel-related motion artifacts. Now MRI has an increasing role in evaluating the small bowel and colon, particularly for judging the extent of wall involvement with various pathological processes. MRI has been shown to be valuable in assessing the severity and extent of ulcerative colitis and Crohn's disease [91,92] (Figure 148.33). MRI is useful for showing the extent of pelvic fistulae from any cause. T2-weighted images display the muscularis propria of the bowel as low signal intensity. Breaks in the muscularis due to fistulae are seen as discontinuities in this layer. Fistulae can be seen without the administration of contrast material. The high signal intensity of granulation tissue is seen surrounded by low signal intensity fibrosis (Figure 148.34).

Because of the intrinsic soft-tissue contrast of T2-weighted images, MRI is used for staging gastrointestinal tract tumors, particularly rectal carcinoma. With high resolution, layers of the rectal wall can be visualized discretely. The muscularis propria appears as low signal intensity, whereas the submucosa appears as higher signal intensity (Figure 148.35). MR is now routinely used to locally stage rectal carcinoma. MRI is also an excellent method for evaluating the pelvis in general and to determine the local extent of tumors.

In addition, MRI can be used to evaluate patients for recurrent tumor after surgery or after radiation therapy. Radiation edema and radiation fibrosis are differentiated from tumor on T2-weighted images and dynamic gadolinium-enhanced images. Fibrosis appears as low signal intensity on T2-weighted images. Recurrent tumor shows nodules of higher-signal tissue. Recurrent tumor enhances rapidly during dynamic injection of gadolinium, whereas postresection changes enhance more slowly.

**MR of the small bowel**

Imaging of the small bowel has changed dramatically in the past two decades [91–93]. Despite important recent advances in small-bowel endoscopy, radiologic imaging is important for patients suspected of having or with established small-bowel disease. Cross-sectional imaging techniques (CT and MRI), used to investigate both extraluminal abnormalities and intraluminal changes, have gradually replaced barium contrast examinations, which are, however, still used to examine early mucosal disease. MR imaging techniques detect endoluminal, mural and extramural enteric details and provide vascular and functional information. Two MR imaging based techniques are currently utilized: MR enteroclysis and MR enterography. In enteroclysis, enteric contrast material is administered through a nasoenteric tube, whereas in enterography, large volumes of enteric contrast material are administered orally. MR enteroclysis ensures consistently better luminal distention than does MR enterography in both the jejenum and the ileum and more...
Figure 148.32 Cholangiocarcinoma. Axial T2 image (a) and three-dimensional GRE images (b) before contrast, (c) during arterial phase, and (d) delayed post contrast demonstrate large central mass (arrow) which demonstrates delayed enhancement following contrast. There is mild peripheral intrahepatic biliary dilation (e) (arrowheads) secondary to obstruction.
allowing the diagnosis of early or subtle structural abnormalities and guiding treatment and decisions in patient care [91–93].

**MR colonography**

MR colonography was introduced after CT colonography. First reports described breath-hold, three-dimensional, GRE sequences that covered the entire enema-filled colon in the coronal plane. Air, carbon dioxide or liquid enemas may be used as colonic distention agents [94].

Three different liquid enema techniques are used: bright lumen, black lumen, and fecal tagging. Both bright and black lumen methods are used after bowel cleansing. The bright lumen is based on a gadolinium-water enema with a gadolinium concentration of at least 10 mmol/L (i.e., 40 mL of 0.5 mol/L gadolinium in 2 L of water) (Figure 148.36). Because of the lack of radiation, a MR fluoroscopy sequence can be applied to monitor filling of the colon. After complete filling, a thin-section, three-dimensional, T1-weighted SGE sequence (3.7/1.1;
flip angle 40°–50°) is performed. With this sequence, the lumen appears bright because of the presence of gadolinium, and polyps are visible as filling defects. A two-dimensional HASTE sequence can be used for delineation of the colonic wall. The black lumen technique is based on a water enema for luminal distention and an intravenous infusion of gadolinium for enhancement of the colonic wall (Figure 148.36). After complete filling, a three-dimensional T1-weighted SGE sequence is performed before and after the intravenous administration of gadolinium. The lumen appears dark with this T1-weighted sequence, and enhancement of the colonic wall and possible inflammatory changes and polyps can be seen. A combination of three-dimensional T1-weighted SGE sequence and balanced GRE sequence makes bright and black lumen colonography possible with one protocol. The fecal tagging technique is based on a diet that contains barium to give stools the same signal intensity as water on T1-weighted GRE images. Patients are instructed to avoid fiber-rich foods and foods with a high concentration of manganese, such as fruit and chocolate. MR colonography starts with filling of the colon with water [92,94]. Intravenous gadolinium is administered, and a three-dimensional T1-weighted SGE sequence is performed. The lumen appears black, and enhancement of the colonic wall and possible polyps are seen. In symptomatic patients, this new technique shows promising results for the detection of polyps equal to or larger than 1 cm in diameter. Its value in polyp detection still needs to be determined in large studies. MR colonography has high diagnostic accuracy for detecting Crohn’s disease activity and determining the extent and activity of the disease [95]. With the integration of 3.0-T MR colonography, fecal tagging, and parallel imaging into research and clinical settings, new MR colonography protocols must be optimized [96].

MRI of perianal fistula
MRI accurately demonstrates the anatomy of the perianal region. On CT the attenuation values for the sphincters, levator ani, fibrotic fistulous tracks, and active fistula are so similar that it is difficult to characterize these structures accurately, unless
the track contains gas or leaked contrast material. The MRI appearance of perianal fistula shows greater concordance with surgical findings than any other imaging evaluation. Many different MRI techniques have been described. MRI in the coronal and axial planes demonstrates fistulous tracks in relation to the sphincter complex, ischiorectal fossa, and levator ani. Imaging in the sagittal and oblique planes is helpful in selected cases such as anovaginal and presacral disease [97]. MRI using pelvic surface coil requires no patient preparation and is well tolerated. Use of endoanal coils was initially hoped to further improve the MRI evaluation of perianal fistula. However, this technique is poorly tolerated in symptomatic patients. Although it provides excellent anatomical detail of the anal sphincters, it fails to provide the overview required for surgical management. The anatomy of the perianal region is well demonstrated on coronal and axial T1-weighted images. In normal subjects, the internal and external sphincters are not separately resolved on MRI obtained with a pelvic surface coil, but the sphincter complex, ischiorectal fossae and levator sling are clearly seen. Unenhanced T1-weighted images provide an excellent anatomical overview of the sphincter complex, levator plate, and ischiorectal fossae. However, fistulous tracks, inflammation, and abscesses appear as areas of low to intermediate signal intensity and may not be distinguished from normal structures such as sphincters and levator ani muscles. On T2-weighted and STIR (short tau inversion recovery) images, pathological processes including fistulae, secondary tracks, and fluid collections are clearly depicted. They appear as areas of high signal intensity in contrast with the lower signal intensity of the sphincters, muscles, and fat (especially on STIR images). The only comparative study of imaging sequences suggested for use in this condition showed that STIR imaging has certain limitations [97]. In some cases, STIR imaging failed to demonstrate secondary tracks, and in others it did not reveal small residual abscesses within edematous inflammatory change [97]. Furthermore, spurious incidences of high signal intensity in inactive tracks were also observed. Fat-suppression techniques used with T2-weighted imaging have also been proposed. We use GRE, T1-weighted, dynamic, intravenous contrast-enhanced MRI combined with T2-weighted imaging to assess perianal fistulae and their complications. With use of this technique, active fistulous tracks, secondary ramifications, and abscesses are clearly demonstrated (see Figure 148.34). The walls of the tracks as well as the abscess cavities enhance. This breath-hold technique is rapid, noninvasive and well tolerated, a particular advantage in patients with acutely inflamed perianal regions.

In summary MRI has an established role in evaluating hepatic, biliary and pancreatic disease processes. It has an important role in staging rectal carcinoma, detecting anal abnormalities and complications related to small bowel involvement of Crohn's disease.

References are available at www.yamadagastro.com/textbook

Further reading

Introduction

Positron emission tomography (PET) is a nuclear medicine technique that allows noninvasive imaging of cellular structure and function utilizing tracers labeled with positron-emitting radioisotopes. This contrasts with other imaging modalities such as computed tomography (CT), and magnetic resonance imaging (MRI), which are based primarily on the evaluation of anatomic structure. Measurement of these physiologic parameters allows PET to delineate functional status and pathologic states, making it a vital tool to both clinicians and researchers.

PET scanners have also evolved during the last decade. PET-CT scanners, combining PET and CT, are now widely available in the clinic, providing both functional and anatomic information together. PET-MRI has also become available, and its clinical applications are being investigated. The principal clinical uses of PET in gastroenterology are in the area of oncology. However, other fields are emerging. Research applications in PET are developing rapidly, including new tracers based on peptides and antibodies to evaluate for disease presence and monitor treatment effect.

Basic principles

PET relies on the detection of ionizing radiation from a positron-emitting radioisotope in order to construct an image [1,2]. In contrast to CT where tissue density is measured via an externally applied x-ray beam, PET relies on tissue accumulation of a systemically administered radiotracer in order to create image contrast. When select proton-rich radionuclides decay, they emit a positron (also known as a positive electron or antielectron, notated $\beta^+ \text{ or } e^+$). This fleeting particle travels a short distance until colliding with an ambient electron in adjacent tissue in an event known as annihilation, during which the masses of the two particles are converted into electromagnetic energy released in the form of two photons ($\gamma$-rays). These photons travel in approximately opposite directions along a straight line and are subsequently detected by the PET scanner, thus allowing event localization, and image reconstruction. The signal intensity for any particular region of interest is proportional to the amount of positron-emitting radiotracer present in the tissue. Much like CT, computer-assisted image reconstruction can be used to convert axial data into a three-dimensional
image, or an alternate planar view (e.g. coronal, sagittal). PET is more sensitive than gamma cameras used in conventional “nuclear medicine” procedures and allows quantitative measurements of tissue concentration of radiotracers using appropriate attenuation correction based on concurrent CT information.

**PET scanners**

**Scanner basics**

As a respective radiotracer distributes throughout tissues of interest, positron emission and subsequent annihilation events ensue, generating photon pairs which are detected and processed to form a cross-sectional image. The fact that emitted photons travel in essentially opposite directions along a straight line enables triangulation of the location of the annihilation event in three-dimensional (3D) space, and forms the basis for PET detector design and arrangement (Figure 149.1).

Standard PET scanners are composed of thousands of pairs of photon detector elements oriented opposite each other around a field of view in which the patient is placed [3]. Annihilation events are registered by a process known as “coincidence detection”, whereby emitted photons must be detected nearly simultaneously by detector pairs along a straight line—a so-called line of response (LOR)—in order to be considered a true annihilation event. Current time windows range from 6–12 nanoseconds depending on the scintillation crystal type and emission angles can be up to ±0.25 degrees can be tolerated from the theoretical 180 degree line. Due to detector ring geometry as well as attenuation through scatter and absorption, non-paired photons are commonly detected by the PET scanner (a so-called “single event”). In fact, approximately 99% of photons registered by the detection crystals are rejected by the PET circuitry because they are not associated with a coincident photon and therefore are not considered representative of a true annihilation event. It is the remaining 1% of photons able to travel through surrounding tissue without attenuation and arrive at the detectors within the coincidence window that provide the data necessary to construct the ultimate PET image.

Of note, it is important to remember that the location of the annihilation event is not the same as the location of the positron emission, therefore error is inherently built into every measurement the scanner records. This is because positrons travel a certain distance after emission from the radionuclide prior to interacting with an ambient electron in an annihilation event. Positrons with higher energies tend to travel farther before annihilation and therefore possess a higher range uncertainty. For example, $^{18}$Fluorine emits positrons around 640 keV which travel about 2.4 mm in tissue, whereas those from $^{82}$Rubidium are emitted around 3.35 MeV and have a range up to 16 mm prior to annihilation. This variation in range uncertainty significantly effects radiotracer selection based on the needs of a particular scan, as well as scan resolution. The overall spatial resolution of PET is ultimately determined by several factors, including detector size, positron energy, and activity dosage. With the realities of range uncertainty, noncollinear annihilation, and attenuation present in all PET scans, the absolute spatial resolution of $^{18}$F-FDG PET can be around 1mm. However, practically in clinical imaging this is around 4 mm–6 mm.

Modern PET scanners utilize adjacent full ring multidetector arrays that axially surround the patient and utilize between 15 000–25 000 detector crystals to collect and process emitted photons. Classically in two-dimensional (2D) PET, crystals from

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**Figure 149.1** Schematic showing PET scanner ring comprised of detector pairs (A, B, C) accepting collinear photons emitted from annihilation events resultant from positron emission in a tumor (blue pentagon) within the subject of interest (tan rectangle).
individual rings collect data to create cross sectional images. These axial images are then combined after acquisition to create a 3D reconstruction. In 3D (volumetric) PET, coincidences between multiple detector rings are recorded, thus increasing the volume of data acquired as well as scan sensitivity. However, up to 60% of this amplified count rate is due to random scatter, thus increasing image noise and decreasing contrast [4]. Utilizing 3D PET in low-scatter studies (e.g. brain), smaller patients, and in cases in which lower activity doses are necessary decreases this effect and takes advantage of the benefits of 3D PET while minimizing its limitations. Using the current generation of PET-CT scanners, 3D acquisition is often a standard practice.

**PET-CT and attenuation correction**

First proposed in the early 1990s and implemented clinically in the early 2000s, combination PET-CT hybrid machines were quickly recognized to possess significant advantages over nonhybrid systems [5,6]. The ability to merge the functional data of PET with the high-resolution anatomic detail of CT provided invaluable data to physicians and surgeons. An additional advantage of these systems is the capability of the CT system to concurrently attenuate PET data. Raw PET images suffer from attenuation, a phenomenon whereby photons emitted from within deeper structures are dampened and scattered more than photons emitted from superficial structures. Traditionally, attenuation was mathematically corrected using an attenuation map generated by a positron source (68Ge) within the PET scanner. However, the CT component of a PET/CT scanner can now produce a faster and more reliable attenuation map for PET data correction without an additional positron emitter, further substantiating the utility of hybrid systems. Today, essentially all modern clinical PET scanners are manufactured as combined PET/CT systems.

**Time of flight PET**

An inherent limitation of traditional PET technology is its inability to determine the exact point along an LOR from where a particular photon originated, leading to increased noise and decreased image resolution [7]. Unless an annihilation event occurs at the exact center of the detector ring, the arrival times of coincident photons will be slightly different. Modern time of flight (TOF) PET is able to measure minute differences in photon arrival time in the range of 500 ps to 600 ps, allowing independent measurement of each coincident photon and backcalculation of the annihilation event’s location, thereby providing better tumor localization and overall resolution. TOF PET is expected to improve as faster scintillators are developed, with next-generation TOF PET scanners possessing resolution times around 200 ps to 300 ps, allowing theoretical image resolution in the sub-centimeter range [8].

**PET-MRI**

The idea of combining PET and MRI arose as early as PET-CT, however technical limitations slowed development [9]. Placement of PET components inside a strong magnetic field and making these components invisible to the MRI while operating both simultaneously has proven difficult, with the first preclinical scanner only described in 2008 [10]. However, since that time companies have developed additional prototype PET-MRI scanners for the evaluation of new hardware, multimodality imaging protocols, and new MRI-based PET attenuation correction [11–13]. PET-MRI was FDA approved in 2011, and the following year the first clinical scanners were introduced into select academic centers where clinical applications are being studied. The superb tissue resolution of MRI combined with the biologic data of PET offers many advantages over current hybrid imaging, virtually ensuring its development and clinical expansion in the coming years.

**PET radiotracers**

PET radiotracers are molecules that are labeled with radionuclides that emit positrons. A host of suitable radionuclides exist for use as PET radiotracers (Table 149.1). The positron-emitting isotopes 11Carbon, 13Nitrogen, and 18Oxygen can be substituted for their respective nonradioactive isotopes in a process called “isotopic labeling” [14]. 11C-methionine, 13N-ammonia, and 18O-water are commonly used PET tracers that utilize this class of radionuclides. Positron-emitting isotopes of halogens, most notably 18Fluorine, can be substituted for a hydroxyl group on any biologic compound in a process known as “analogical labeling” [14]. The most common PET radiotracer employing this technique is the glucose analogue 2-deoxy-2-[18F]fluoro-D-glucose (18F-fluorodeoxyglucose, or 18F-FDG), which is widely used in clinical PET imaging. In the research setting, radionuclides like 124Iodine and 89Zirconium have been conjugated to biologic targeting moieties (e.g. antibody or aptamer) in an

<table>
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<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Positron decay (%)</th>
<th>Daughter atom</th>
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</thead>
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<tr>
<td>11C</td>
<td>20.4min</td>
<td>99.8</td>
<td>11B</td>
</tr>
<tr>
<td>13N</td>
<td>9.96min</td>
<td>100</td>
<td>13C</td>
</tr>
<tr>
<td>18O</td>
<td>2.07min</td>
<td>99.9</td>
<td>18N</td>
</tr>
<tr>
<td>18F</td>
<td>109.7min</td>
<td>96.9</td>
<td>18O</td>
</tr>
<tr>
<td>64Cu</td>
<td>12.7 hours</td>
<td>19</td>
<td>64Ni</td>
</tr>
<tr>
<td>68Ga</td>
<td>68.1min</td>
<td>90</td>
<td>68N</td>
</tr>
<tr>
<td>78Br</td>
<td>101min</td>
<td>76</td>
<td>78Se</td>
</tr>
<tr>
<td>82Rb</td>
<td>1.27min</td>
<td>96</td>
<td>82Kr</td>
</tr>
<tr>
<td>89Zr</td>
<td>78.4 hours</td>
<td>22</td>
<td>89Y</td>
</tr>
<tr>
<td>124I</td>
<td>100.2 hours</td>
<td>23</td>
<td>124Te</td>
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approach known as “immuno-PET” in order to localize target tissues.

Radionuclides vary widely in chemical reactivity and half-life depending on their intended use. Most PET radiotracers have a relatively short half-life and high tissue specificity, allowing for minimal tracer doses and consequent radiation exposure. However, some longer half-life radioisotopes must be used when imaging slower physiologic processes or when the tracer requires time to accumulate in target tissue. Synthesis of PET radiotracers involve two main components: (1) production of the positron emitter, and (2) incorporation of the radionuclide into a molecule of choice. Positron-emitters are generated in accelerators, commonly small medical cyclotrons, at commercial and research facilities [15]. Cyclotron beams are used to bombard specific atoms in order to create a PET radioisotope, which must then be incorporated into a radiotracer. Given the options afforded with isotopic, analogic, and chelator-based synthesis, there are theoretically an unlimited number of PET radiotracers that can be formed. Simple molecules to measure blood volume and blood flow, amino acids to study protein synthesis, fatty acids and sugars to study metabolic pathways, ligands to map receptor distribution, and antibodies to identify membrane targets, are just a few of the hundreds of examples of tracers that have been utilized both clinically and in the research setting. Short half-life radiotracers like 18O-water necessitate on-site synthesis and limit their use to highly specialized centers. By comparison the most commonly used PET radiotracer, 18F-FDG, has a much longer half-life enabling its production at regional facilities which then manage distribution to clinical sites typically through commercial suppliers. Certain radionuclides like 123I and 89Zr possess half-lives on the order of days, allowing for synthesis and distribution by a handful of national centers. Once a radionuclide is obtained, it must be quickly incorporated into a tracer as a purified, sterile, isotonic, pyrogen-free solution [14]. Because of the many types of specialized expertise including physics, chemistry, computer science, imaging, and medicine, a collaborative team with diverse expertise is needed in order to develop and maintain an active PET program.

2-Deoxy-2-[18F]fluoro-D-glucose (FDG)

18F-FDG is by far the most clinically prevalent PET radiotracer, currently used in over 95% of scans [16]. The tracer's utility in oncology derives from the high utilization of glucose by many solid tumors [17], as well as the structural similarities between glucose and 18F-FDG [3,18]. Cellular glucose transport and utilization is highly complex and has been the subject of a great deal of research. Briefly, after cells take up glucose and 18F-FDG via specific membrane-bound transporters, both undergo phosphorylation by hexokinase in the cytoplasm to yield glucose-6-phosphate which continues down the glycolytic pathway in order to provide the cell with energy. However, due to its modification fluorodeoxyglucose-6-phosphate is unable to be metabolized further, thus causing it to accumulate in the cell. This accumulation, along with subsequent radioisotope decay and annihilation events, allows 18F-FDG to create PET contrast between high glucose-utilizing malignant cells and the surrounding tissue to produce a clinically relevant image. This basic principle has made 18F-FDG PET an integral tool in modern cancer staging and detection.

Clinical applications of PET in gastroenterology

Since its initial development in the 1950s, PET image quality and reliability have vastly improved. While dozens of applications for PET have been explored over the decades, the greatest advances have occurred in the characterization and localization of solid tumors. Regarding gastrointestinal cancers, the United States Health Care Financing Administration (HCFA), now the Centers for Medicare and Medicaid Services, or CMS, first announced Medicare coverage in 1999 for 18F-FDG PET in the evaluation of patients with colorectal cancer and rising carcinoembryonic antigen (CEA) levels. In December 2000, HCFA issued a decision memorandum broadening the indications for 18F-FDG PET covered by Medicare to include diagnosis, staging and restaging of nonsmall cell lung cancer, colorectal cancer, esophageal cancer, lymphoma, melanoma, and head and neck (excluding thyroid and brain) cancers; myocardial viability studies; and presurgical evaluation of refractory seizures [19]. A subsequent survey of 22 institutions found no adverse reactions in over 80,000 positron-emitting radiopharmaceutical administrations, highlighting the safety of PET [20]. As of 2009, evaluation of head and neck cancers, esophageal cancer, colorectal cancer, nonsmall cell lung cancer, melanoma, breast cancer, lymphoma, cervical cancer, thyroid cancer, and indeterminate solitary pulmonary nodule are covered by CMS reimbursement for diagnosis, staging, restaging, or monitoring [7]. CMS recently eased restrictions on radionuclide approval and thereby encouraged further PET development by relinquishing Medicare coverage determinations for new FDA-approved radiopharmaceuticals to local jurisdictions when national coverage determinations are not present [21]. It has also eliminated a previous restriction of only one PET scan for planning an initial treatment strategy in patients with suspected malignancy.

In the treatment of solid tumors, a lesion's location relative to other anatomic structures is critical information on which a therapeutic plan is based. As PET images are dependent upon relatively specific radiotracer uptake in tumor tissue, PET in isolation cannot reliably give the clinician necessary information about extent of disease or involvement of adjacent structures. A major advance over the past decade has been the development of combined PET/CT and PET/MRI scanners, which can simultaneously provide both functional and anatomical imaging [5,22,23], with performance that is superior to
PART 5 Diagnostic and therapeutic modalities in gastroenterology

Recent studies have focused on the added value of dual imaging modalities.

In suspected metastatic or recurrent colorectal cancer, the reported sensitivity of whole-body or local/pelvic 18F-FDG PET is 87% to 100%, and specificity is 67% to 100% [32–43]. Values for local/pelvic disease are equivalent or superior (sensitivity 95% [Confidence interval [CI], 91% to 98%], and specificity 98% [CI, 96% to 99.7%]). For hepatic involvement, estimated sensitivity and specificity are even higher at 96% (CI, 94% to 99%), and 99% (CI, 98% to 100%), respectively, and 18F-FDG PET has out-performed CT (sensitivity 65% to 89%, specificity 62% to 89%) in all major studies comparing the two modalities [32,35,37,44]. While MRI does appear to add value over CT alone, PET is still the most sensitive of the technologies in the detection of recurrent disease. A meta-analysis and large systematic review reported per-patient sensitivities for nonhelical CT, helical CT, MRI, and 18F-FDG PET of 60%, 65%, 76%, and 95%, respectively [44] and superior sensitivity and specificity for 18F-FDG PET in both intra- and extrahepatic disease [45].

Colorectal cancer

Increased 18F-FDG avidity in hepatic metastases from colorectal cancer was demonstrated at a very early stage in PET technology development [29]. Later studies suggested that 18F-FDG PET could be useful in differentiating recurrent rectal cancer from surgical scar or a nonmalignant mass due to its increased glycolytic activity [30,31]. Subsequently, other indications for 18F-FDG PET have been investigated including the evaluation of patients with suspected colorectal cancer recurrence, preoperative staging of patients with known recurrence, and in staging of primary disease (Figure 149.2). Recent studies have focused on added value of dual imaging modalities.

In suspected metastatic or recurrent colorectal cancer, the reported sensitivity of whole-body or local/pelvic 18F-FDG PET is 87% to 100%, and specificity is 67% to 100% [32–43]. Values for local/pelvic disease are equivalent or superior (sensitivity 95% [Confidence interval [CI], 91% to 98%], and specificity 98% [CI, 96% to 99.7%]). For hepatic involvement, estimated sensitivity and specificity are even higher at 96% (CI, 94% to 99%), and 99% (CI, 98% to 100%), respectively, and 18F-FDG PET has out-performed CT (sensitivity 65% to 89%, specificity 62% to 89%) in all major studies comparing the two modalities [32,35,37,44]. While MRI does appear to add value over CT alone, PET is still the most sensitive of the technologies in the detection of recurrent disease. A meta-analysis and large systematic review reported per-patient sensitivities for nonhelical CT, helical CT, MRI, and 18F-FDG PET of 60%, 65%, 76%, and 95%, respectively [44] and superior sensitivity and specificity for 18F-FDG PET in both intra- and extrahepatic disease [45].
18F-FDG PET has repeatedly validated its performance through both qualitative and semi-quantitative analytic methodologies, such as the standardized uptake value (SUV), or SUV corrected for lean body mass (SUL) [46], which normalizes signal intensity by radioactive dose injected, body weight, and the target-to-background ratio, which compares signal intensity within and outside a region of interest [33,34,39,40].

18F-FDG PET/CT performed better than 18F-FDG PET alone in detecting recurrent colorectal cancer, with sensitivity of 89%, specificity of 92%, and overall accuracy of 90%, compared with 80%, 69%, and 75%, respectively [47]. This advantage also extends to the detection of recurrent rectal cancer after abdominoperineal resection [48]. If a dual-modality study is obtained, dedicated interpretation of the CT portion of the 18F-FDG PET/CT scan improves overall performance (sensitivity, specificity, and accuracy of 99%, 100%, and 98% compared with 91%, 63%, and 83% for the PET/CT report alone; P < 0.05) [49].

After a patient has undergone initial treatment, recurrence may be suspected on the basis of symptomatology, physical findings, rising CEA levels, or anatomical imaging studies. In a study of 22 patients with previous colorectal cancer resection who had abnormal CEA but normal anatomical imaging studies, 15 patients were ultimately considered to have recurrent disease. 18F-FDG PET detected abnormalities in 17 patients, including the 15 with proven recurrence, yielding a positive predictive value of 89% and a negative predictive value of 100% [41]. Furthermore, 18F-FDG PET may predict which patients with abnormal CEA might benefit from laparotomy [50]. It may help triage patients with CEA elevations under 25 ng/mL into potentially resectable and unresectable subgroups, while primarily confirming advanced disease in those with higher CEA levels [51]. If not performed concurrently with CT, 18F-FDG PET can still provide additional value for patients both with and without inconclusive findings on traditional imaging. The additional value of 18F-FDG PET was examined in 103 patients with suspected or proven colorectal cancer recurrence who separately underwent conventional imaging including CT [42]. In 12 of 60 patients considered to have resectable disease on conventional imaging, 18F-FDG PET detected additional disease in nine and excluded disease in three, yielding additional diagnostic value in 20%. In 13 patients with inconclusive conventional imaging or isolated elevated CEA, 18F-FDG PET was of additional diagnostic value in 62%.

Accurate presurgical staging is essential in determining a patient's eligibility for resection of both primary and metastatic lesions. 18F-FDG PET helps delineate intra- and extrarectal disease not detected by conventional imaging [52,53]. However, a study directly comparing 18F-FDG PET results with surgical resection specimens found that performance was highly dependent on tumor size, preoperatively identifying only 25% of hepatic lesions smaller than 1 cm, compared with 85% of lesions larger than 1 cm [54]. A prospective evaluation of 53 patients with potentially resectable hepatic metastases revealed comparable sensitivities (75% vs 76%), and accuracies (88% vs 86%) for 18F-FDG PET versus CT, with 18F-FDG PET providing additional information in around 10% of patients [55]. This is comparable to the 11% reported in an earlier study [56].

As of the writing of this text, only one study has assessed 18F-FDG PET in the staging of primary colorectal cancer [57]. The sensitivity and specificity of 18F-FDG PET for the primary tumor were 100% and 43% respectively. For liver metastases, the sensitivity and specificity were 88% and 100%, compared with 38% and 97% for CT. When looking for lymph node metastases, the sensitivity and specificity of 18F-FDG PET were 29% and 96%, compared with 29% and 85% for CT. A more recent study found the accuracy of 18F-FDG PET for tumor, nodal, and metastatic staging to be 82%, 66%, and 89% respectively, compared with 77%, 60%, and 69% for helical CT [58]. Thus, the utility of 18F-FDG PET appears greater in detecting distant metastases than evaluating the primary tumor or local nodal basin. Whole-body 18F-FDG PET/CT colonography has also been proposed for initial staging of patients with colorectal cancer [59], but at this time is not widely used clinically.

When investigating its role in detecting premalignant lesions, van Kouwen and colleagues reported increasing sensitivity of 18F-FDG PET for colorectal adenomas as a function of size, for example: 21% for 1 mm to 5 mm versus 72% for >11 mm, and grade of dysplasia for example 33% for low-grade versus 76% for high-grade dysplasia versus 89% for carcinoma [60]. Others have reported limited sensitivity of 18F-FDG PET for premalignant lesions and cancers under 2 cm [61].

While 18F-FDG PET has demonstrated utility in multiple clinical studies, its ultimate value lies in affecting patient outcomes. Several investigators have reported on the impact of 18F-FDG PET on medical decision-making. In a meta-analysis by Huebner and colleagues, it was estimated that 18F-FDG PET affected management in 29% (95% CI, 25% to 34%) of patients undergoing evaluation for recurrent colorectal cancer [62]. Subsequent studies have reported similar results, with 18F-FDG PET affecting management in 23% of patients undergoing presurgical evaluation of hepatic metastases [40], 20% to 61% of patients suspected of having metastatic or recurrent colorectal cancer [28,46—49], and 17% of patients with primary rectal cancer [63]. In a study of 76 patients, 18F-FDG PET/CT and contrast-enhanced CT provided similar information about hepatic metastases, whereas PET/CT was superior in detecting recurrent intrahepatic tumors after hepatectomy, extrarectal metastases, and local recurrence, in total affecting management in 21% of cases [64]. 18F-FDG PET was more accurate than conventional imaging tests in predicting the resectability of recurrent disease (82% vs 68%; P = 0.02) [65]. In a systematic review, Wiering and colleagues reported a change in management due to 18F-FDG PET in 32% of patients, but a slightly lower 25% when only the highest quality studies were considered [45]. 18F-FDG PET/CT was reported to affect patient management in 7 of 23 patients with suspected hepatic metastases or recurrent disease [66]. More important than any impact on decision making is the observation that patients who underwent
hepatic resection for metastases after staging with $^{18}$F-FDG PET had a 5 year actuarial survival of 58% compared with a median of 30% in historic controls without preoperative PET examination [67], though this gap may have closed in recent years due to improvements in therapy.

The ability to monitor response to systemic therapies is another clinically relevant use for $^{18}$F-FDG PET. Decreases in $^{18}$F-FDG uptake after chemotherapy have been shown to correlate with response to chemotherapy [68,69]. This prognostic value is likely highest in patients with locally advanced rectal cancer, where an immediate postchemotherapy decrease in maximum tumor SUV has shown to be able to distinguish treatment responders from nonresponders with sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of greater than 80% [70–72]. In contrast, because reactive inflammatory tissue is also $^{18}$F-FDG-avid, PET may not be able to accurately assess the response to radiation therapy in the short-term [73,74]. However, one pilot study has suggested that $^{18}$F-FDG PET might be of incremental value in selecting patients with rectal cancer for sphincter-preserving surgery after preoperative radiation and chemotherapy [71]. $^{18}$F-FDG PET may be useful in predicting the response of liver metastases to treatment with bevacizumab and irinotecan [75].

In patients with unresectable liver metastases, PET has been performed with $^{18}$F-fluorouracil before 5-fluorouracil chemotherapy to determine its potential role in predicting prognosis [76]. Overall, patients with higher values for $^{18}$F-fluorouracil uptake were more likely to achieve stabilization of disease with chemotherapy, but trapping of $^{18}$F-fluorouracil varied among metastases even within the same patient. Quantitative modeling of $^{18}$F-fluorouracil uptake has been investigated as a way to optimize treatment schedules for individual patients [77]. Specific kinetic parameters of $^{18}$F-FDG PET may be useful in determining prognosis with 5-fluorouracil/folinic acid/oxaliplatin chemotherapy [78].

**Esophageal cancer**

Multiple studies have compared $^{18}$F-FDG PET and CT for staging of esophageal cancer [79–83]. The specificity of the two tests appears to be comparable in the evaluation of nodal disease (PET 79% to 94%, CT 73% to 100%), while the sensitivity of $^{18}$F-FDG PET appears to be superior (PET 69% to 92%, CT 28% to 46%). As with colorectal carcinoma, size appears to be a critical factor for the test’s sensitivity. In an initial study by Flamen et al. [84], $^{18}$F-FDG PET was able to detect 70 out of 74 esophageal lesions, failing to detect four T1 lesions all measuring less than 8 mm. In a prospective series of 81 patients who underwent $^{18}$F-FDG PET and then surgical resection, 43% of pT1 were identified. Sensitivity increased with the depth of tumor invasion, and was 83% at pT2, 97% at pT3, and 100% at pT4 [85]. For both $^{18}$F-FDG PET and CT, detecting local nodal involvement is problematic. In one study, the overall accuracy in determining resectability was 88% for $^{18}$F-FDG PET, and 65% for CT (P = 0.04), but neither modality could assess the extent of wall invasion [81]. Differences in accuracy of similar magnitude have been found in other studies [79,80,83]. However, in a prospective study of 58 patients comparing CT and $^{18}$F-FDG PET in the evaluation of abdominal lymph node metastases, the investigators observed a sensitivity of only 34% for PET and 75% for CT. Evaluation of intrathoracic lymph nodes yielded a slightly improved yet still inferior (42% vs. 75%) sensitivity [86].

As with colorectal cancer staging, an important contribution of $^{18}$F-FDG PET appears to be its ability to detect distant metastases not visible on anatomical imaging, thus altering management (Figure 149.3). Flamen et al. [84] reported superior accuracy for the detection of metastatic disease when compared with combined CT/EUS (82% vs. 64%) due largely to PET’s notably higher sensitivity (74% vs. 47%). Additional diagnostic value was afforded to 22% of patients, with up-staging in 15% and down-staging in 7% [84]. Of note, upstaging was from M0 to M1 disease, thus preventing unnecessary surgery in these patients. Heeren et al. [87] reported PET accuracy at 86% compared to CT/EUS at 69%, with PET upstaging 20% of patients to M1 disease. PET/CT delineated tumor better than CT alone in another study, contributing to radiotherapy treatment planning [88].

Differences in survival have been reported based on stratification by initial $^{18}$F-FDG PET result [80]. Survival at 30 months was 60% in patients with localized disease compared with 20% in patients with distant disease (P = 0.01), suggesting that $^{18}$F-FDG PET results may be of prognostic value. The number of PET abnormalities at baseline is an independent predictor of survival [89]. Serial $^{18}$F-FDG PET appears to have a strong correlation with pathological response to neoadjuvant chemoradiation therapy in locally advanced esophageal cancer, with PET major responders surviving a median of 16.3 months compared with 4 months for PET nonmajor responders [90].

Many studies have evaluated the relationship between SUV intensity and overall survival. In a systematic review of 12 studies, all demonstrated a higher primary tumor maximum SUV was associated with increased mortality, though only seven studies reached statistical significance [91]. Due to its correlation with pathologic stage, maximum SUV’s effect on survival is likely confounded by tumor size. In several smaller studies, peak SUV was associated with survival in univariate, but not multivariate analysis controlling for pathologic stage [92,93]. However, in a retrospective study of 184 patients with predominantly (91%) squamous cell carcinoma, maximum SUV remained independently and significantly associated with overall survival, even when controlling for pathologic stage (5 year survival SUV$_{\text{max}} \geq 4.5$ was 47% vs. 76% in those with SUV$_{\text{max}} \leq 4.5$) [94]. Interestingly, in a similarly sized retrospective study of 189 patients with esophageal adenocarcinoma who underwent chemoradiation as primary treatment, maximum SUV did not independently predict survival [95].
SUV ≥ 4.0 had an overall survival of only 7 months, compared to 32 months in the lower SUV subgroup. This result was confirmed in multivariate analysis to be an independent predictor of survival and was in agreement with other published results [108].

Two important factors may affect the results of \( ^{18} \)F-FDG PET in pancreatic imaging. First, hyperglycemia can result in false-negative studies in pancreatic cancer [96,109]. The cancer itself may cause endocrine insufficiency, and hyperglycemia results in greater competition between glucose and \( ^{18} \)F-FDG for uptake into cells. In patients with normal serum glucose, the sensitivity and specificity of \( ^{18} \)F-FDG PET in diagnosing pancreatic cancer were reported as 98% and 84%, compared with 63% and 86% in hyperglycemic patients [96]. Second, inflammation can induce \( ^{18} \)F-FDG uptake as intense as that seen in tumor, either in the setting of pancreatic masses without clear evidence of acute pancreatitis, or during and after attacks of acute pancreatitis [110]. If serum C-reactive protein levels are elevated, the specificity of PET may fall to 50% [110].

Multiple imaging modalities can be used in evaluating patients with suspected pancreatic malignancy. One study reported sensitivity and specificity for four different modalities in patients with suspected pancreatic cancer: 94% and 82% for \( ^{18} \)F-FDG PET, 89% and 73% for CT, 97% and 64% for EUS, and 89% and 45% for abdominal ultrasound [102]. Subsequent

**Pancreatic cancer**

The initial HCFA decision memorandum in December of 2000 did not include pancreatic imaging as an approved indication for \( ^{18} \)F-FDG PET under Medicare. However, pancreatic imaging is considered a recognized application of \( ^{18} \)F-FDG PET by some experts [53] and was eligible for National Oncology PET Registry (NOPR) coverage as of 2006. Various studies have evaluated \( ^{18} \)F-FDG PET in the diagnosis of pancreatic cancer and its differentiation from chronic pancreatitis [96–104]. The reported sensitivity of PET in this setting is 85% to 96% with specificity of 78% to 100%, compared with 65% to 89% and 62% to 89% for CT. \( ^{18} \)F-FDG PET may be useful in assessing pancreatic masses that are indeterminate for malignancy on conventional imaging, with sensitivity of 68% to 96% and specificity of 78% to 100% [105]. Beyond visual interpretation of images, semi-quantitative analysis has demonstrated differences between signal intensity, such as SUV, in tumor and chronic pancreatitis [98,100,103,104,106]. In one study, \( ^{18} \)F-FDG PET suggested potential alterations in clinical management in 43% of patients [99]. However, it is not the preferred modality in primarily staging extent of invasion or local-regional involvement, as CT/EUS have superior spatial resolution. \( ^{18} \)F-FDG PET has demonstrated its use in prognosticating pancreatic cancer outcomes. Sperti et al. [107] reported that patients with an SUV ≥ 4.0 had an overall survival of only 7 months, compared to 32 months in the lower SUV subgroup. This result was confirmed in multivariate analysis to be an independent predictor of survival and was in agreement with other published results [108].

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**Figure 149.3** \( ^{18} \)F-Fluorodeoxyglucose positron emission tomography (\( ^{18} \)F-FDG-PET)/computer tomography (CT) staging of gastroesophageal (GE) junction adenocarcinoma. Coronal \( ^{18} \)F-FDG-PET scan (a) and corresponding fused images (b) demonstrate primary cancer at the GE junction (arrowhead in a and b) and hypermetabolic gastrohepatic ligament lymph nodes (arrow in a and b). (c) \( ^{18} \)F-FDG PET fused images demonstrate one metastatic bony lesion at T3 vertebra (arrow in c), (d) one subcutaneous metastatic lesion in the right upper quadrant (arrow in d), (e) and one suspicious intramuscular left subscapularis hypermetabolic focus (arrow in e).
studies found sensitivity for detecting pancreatic cancer of 87% for 18F-FDG PET, 53% for CT and 93% for EUS [111], and 87% for 18F-FDG PET, 87% for MRI, and 98% for EUS [112]. Overall accuracy values (defined as area under receiver operating characteristic curves, with one reflecting a perfect test) for differentiating malignant from benign pancreatic masses have been reported for various imaging strategies [109]. Overall accuracy was 0.86 for 18F-FDG PET, 0.93 for endoscopic retrograde cholangiopancreatography (ERCP), 0.82 for CT, and 0.95 for the combination of 18F-FDG PET and ERCP. In the subgroup of euglycemic patients with contradictory or indeterminate CT and ERCP results, 18F-FDG PET was accurate in 84% of cases. The ability for PET to detect indeterminate CT lesions was even higher (100%) in another study [99]. More recently, combination PET-CT studies have also been shown to have superior sensitivity to either PET, or CT in isolation [113–115].

18F-FDG PET has also been studied for staging of metastatic disease. One study of 18F-FDG PET in pancreatic cancer found sensitivity and specificity of 49% and 63% for lymph node staging and 70% and 95% for hepatic metastases [109]. As in colorectal cancer, 18F-FDG PET may miss smaller metastases (<1 cm). A study designed specifically to assess the detection of hepatic metastases from pancreatic cancer found sensitivity of 90% and specificity of 91% for 18F-FDG PET, compared with 69% and 100% for CT, and 82% and 100% for abdominal ultrasound [116]. In another investigation, the sensitivity of 18F-FDG PET for hepatic and extrahepatic disease was 78% compared with 33% for CT [111]. 18F-FDG PET has also been used to monitor patients after therapy [117,118]. Survival in patients without measurable pancreatic 18F-FDG uptake 1 month after chemotherapy was improved compared with patients with residual 18F-FDG uptake (319 vs 139 days; P = 0.034). When used for detecting malignancy in cystic tumors of the pancreas, 18F-FDG PET had a sensitivity of 94% and specificity of 97% compared with 65%, and 87% for CT [119].

**Hepatic imaging**

18F-FDG PET has been evaluated for both primary and secondary tumors in the liver. The sensitivity of 18F-FDG PET for hepatocellular carcinoma (HCC) is poor [120]. In one study, only 50% of sonographically detectable HCCs demonstrated increased 18F-FDG uptake [121]. Several other studies have corroborated a near 50% sensitivity [122,123] relative to >90% for CT. HCC’s low expression of GLUT-1 transporters as well as high baseline expression of glucose-6-phosphatase in normal liver are theorized to be the etiology of this relatively low value [124,125]. However, in the subset of patients with HCC who have positive scans, 18F-FDG PET is highly correlative to pathologic tumor grade [126], with one study reporting 0% of well-differentiated tumors showing increased 18F-FDG uptake compared with 88% of moderately or poorly differentiated tumors [121].

18F-FDG PET has demonstrated utility in both evaluating treatment response, as well as monitoring patients for recurrence. Torizuka et al. [127] reported on the metabolic activity of 32 tumors after transcatheter arterial chemoembolization (TACE), demonstrating that a posttreatment decrease in or absence of 18F-FDG uptake indicated >90% necrosis and relative therapeutic efficacy. Another study showed that in patients who have undergone HCC therapy who have rising α-fetoprotein levels and normal conventional imaging, 18F-FDG PET had 73% sensitivity and 100% specificity for detecting recurrent disease [128]. 18F-FDG PET/CT may also have a role in monitoring response to radiofrequency ablation [129,130], or yttrium 90 glass microsphere treatment [131] of unresectable metastases.

In contrast to poor results in the diagnosis of HCC, 18F-FDG PET can be useful in evaluating metastatic disease to the liver [132], as discussed previously. One study of such patients with various primary tumors and possible liver involvement found overall sensitivity of 97% and specificity of 88% for 18F-FDG PET compared with 93% and 75% for CT (not statistically different) [133]. 18F-FDG PET yielded new information for 23% of patients, including demonstrating liver metastases in 17% of patients in whom other imaging was equivocal or negative. In patients undergoing CT-guided fine needle aspiration (FNA) of liver lesions, 18F-FDG PET correlated with FNA diagnosis in 96% of positive, and 86% of negative biopsies [134], numbers likely to increase as PET technology has improved.

18F-FDG PET has also been examined in the setting of indeterminate hepatic lesions. In a series of 110 patients with hepatic lesions 1 cm or larger on CT, all liver metastases from adenocarcinomas and sarcomas as well as all cholangiocarcinomas showed increased 18F-FDG uptake values, whereas only 70% of HCCs had increased uptake [135]. All benign lesions had poor uptake and PET Signal in abscesses was either equivocal or elevated. 18F-FDG may have a role in evaluating other primary hepatic tumors like cholangiocarcinoma, although uptake appears highly dependent on the tumor type. Anderson et al. [136] reported that sensitivity for the nodular type of cholangiocarcinoma was 85% compared with only 18% for infiltrating morphology. Ultimately, the role of 18F-FDG in discriminating benign and malignant disease in the bile duct remains controversial, with multiple studies showing either equivalency or inferiority to CT, MRI, or MRCP [137,138].

**Neuroendocrine tumors**

Neuroendocrine tumors (NET) are a heterogeneous group of neoplasms that originate from the neural crest. Given the fact that these tumors are characterized by their ability to overexpress somatostatin receptors (SST) in most cells deriving from neuroendocrine dispersed cells [139], somatostatin receptor scintigraphy (SRS) has been used in evaluation of these tumors. PET imaging using 18F-FDG has lower sensitivity than conventional SRS with 111In-DTPA-pentetreotide (OctreoScan) for the
evaluation of these types of tumors due to the fact that most of the NET are well-differentiated tumors with low metabolic activity and slow growth [140]. In one prospective study of 96 patients, the overall sensitivity of $^{18}$F-FDG PET was 58% versus 89% for OctreoScan [140]. However, for poorly differentiated neuroendocrine tumors with loss of somatostatin receptor and a proliferation index greater than 15, the sensitivity of $^{18}$F-FDG imaging became greater than $^{11}$In-DTPA-pentetreotide (OctreoScan) (92% vs. 69%) [140].

Recently, another group of PET tracers, $^{68}$Ga-DOTA-peptides which are somatostatin receptor analogs labelled to the positron emitter $^{68}$Ga, has been used for the evaluation of neuroendocrine tumors. Two different preparations of octreotide, $^{68}$Ga-DOTATOC and $^{68}$Ga-DOTANOC, and one of octreotide, $^{68}$Ga-DOTATATE, are most commonly used. These agents can be used for disease staging, evaluation of patients with known disease to detect residual, recurrent or progressive disease (restaging), determination of SST receptor status (patients with SST receptor-positive tumors are more likely to respond to radionuclide therapy), and selection of patients with metastatic disease for SST receptor radionuclide therapy (with $^{177}$Lu or $^{90}$Y-DOTA-peptides) [141]. These agents have a higher sensitivity for the detection of well-differentiated neuroendocrine tumors compared to CT/MRI [142–144] and to SRS using $\gamma$-camera [143]. $^{68}$Ga-DOTA-peptide is also superior to $^{18}$F-FDG for imaging of well-differentiated NET [145].

For example, $^{68}$Ga-DOTATOC has been shown to be superior to conventional CT imaging and $^{11}$In-DTPA -pentetreotide (OctreoScan) single photon emission computed tomography (SPECT) imaging for the evaluation of neuroendocrine tumors with a sensitivity of 97%, a specificity of 92%, and an accuracy of 96% [146]. $^{68}$Ga-DOTATOC imaging can provide further clinically relevant information in up to 14% of patients compared to SPECT, and up to 21% of patients compared to conventional CT imaging [147].

$^{68}$Ga-DOTANOC, another $^{68}$Ga-DOTA-peptide, has also been shown to be superior to conventional imaging with a reported sensitivity and specificity of 78.3% and 92.5%, respectively, for primary tumor, and 97.4% and 100% for metastases [144].

Another study using DOTANOC showed that the agent can detect occult primary sites in the abdomen in up to 59% of patients, compared to 39% for SRII imaging, and 20% for CT [148]. This is important given that failure to identify the primary tumor has been demonstrated to have a negative impact on the survival of patients with gastroenteropancreatic neuroendocrine tumors [149]. In another study of patients with negative or equivocal findings on $^{11}$In-DTPA -pentetreotide imaging, $^{68}$Ga-DOTATATE PET identified 74% of cases of disease and changed management in 71% of patients [150].

In addition to $^{68}$Ga-labelled somatostatin analogues, other PET tracers have been used to evaluate patients with NET. Thus, based on the concept of amine precursor uptake and decarboxylation (APUD), the $^{18}$F- and $^{11}$C-labelled amine precursors L-dihydroxyphenylalanine and 5-hydroxy-L-tryptophan (5-HTP) have been utilized for PET imaging of NET.

Carcinoid tumors synthesize serotonin from 5-HPA. PET using the $^{11}$C-labeled serotonin-precursor 5-HPA has been shown to be a sensitive modality for NET imaging, surpassing both SRS and CT [151–153]. In one study 38 consecutive NET patients underwent $^{11}$C-5-HPA-PET and morphological imaging by CT within 12 weeks prior to surgery with 83.8% sensitivity and 100% specificity for lesion detection [154].

$^{18}$F-fluorodihydroxyphenylalanine ($^{18}$F-DOPA) another agent being explored for imaging of neuroendocrine tumors has demonstrated excellent performance for lesion identification (reported sensitivities between 65% to 96%) [153,155–159]. Koopmans et al. [153] found that the diagnostic performance of PET was superior to the combination of SRS with CT. Various groups have reported that $^{18}$F-FDOPA PET performs best in the midgut carcinoid subgroup of neuroendocrine tumors, possibly because of their often prominent metabolic activity [155,159].

**GIST**

$^{18}$F-FDG PET-CT has a role in initial staging, monitoring response to therapy and detection of recurrent gastrointestinal stromal tumors (GIST). $^{18}$F-FDG PET of gastrointestinal stromal tumor patients at baseline is useful in establishing maximum tumor activity levels and for accurate staging.

$^{18}$F-FDG PET can detect response to imatinib mesylate treatment in patients with malignant gastrointestinal stromal tumors [160–162] as early as 1 week after starting therapy [163,164]. A good response to therapy demonstrated on $^{18}$F-FDG PET imaging is associated with a longer progression-free survival [162]. $^{18}$F-FDG PET is superior to CT in predicting early response to therapy in recurrent or metastatic GIST patients [165].

**Other diseases**

Published sensitivities for $^{18}$F-FDG PET range from 47% to 96% for the detection of gastric cancer and from 23% to 73% for the detection of lymph node involvement [166–170]. Physiologic $^{18}$F-FDG uptake is a diagnostic pitfall in detection of disease in the stomach. In gastric malignancy $^{18}$F-FDG PET is generally not helpful in determination of the T-stage of the lesion and characterization of all perigastric lymph nodes as uptake within the primary tumor may obscure adjacent nodal uptake; however the identification of nonperigastric nodes can have a significant impact on patient management and surgical planning [171].

$^{18}$F-FDG PET results may predict response to preoperative chemotherapy in gastric cancer. Patients with a metabolic response appear to have improved survival compared with metabolic nonresponders [172]. $^{18}$F-FDG PET facilitated early detection of hereditary diffuse gastric cancer in an asymptomatic carrier of a germline E-cadherin mutation [173].
Gastrointestinal tract lymphoma may present as primary lymphoma or as disseminated nodal disease secondarily involving the gastrointestinal tract with the most common histology being diffuse large B-cell lymphomas followed by MALT lymphoma. Depending on the geographic region, studies showed that the most frequently involved organ was either the stomach or the small intestine, followed by colon and other gastrointestinal organs including pancreas and liver [174,175]. Despite the physiologic 18F-FDG uptake in the bowel, 18F-FDG PET has value in staging of the disease, and evaluation of response to treatment particularly when pretreatment PET results are positive [176].

18F-FDG PET has been studied in both children and adults and has been found to have an excellent sensitivity for detection of acute bowel inflammation. However, the specificity is lower in some of the studies as differentiation of 18F-FDG uptake between inflammation caused by ischemic damage, infection and inflammatory bowel disease (IBD) remains challenging. In one retrospective study of 23 patients with suspected IBD overall sensitivity was excellent (98 %) with a lower specificity of (68%) [177]. Other authors report better specificity (89%) for lesion characterization [178].

18F-FDG exhibits good correlation with the clinical, endoscopic and biological activity of Crohn's disease [179,180] which enables monitoring of response to treatment by documenting the disease activity before and after treatment [181].

Incidental gastrointestinal uptake may be seen in approximately 3% of PET or PET/CT studies performed for pulmonary or other imaging, and often reflects clinically significant lesions, with pathology including unsuspected gastrointestinal malignancy [182–185].

Non-FDG PET

Because of its favorable decay characteristics, 18F has also been utilized in biologic compounds apart from FDG, most notably the thymidine analogue 18F-3'-deoxy-3'-fluorothymidine (18F-FLT). 18F-FLT PET takes advantage of thymidine kinase 1, which leads to the sequestration of 18F-FLT after phosphorylation, due to its upregulation in malignant and other rapidly proliferating cells. Since its development in the late 1990s [186], 18F-FLT PET has been studied in a host of gastrointestinal malignancies, with varied results. In colon cancer, 18F-FLT can reliably identify primary tumors, but its overall uptake is lower than 18F-FDG [187] and liver metastases cannot be visualized by 18F-FLT due to hepatic glucuronidation leading to high background uptake [188]. In a recent study, decrease in 18F-FLT uptake during systemic therapy was able to predict disease-free survival. However, this was also successfully prognosticated by pretreatment 18F-FDG uptake levels. In one study evaluating its use in esophageal squamous cell carcinoma, 18F-FLT was able to better delineate gross tumor volume when compared to 18F-FDG, leading to more accurate radiation treatment planning. However, mean SUV was about half that of 18F-FDG, and 18F-FLT failed to identify tumors in around 20% of patients [184]. Similarly, 18F-FLT SUV values in gastric cancer are typically lower than 18F-FDG with the exception of signet ring cell tumors where they approach statistical equivalency [189]. In a series of 45 gastric cancer patients, 18F-FLT PET demonstrated superior sensitivity by identifying all primary tumors, while 18F-FDG failed to detect 14 tumors due to high background gastric uptake. Additionally, while 18F-FLT PET does not accurately predict pathologic response prior to neoadjuvant chemotherapy, it does demonstrate good correlation with histologic proliferation (Ki-67) and treatment response after systemic therapies are initiated [190].

Future directions

PET has been called the most sensitive and specific means of studying, through imaging, molecular processes in humans in vivo [191]. The development of a micro-PET scanner for small animals, combined with rapidly growing experimental capabilities in molecular biology, presents the opportunity to carry out molecular imaging assays in vivo, including studies of protein and gene expression [192].

In the clinical arena, the number of clinical PET facilities continues to grow, and PET is becoming an essential diagnostic tool for the management of many patients with cancer. Given the ability to produce 18F-FDG off-site and its commercial availability in the USA, there is no longer a need for clinical PET centers to operate on-site cyclotrons, which has eliminated a significant barrier to PET usage. Additionally, the relaxation of regulatory restrictions and expansion of coverage by CMS has further facilitated PET’s expansion. Newer radiopharmaceuticals utilizing 18F as well as other functional and ligand-targeted radiotracers will extend the range and scope of processes that PET can investigate. The availability of PET/CT and PET/MRI scanners is likely to increase, providing both functional and anatomical information simultaneously with minimal incremental burden to patients.

References are available at www.yamadagastro.com/textbook

Further reading

CHAPTER 150

Radionuclide imaging in the gastrointestinal tract

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Introduction

Diagnostic tests using radiopharmaceuticals and nuclear medicine techniques have been utilized by gastroenterologists for decades; the first publication regarding the use of radionuclides to quantify gastric emptying was reported in Lancet in 1966 [1]. Nuclear medicine studies depend on physiology and function, and thus provide information often not available from anatomical imaging methods, e.g., ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI).

Radiopharmaceuticals

A radiopharmaceutical is a chemical, drug, or molecule that is bound to a radionuclide (Technetium-99m [Tc-99m], Iodine-123 [I-123], Indium-111 [In-111], Fluorine-18 [F-18]). It is administered to a patient by a specified route (e.g., intravenous, oral, etc.) which is dependent on its purpose. A radiation detector or imaging instrumentation is required to detect the radiopharmaceutical. The pharmaceutical determines its distribution, localization, and uptake within the body. The radionuclide is merely a “radiotracer.”

A radionuclide is an unstable chemical isotope that emits radiation (gamma rays) as it decays to a more stable isotope. Different radionuclides decay at different rates. For example, Tc-99m has a 6h physical half-life. If 10 millicuries (mCi) of radioactivity is administered to a patient, 5mCi will remain undecayed and detectable 6h later. The half-life of I-123 is 13h; In-111, 2.8 days; and F-18, 2h [2].

Different routes of administration result in different organ and body distributions. Tc-99m sulfur colloid (Tc-99m SC) administered intravenously will be extracted by the liver, spleen (liver–spleen scan), and bone marrow (marrow scan), but when given orally is not absorbed and transits through the gastrointestinal tract (gastric emptying study).

Diagnoses are based on physiological deviations from normal in uptake, localization, distribution, and clearance. Diagnostic radiopharmaceuticals are administered in subpharmacological doses, that is, they have no pharmacological effect in humans. Allergic reactions are quite rare. Radioactive iodine can be given to patients with a history of proven iodine allergy without fear of adverse reaction. Radiation exposure to the patient from diagnostic radiopharmaceuticals is generally low, sometimes greater than a chest X-ray, but usually less than a CT scan.

Radiation detection instrumentation

Three general types of instrumentation are used to detect radiopharmaceuticals in the body. (1) Nonimaging radiation detectors (well-counters) which quantify radiation in body tissues or fluids (blood or urine), e.g., blood volume and glomerular filtration...
rate. (2) Radiation nonimaging detection probes used for thyroid uptake measurements or intraoperative tumor localization. (3) Imaging gamma cameras which are of two general types, single-photon and dual-photon (positron) detectors.

Examples of radionuclides that give off a single gamma ray with each decay (single photon) are Tc-99m, I-123, and In-111. The gamma rays are detected by scintillation crystals in the gamma camera detector head, which then give off a proportional amount of light which is detected by the camera electronics. The greater the radiation, the more light emitted, and the better the image quality.

The camera detector head(s) are placed adjacent to the patient and an image is acquired in one or multiple views. Images can be acquired as single static images or dynamic imaging (1 s or 1 min frames), e.g., blood flow in a three-phase bone scan, hepatobiliary iminodiacetic acid (HIDA) imaging, gastric emptying, or gastrointestinal bleeding (Figure 150.1). Three-dimensional cross-sectional images (single-photon emission computed tomography or SPECT), may be acquired to aid in detection and localization. For this purpose, the camera rotates about the patient’s body, acquiring two-dimensional images at every 3 degree rotation, which are then reconstructed into cross-sectional slices using the same mathematical algorithms as CT or MRI.

Radionuclides that give off two photons per emission (positrons), e.g., F-18, Carbon-11 (C-11), Nitrogen-13 (N-13), and Oxygen-15 (O-15), are detected by positron emission tomographic (PET) cameras. Positrons are antimatter, i.e., positive electrons. With each radionuclide decay, positron particles are emitted. The positrons then interact with a negatively charged particle (electron), both are annihilated and produce two gamma rays emitted 180 degrees apart. PET fixed scintillation or solid state crystal detectors encircle the patient. Specialized electronics (coincidence circuitry) detect the simultaneous emissions. The technical advantages of PET over SPECT include a higher count rate, better resolution, and fewer reconstruction artifacts. The cross-sectional images can be reformatted into whole-body displays, called maximal intensity projection (MIP) images [2]. For a larger region than the brain or heart, the bed position can move in sequential increments for the length of the body.

The physiological processes that PET may be able to image is practically unlimited because positron radionuclides (C-11, O-15, N-13, and F-18 [fluorine can replace hydrogen]) can potentially radiolabel any biological molecule.

Positron emission tomography and many SPECT cameras have CT scanners as part of the imaging system (hybrid SPECT/CT and PET/CT). The two studies are acquired sequentially with the patient in the same position on the same table, moving from one imaging instrument to the other. After acquisition, the images are registered and fused (overlapped). This combines the functional/physiological information from the PET or SPECT with the anatomical information of the CT scan. PET/MRI scans are under active development.

**Common gastrointestinal nuclear medicine studies**

This chapter reviews single-photon and dual-photon nuclear medicine imaging studies most pertinent to the modern practice of gastroenterology.

**Cholescintigraphy**

Radionuclide hepatobiliary imaging (cholescintigraphy or HIDA) has long been one of the most commonly requested gastrointestinal nuclear medicine studies. I-123 labeled Rose Bengal was the first radiopharmaceutical used. However, in 1976, the Tc-99m HIDA radiopharmaceuticals were introduced, which produced superior image quality and are still used today. Two radiopharmaceuticals are approved by the US Food and Drug Administration (FDA) for clinical use:

1. Tc-99m disofenin (FDA name), DISIDA (chemical abbreviation for diisopropyl-IDA), or Hepatolite (commercial name).
2. Tc-99m mebrofenin, bromotrimethyl-IDA, or Choletec.

Tc-99m mebrofenin has somewhat higher liver extraction (98% vs 89%) and more rapid hepatic clearance (17 vs 23 min half-time) than Tc-99m disofenin and is increasingly the agent of choice.

After intravenous injection, Tc-99m HIDA is extracted by hepatocytes and travels the same metabolic pathway as bilirubin, except it is not conjugated. On exiting from the hepatocyte, the radiotracer follows bile drainage into the duodenum and transits the intestines. This makes possible physiological imaging of hepatic function, gallbladder contraction, and biliary flow. Tc-99m HIDA is subject to competitive inhibition in patients with elevated serum bilirubin levels. However, studies can be diagnostically useful with bilirubins as high as 25–30 mg/dL, although image quality decreases. Normal pharmacokinetics are altered, with delayed extraction and clearance.

Preparation for cholescintigraphy requires that the patient ingests nothing by mouth for 3–4 h prior to starting the study. This allows time for the gallbladder to relax after contraction stimulated by endogenous cholecystokinin (CCK) released from the proximal small bowel after meal ingestion. A contracted gallbladder may not permit radiotracer to enter and could result in a false-positive study for acute cholecystitis (non-filling of the gallbladder). Conversely, if the patient has fasted for more than 24 h, the gallbladder may be filled with viscous concentrated bile which can also prevent HIDA radiotracer entry. Sinalide, an analog of CCK, is often administered 30 min prior to injection of the radiopharmaceutical in order to empty the gallbladder in these patients. Opiate drugs should be withheld for at least 6 h prior to the study because they contract the sphincter of Oddi and may produce a picture of partial biliary obstruction, potentially complicating interpretation.

The standard study lasts 1 h (1-min sequential frames) after Tc-99m injection. By 60 min, the gallbladder fills and bile is secreted into the biliary ducts and clears into the intestinal tract. If this has not happened, modifications to the protocol may be...
Figure 150.1 Cholescintigraphy with morphine sulfate. (a) Sequential images over 60 min. The right lobe has an abnormal appearance due to a loculated pleural effusion. Normal hepatic uptake and biliary clearance of the radiotracer into the common duct (CD) and duodenum (D) and more distal small bowel are shown. However, there is no filling of the gallbladder. (b) After morphine sulfate injection, imaging continues for 30 min. The gallbladder (GB) progressively fills, ruling out acute cholecystitis. Transit of radiotracer is seen in the bowel.
necessory, e.g., delayed imaging or administration of morphine sulfate (MS).

**Acute cholecystitis**

Clinically suspected acute cholecystitis is the most common indication for cholecintigraphy. The study identifies the specific underlying pathophysiology, i.e., obstruction of the cystic duct, manifested by nonfilling of the gallbladder (see Figure 150.1) [3]. Although ultrasonography is valuable in the work-up of patients with suspected biliary colic, it has inferior sensitivity and specificity compared to cholecintigraphy for the diagnosis of acute cholecystitis. Gallstones are seen on ultrasonography in most patients with acute cholecystitis. However, gallstones are often asymptomatic and unrelated to the patient’s pain. Gallbladder wall thickening and pericholecystic fluid are non-specific findings and have numerous causes. The sonographic Murphy’s sign is operator dependent and not always reliable. Cystic duct stones are rarely seen because of their small size. However, ultrasonography can detect other causes for pain, e.g., biliary dilatation due to biliary obstruction or pancreatitis.

Obstruction of the cystic duct is the usual initiating event for acute cholecystitis. After obstruction, the gallbladder wall becomes edematous, followed by inflammatory cell infiltration, then hemorrhage and necrosis, and without intervention, ultimately gangrene and perforation and other complications. Cholecintigraphy becomes positive for acute cholecystitis as soon as the cystic duct is obstructed.

Many published investigations have found high accuracy of cholecintigraphy to diagnose acute cholecystitis. The sensitivity is greater than 95% and the specificity 90% [4]. False-positive studies may occur in sick hospitalized patients with a concomitant illness, those who have been fasting for a prolonged period of time or receiving hyperalimentation, and very rarely chronic cholecystitis.

Nonvisualization of the gallbladder at 60 min is abnormal. However, further imaging is required to confirm the diagnosis of acute cholecystitis. Persistent nonvisualization at 3–4 h after injection is diagnostic. Visualization of the gallbladder excludes cystic duct obstruction and acute cholecystitis. The majority of patients with delayed gallbladder nonvisualization (between 1 and 4 h) have chronic cholecystitis. An alternative to delayed imaging is the administration of MS, 0.04 mg/kg intravenously (see Figure 150.1). MS contracts the sphincter of Oddi, increases intrabiliary pressure, and produces preferential bile flow towards and through the cystic duct if it is patent. MS is often preferable to delayed imaging in patients with nonvisualization of the gallbladder at 60 min. The study can be completed in 90 min, rather than the 3–4 h required with delayed imaging [5]. Diagnostic accuracy is similar.

The scintigraphic “rim sign” is seen in 25%–35% of patients with acute cholecystitis. This imaging finding is manifested as increased radiotracer uptake in the liver adjacent to the gallbladder fossa (Figure 150.2). Although not highly sensitive for the diagnosis of acute cholecystitis, it is very specific. Its presence has important clinical implications because it indicates an increased likelihood of complications, e.g., gangrene and perforation. The rim sign is caused by severe inflammation spreading from the gallbladder to the adjacent liver. The liver inflammation produces increased blood flow and thus higher than normal delivery and liver extraction of the HIDA tracer.

**Acute acalculous cholecystitis**

This is a specific clinical entity that occurs in seriously ill hospitalized patients, e.g., in conjunction with extensive burns, extensive trauma, or postoperative complications. The disease has a high morbidity and mortality. As the name suggests, it comprises acute cholecystitis without stones. The majority of patients have cystic duct obstruction; however, the obstruction is not due to cholelithiasis, but rather inflammatory debris, inspissated bile, and local edema. The problem is that some patients do not have an obstructed duct, but have direct inflammation of the gallbladder wall caused by sepsis, ischemia, or toxemia. It is in these subgroups of patients that false-negative studies (gallbladder filling with cholecystitis) may occur. Instead of the >95% sensitivity for the acute calculous disease, the sensitivity of HIDA imaging for acute acalculous cholecystitis is 75%–85%. If a patient is suspected of having a false-negative study, two approaches may help. First, after gallbladder filling, sinalcide can be given. A diseased gallbladder does not contract well. Good contraction rules out gallbladder disease; however, poor contraction occurs with both acute and chronic disease. Second, a radiolabeled leukocyte study can confirm or exclude inflammation of the gallbladder.

**Chronic cholecystitis**

**Chronic calculous cholecystitis** presents with symptoms of recurrent biliary colic and imaging evidence of cholelithiasis, and then usually leads to cholecystectomy. Gallbladder histopathology shows evidence of chronic inflammation, fibrosis, and stones.
**Chronic acalculous gallbladder disease** occurs in at least 10% of patients who have cholecystectomy for chronic cholecystitis [6]. Chronic acalculous disease is clinically and histopathologically indistinguishable from chronic calculus cholecystitis, except for the absence of gallstones. Symptoms resolve with cholecystectomy. The clinical challenge is to make the diagnosis preoperatively and noninvasively.

More than two dozen published investigations have reported that sincalide (CCK) cholescintigraphy with calculation of a gallbladder ejection fraction (GBEF) to be diagnostic of chronic acalculous gallbladder disease and predictive of clinical response to cholecystectomy [7]. One, albeit relatively small, well-designed prospective investigation of randomized patients who had a low GBEF to either surgical or nonsurgical therapy [8]. Of those patients who had cholecystectomy, greater than 91% had resolution of their symptoms and histopathological evidence of chronic cholecystitis. Those with a low GBEF who did not have surgery continued to be symptomatic. Other studies have involved larger numbers of patients, but were retrospective and nonrandomized [7]. Although a few reports have not found CCK cholescintigraphy predictive, the weight of the evidence suggests that CCK cholescintigraphy can predict which patients will benefit from cholecystectomy. A large multicenter prospective randomized study is needed to confirm these findings.

In order to initiate a multicenter prospective randomized investigation, a standardized methodology for sincalide infusion is needed. Various different methods of infusion have been used in different publications and in practice, with wide variation in dose, infusion length, and normal values [7]. Studies have shown that a commonly used method (0.02 μg/kg infused over 3 min) has a wide range of response in normal subjects and many have false positives (low GBEF shown to be normal with slower infusions of 30–60 min) [9,10]. A recent multicenter investigation in 60 normal subjects compared three sincalide infusion methods, 15 min, 30 min, and 60 min infusions of (0.02 μg/kg) on separate days in the same subjects [11]. The study found that the 60 min infusion method had the least variation (lowest coefficient of variation) with the narrowest range of normal for GBEFs (Figure 150.3). The lower range of normal was determined to be 38%. Consensus recommendations were

![Figure 150.3 Cholescintigraphy in chronic acalculous gallbladder (GB) disease. This 52-year-old female has recurrent biliary colic. Ultrasonography was negative. The gallbladder filled during the first 60 min of the study (not shown). Sequential 2-min images are shown during the 60 min infusion of sincalide (cholecystokinin). A region of interest is drawn on computer around the gallbladder and a time activity study generated. Very poor gallbladder contraction is seen. The calculated gallbladder ejection fraction (GBEF) was 10% (abnormal <38%). Histopathology showed a chronically inflamed gallbladder without stones.](image-url)
published after a conjoint meeting of expert gastroenterologists, surgeons, and nuclear medicine physicians, which recommended that the 60 min infusion method become the standard [12].

A common misconception is that reproduction of the patient’s pain during CCK infusion is diagnostic of chronic gallbladder disease. Although limited data from the 1970s suggested this might be true, subsequent investigations have disproved its diagnostic utility [13]. In addition to contracting the gallbladder and relaxing the sphincter of Oddi, CCK has physiological effects that can produce adverse symptoms, e.g., increasing intestinal motility which can cause abdominal cramping. Approximately half of normal subjects when given a 3 min or shorter sincalide infusion have these symptoms [9,10]. When these same patients are administered the dose as a slow infusion over 30 or 60 min, none have pain. Neither normals nor patients have adverse symptoms from the slow infusion of sincalide. Furthermore, in the prospective study reported above, using a slow infusion, no patients with disease had adverse symptoms with CCK infusion. Thus, abdominal cramping during CCK infusion is related to the method of infusion and not to the presence or absence of disease.

Cholecystokinin cholescintigraphy should be ordered and interpreted in the proper clinical setting. Most published investigations that have confirmed the utility of CCK cholescintigraphy to diagnose chronic acalculous gallbladder disease were performed in outpatients who had had a medical work-up to exclude other diseases and were followed for months and years prior to CCK cholescintigraphy, allowing time for other diseases to become manifest. Some clinicians today, convinced of the utility of the test, are requesting the study after a first episode of pain and with minimal other medical evaluation. The likelihood of disease in this latter referable group is lower than in the published investigations, thus the accuracy of the test in this population is likely to be lower. The posttest probability of a test is affected by the pretest likelihood of the disease (Bayes’ theorem). Thus, in a high likelihood population, a positive test is likely to be a true positive, but, in a low likelihood population, a positive test is likely to be a false positive. CCK cholescintigraphy is a confirmatory test, not a screening test.

Cholecystokinin cholescintigraphy should be performed in an outpatient setting, not during an emergency room visit or during hospitalization. Acute illnesses and various drugs may inhibit gallbladder contraction, e.g., calcium channel blockers, progesterone, octreotide, theophylline, and benzodiazepine can cause reduced gallbladder contraction [14].

### Biliary obstruction

Acute high-grade biliary obstruction is often diagnosed by ultrasonography which demonstrates dilated biliary ducts. However, dilation may take 24–72 h to become apparent after an obstructive event. Cholescintigraphy can confirm the diagnosis immediately after onset because it demonstrates the underlying pathophysiology, obstruction to bile flow.

The cholescintigraphic images of acute biliary obstruction demonstrate good hepatic function (rapid hepatic extraction of tracer from blood), but no secretion into biliary ducts (i.e., a persistent hepatogram) (Figure 150.4). The lack of bile secretion is caused by the high back-pressure caused by the obstruction. Further delayed imaging is usually unchanged. The accuracy of cholescintigraphy for the diagnosis of high-grade obstruction is >97% [15,16].

#### Partial biliary obstruction

This often presents with intermittent biliary colic-like pain. The diagnosis can be challenging. With low-grade, partial, or intermittent obstruction, biliary ducts are often not dilated and small stones not visualized. Cholescintigraphy shows good hepatic function, prompt secretion into biliary ducts and gallbladder, but retention of radiotracer in the biliary ducts and delayed transit into the small intestines.

The accuracy for diagnosis of partial biliary obstruction is high. Sensitivity for cholescintigraphy is reported to be 97% vs 78% for sonography [17], with similar specificity (86%). Patients who have had prior obstruction may have persistent ductal dilatation after successful therapy. In these patients, anatomical imaging (e.g., US, CT, MRI) would not be able to distinguish obstructed from nonobstructed ducts. Cholescintigraphy can make the diagnosis. Of 125 patients thought to have early, partial, or intermittent biliary obstruction, sonography and scintigraphy disagreed in 23%. Scintigraphy diagnosed obstruction in 13 patients without evidence of dilated ducts, and seven patients with dilatation from prior obstruction showed normal clearance, excluding obstruction.

#### Differentiation of biliary obstruction from hepatic dysfunction

The longer the time an obstruction remains untreated, the greater the likelihood of developing hepatic dysfunction. Differentiating primary hepatic dysfunction from dysfunction secondary to obstruction can be challenging. Cholescintigraphy can often do this. However, delayed imaging may be needed to see biliary clearance, with imaging up to 24 h, because of the delayed HIDA pharmacokinetics. If bile transit to the intestines is seen within 24 h without biliary retention, the diagnosis is primary hepatic dysfunction.

#### Biliary atresia

Biliary atresia presents as cholestatic jaundice in the neonate. It is caused by progressive inflammatory sclerosis that obliterates extrahepatic and intrahepatic biliary ducts. Early diagnosis is critical and must be made within the first 60 days of life to prevent irreversible liver failure. Treatment requires a palliative hepatopportoenterostomy (Kasai procedure), but ultimately liver transplantation. The differential diagnosis includes neonatal hepatitis of various etiologies.

Patient preparation for cholescintigraphy includes 3–5 days of phenobarbital to activate liver excretory enzymes and increase
however, a high-grade obstruction of the cyst will have no filling due to the high back-pressure.

**Postcholecystectomy syndrome**
In the immediate postcholecystectomy period, cholescintigraphy can be quite useful for the diagnosis of surgical complications, e.g., biliary leakage or obstruction. However, recurrent biliary colic occurring months or years after cholecystectomy is referred to as the postcholecystectomy syndrome. The most common biliary causes are recurrent or residual biliary duct stones. Biliary stricture and sphincter of Oddi dysfunction are other less common causes. All of these produce a scintigraphic picture of partial biliary obstruction, i.e., delayed biliary duct clearance and delayed biliary-to-bowel transit [18].

**Choledochal cysts**
These are not true cysts, but rather congenital dilations of bile ducts, usually involving the common hepatic or common bile ducts, but may be anywhere in the biliary system. Patients may be asymptomatic throughout life. Or, they may present clinically in childhood with biliary obstruction, pancreatitis, or cholangitis. During a work-up for pain, the clinical question may be whether a cystic structure seen on anatomical imaging is connected to the biliary system and thus a choledochal cyst or some other pathology. With cholescintigraphy, choledocal cysts normally fill slowly and clear slowly, confirming a biliary connection. However, a high-grade obstruction of the cyst will have no filling due to the high back-pressure.

**Postcholecystectomy syndrome**
In the immediate postcholecystectomy period, cholescintigraphy can be quite useful for the diagnosis of surgical complications, e.g., biliary leakage or obstruction. However, recurrent biliary colic occurring months or years after cholecystectomy is referred to as the postcholecystectomy syndrome. The most common biliary causes are recurrent or residual biliary duct stones. Biliary stricture and sphincter of Oddi dysfunction are other less common causes. All of these produce a scintigraphic picture of partial biliary obstruction, i.e., delayed biliary duct clearance and delayed biliary-to-bowel transit [18].

**Sphincter of Oddi dysfunction**
This is a partial biliary obstruction at the level of the sphincter of Oddi. It is the cause for pain in up to 14% of patients with the postcholecystectomy pain syndrome. To make the diagnosis, cholangiography (MRCP or ERCP) must exclude stones, tumor, and biliary stricture as the cause. Sphincterotomy is the
usual therapy. However, ERCP is associated with serious side effects, particularly pancreatitis. A noninvasive screening test would be valuable to determine which patients require invasive work-up. Cholescintigraphy permits the physiological assessment of biliary duct drainage, which correlates well with the washout of contrast material from the biliary tract observed on ERCP [19]. Thus cholescintigraphy can be used as a screening test. The findings include delayed clearance from the common duct and delayed transit to the bowel.

Quantification of cholescintigraphy has been used to improve the accuracy over image analysis alone. Various methods have been proposed [19,20]. After acquisition, regions of interest (ROI) are drawn around biliary ducts or the hepatic hilum, time-activity curves generated, and quantitative parameters of bile clearance determined. Of the several methods reported, it is uncertain which is most accurate. One semi-quantitative method combining image analysis and quantification has found clinical utility [20]. A unique aspect of this particular protocol is the infusion of sincalide prior to the study to increase bile flow and “stress” the biliary ducts, bringing out an otherwise more subtle obstruction. The reported accuracy is high, albeit studied in a limited number of patients. This method can be used to screen patients to determine which require ERCP or which are likely to have a nonbiliary cause of pain (Figure 150.5).

**Biliary leak**

Bile leaks usually occur as a complication of cholecystectomy or biliary tract surgery. Although ultrasonography and CT can detect fluid collections, the etiology can be uncertain.

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**Figure 150.5** Cholescintigraphy in sphincter of Oddi obstruction. A 38-year-old female with chronic recurrent biliary colic that started 5 months postcholecystectomy. Sequential Tc-99m HIDA 2 min images over 1 h show clearance into the biliary ducts, but persistent retained activity in the ducts and little bile transit into the intestines. The common bile duct (CBD) time–activity curve shows a progressive rise in activity, consistent with a partial biliary obstruction. No stones or biliary stricture were found on further evaluation. Sphincterotomy was performed with subsequent symptom resolution. ROI, region of interest.
Cholescintigraphy can determine whether the fluid collection is of biliary origin, rather than caused by ascites, infection, etc. It can also provide an estimate of the rate of leakage. Slow bile leaks often resolve spontaneously with conservative therapy, whereas more rapid leaks usually require intervention. Before percutaneous drainage of a biloma, cholescintigraphy can help ensure that biliary obstruction is not the underlying cause. With obstruction, bile leakage cannot be effectively treated by percutaneous drainage without addressing the underlying obstruction.

Bile leakage is often seen on cholescintigraphy as progressively increasing radiotracer collection in the region of the gallbladder fossa or hepatic hilum. The radiotracer may move into the subdiaphragmatic space, over the dome of the liver, into the colonic gutters, or spread diffusely as free bile throughout the abdomen. Peritoneal tubing, drains, and collection bags may show accumulation and sometimes be the only evidence of leak.

**Other indications for cholescintigraphy**

**Postoperative complications of liver transplantation**

Cholescintigraphy can differentiate bile leaks and obstruction from rejection-related hepatic dysfunction [21].

**Surgical biliary diversion procedures**

Biliary scintigraphy is useful for evaluating the patency of biliary diversion procedures, e.g., choledochojejunostomy. Scintigraphy can confirm bile leakage, determine functional patency of the anastomosis, and demonstrate evidence of recurrent obstruction. It can distinguish obstructed dilated ducts from those that are chronically dilated but not obstructed. In Billroth II anastomoses, afferent loop patency can be evaluated. Scintigraphy has also been used to diagnose and estimate the severity of enterogastric bile reflux.

**Tc-99m labeled red blood cells – cavernous hemangioma of the liver**

Tc-99m red blood cell (RBC) scintigraphy has been used for decades to confirm the diagnosis of cavernous hemangioma of the liver. Today MRI is more commonly used for this purpose, because of its superior anatomical resolution and high sensitivity for detecting small lesions and those adjacent to vascular structures. However, the specificity of MRI is less than Tc-99m labeled RBC, because a number of benign and malignant lesions may have findings similar to hemangioma. Only a very few false-positive Tc-99m RBC studies have been reported in as many decades. With SPECT, sensitivity approaches 100% for detection of hemangiomas greater than 1.4 cm in size [22]. Sensitivity decreases for small size hemangiomas, although hemangiomas as small as 0.5 cm may be detected.

For this study, the patient’s own RBCs are radiolabeled with Tc-99m pertechnetate. Because of slow influx into the hemangioma, the lesion may appear cold early after injection of radiolabeled red cells, i.e., less activity than adjacent liver; however, within 2 h, the hemangioma shows increased activity compared to normal liver. Other causes for liver masses, benign and malignant, appear cold on imaging.

**Tc-99m sulfur colloid liver–spleen scanning**

Before the advent of CT, Tc-99m SC was routinely used for liver and spleen imaging, to evaluate benign and malignant disease in the liver. CT has replaced Tc-99m SC for most indications because of its superior anatomical image resolution. However, Tc-99m SC liver is still valuable for answering some specific clinical questions.

Tc-99m SC is extracted by the reticuloendothelial cells of the liver (Kupffer cells). Because most benign and malignant tumors do not have Kupffer cells, these liver masses have no uptake and are cold on liver–spleen scans.

**Focal nodular hyperplasia**

Focal nodular hyperplasia (FNH) is a benign tumor that includes all three liver cell types, i.e., hepatocytes, biliary ducts, and Kupffer cells. Differentiating this hepatic mass from others (e.g., hepatic adenoma) can be important because FNH is usually asymptomatic while the latter bleed. Approximately two-thirds of FNH tumors will demonstrate uptake of Tc-99m SC, which is diagnostic.

Tc-99m HIDA cholescintigraphy also has a characteristic diagnostic pattern with FNH, and is arguably more accurate. Cholescintigraphy shows increased blood flow, normal or increased uptake relative to adjacent liver, and, importantly, delayed clearance of the tracer from the tumor. Other tumors, even those with hepatocytes (e.g., hepatic adenoma, hepatocellular carcinoma) typically have decreased uptake, because of their poor function.

**Budd–Chiari syndrome (hepatic vein thrombosis)**

This has a characteristic pattern with Tc-99m SC, i.e., normal uptake in the caudate lobe, but reduced uptake in the rest of the liver. The impaired venous drainage of the liver results in poor hepatic function and thus poor radiotracer uptake. The caudate lobe retains good function because of its direct venous drainage into the inferior vena cava.

**Chronic hepatic dysfunction**

Patients with cirrhosis have a characteristic pattern based on the abnormal pathophysiology of portal hypertension, i.e., decreased hepatic uptake due to poor function, and increased uptake in the spleen and bone marrow (colloid shift).

**Splenosis**

Tc-99m SC is useful to confirm the diagnosis of splenosis or the presence of splenic remnants. Because of its high target to background ratio, small foci of splenic tissue can be detected. SPECT further increases detectability. Tc-99m damaged RBCs, which have been heated or chemically treated, have been used for this purpose, because they have splenic uptake with minimal or no
liver uptake. Although perhaps superior in the detection of small foci of splenic tissue adjacent to the liver, this latter technique is not routine because of the increased technical complexity required. Tc-99m SC will detect most ectopic splenic tissue.

Gastrointestinal motility
Measurement of radionuclide esophagogastrointestinal transit is an area of increasing interest and growth. The major advantage of radionuclide techniques over most other methodologies is the ability to quantify pathophysiological processes.

Esophageal motility
For the evaluation of suspected esophageal motility disorders, barium swallow and or endoscopy is often initially performed to exclude an anatomical lesion. Although esophageal manometry is routinely used to evaluate primary esophageal motor disorders, it has limitations, e.g., in achalasia, quantification of the volume of retained food is not possible, limiting its ability to assess the effectiveness of therapy.

Esophageal transit scintigraphy is noninvasive and quantitative. Different methodologies have been described [23]. Typically dynamic rapid sequence swallowing scintigrams (0.5 s/frame) are acquired during a patient swallow of a small volume of water mixed with Tc-99m SC. Qualitative image analysis with cine display is often sufficient to diagnose abnormal esophageal transit. However, one strength of the radionuclide method is quantification. This is particularly valuable for determining the effectiveness of therapy [24]. An esophageal transit time or the percent residual esophageal activity is measured. Semisolid food swallows have been reported to be more sensitive for abnormal motility than liquid swallows (Figure 150.6).

The sensitivity for detection of abnormal radionuclide esophageal transit is reported in the older literature to be only 50%–75%. However, more recent studies have reported considerably higher sensitivity [25]. Detection of achalasia has a very high sensitivity (>90%).

Esophageal scintigraphy is probably underutilized. Some suggest that it should be used as a screening test. Today it is most commonly used to evaluate response to therapy [26].

Gastroesophageal reflux
The radionuclide gastroesophageal reflux study is a sensitive noninvasive method for detecting reflux. Previously, the methodology used for adults mimicked the radiographic method, that is, a stepwise increase in abdominal pressure using an inflatable binder to produce detectable reflux events. However, this method is not physiological. A method developed and successfully used for pediatric patients is applicable to adults. This method has proven to be very sensitive for the detection of gastroesophageal reflux events, due to the rapid framing rate used for acquisition (10 s frames × 1 h) [27]. Early reports of low sensitivity for detecting reflux events date back to when framing rates of 30 s or longer were used, resulting in poor temporal resolution and the inability to detect repetitive events (Figure 150.7).

For children, formula or milk mixed with Tc-99m SC is ingested. For adults, orange juice is commonly used. Various methods have been described for quantification, often using a time–activity curve to detect and quantify reflux events. A simple method is to count the reflux events and to note whether they are long events (>10 s) or short, and high (more than half the distance to the mouth) or low events, and then sum the results. Evidence for aspiration is routinely sought on these studies.

Gastric emptying
The radionuclide gastric emptying study has been the gold standard for the evaluation of gastric motility for decades because it is noninvasive and quantitative [28].

Various radiolabeled meals have been used. The most common has been an egg meal, often as a sandwich. Good radiopharmaceutical binding to the meal is mandatory for accurate determination of solid emptying. During cooking, Tc-99m SC binds tightly to the albumen in egg white. Liquid gastric emptying can be performed as a separate test, done sequentially with the solid study or simultaneously using two different radionuclides with different photopake energies, e.g., Tc-99m (140 keV) for the solid meal and In-111 diethylenetriaminedipentacetic acid (DTPA) (175 and 225 keV) for the liquid.

The physiology of the stomach is complex. However, put simply, it has two functionally distinct compartments. The distal stomach or antrum is responsible for solid emptying. Phasic contractions of the antrum grind up the food into small enough particles to pass through the pylorus. The proximal stomach or fundus is responsible for liquid emptying. Tonic contraction of the fundus produces a pressure gradient from the proximal to the distal stomach that results in liquid emptying.

This difference in solid and liquid gastric function can be seen on radionuclide studies when one draws ROI around the stomach on the separate liquid and solid studies and generate time–activity curves. Solids have a delay before emptying begins, the lag phase, which is the time it takes to break down the solid food into small particles and then emptying occurs in a generally linear manner (Figure 150.8). Liquids have no delay before emptying begins and empty in a monoeXponential pattern (Figure 150.9).

Normal values for gastric emptying studies must be based on the specific meal and methodology used. The rate of solid emptying is determined by multiple factors, e.g., the meal volume, particle size, and the amount of calories, carbohydrates, fat, and protein, etc. Normal values must be validated for the specific meal used. If the patient does not eat the entire meal, the standard normal values will overestimate emptying.

There has been concern amongst gastroenterologists that different imaging clinics use different methodologies, different meals, different quantitative methods, and thus have different normal values, making it difficult for the clinician to compare
Figure 150.6 Esophageal transit scintigraphy in achalasia. Esophageal swallow study of 24 min duration. Sequential 15 s images (posterior view) after ingestion of a cornflake and milk meal demonstrates very slow and delayed clearance from the esophagus. A region of interest (ROI) drawn around the esophagus generates a time–activity curve confirming the very slow clearance and quantification. The drop in counts at 16 and 24 min is due to the ingestion of additional clear liquids.

The results between clinics. In 2007, a consensus panel of gastroenterologists and nuclear medicine physicians agreed upon a standardized methodology for solid gastric emptying studies. The consensus recommendations were published in both the gastrointestinal and nuclear medicine literature by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine [29].

The published consensus recommendations specify a simplified protocol, a standardized protocol, validated normal values, and a 4 h length study. The protocol chosen was that of Tougas et al., with 1 min image acquisition at time 0, 1, 2, and 4 h after ingestion of the meal (egg white sandwich with jam and water) [30]. The recommendation for a 4 h study is based on publications showing increased detection of gastroparesis at 4 h...
troparesis who have normal solid emptying, almost a third will have delayed liquid emptying [35,36]. The reason for this discrepancy is not fully understood. However, as described above, the mechanisms of liquid and solid emptying are different, one measuring fundal emptying and the other antral emptying. Both may produce similar symptoms of gastroparesis.

**Intestinal motility**

Small and large bowel radionuclide intestinal transit studies are not widely performed, although methods have been described, and there is increasing interest. One approach uses a radiopharmaceutical in a resin-coated capsule that does not break down until it reaches higher pH in the small bowel [37]. While this is physiologically appealing, the radiopharmaceutical is not approved for clinical use and not likely to be in the foreseeable future. Another approach is to use two isotopes with different photopeaks that can be imaged simultaneously, e.g., the Tc-99m SC egg meal for gastric emptying and In-111 DTPA for intestinal transit [38]. The test requires imaging to 6 h on day 1 for

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**Figure 150.7** Radionuclide gastroesophageal reflux study. This neonate being worked up for failure to thrive ingested her usual formula meal with Tc-99m sulfur colloid. Ten second sequential frames show frequent episodes of reflux of varying length, but mostly high level (above mid-esophagus). The black dot in the left upper corner is a radioactive marker to show the level of the mouth.
small bowel transit and single images on day 2, 3, and 4 for large intestinal transit.

Quantification is not as straightforward for intestinal transit as it is for gastric emptying. With gastric emptying, the emptying at each time interval is determined as a percent of the radioactivity initially in the stomach. However, unlike the stomach, the small and large bowel do not have a time zero where all the activity is in one place, but rather the activity is entering the small and large intestines over a period of time. This requires some form of semiquantification or index of transit. Various methods have been described [37,38].

**Gastrointestinal bleeding**

The radionuclide gastrointestinal bleeding study has been used clinically for decades [39]. The patient's RBCs are labeled with Tc-99m. High labeling efficiency is important because
Angiographers often request that the radionuclide gastrointestinal bleeding study be performed prior to contrast angiography, for two reasons. First, if the radionuclide study is negative, a contrast study is likely to be negative. Second, if the radionuclide study is positive, it can guide the angiographer to the approximate bleeding site, saving time and contrast media.

There has been some controversy over the years regarding the accuracy of the radionuclide method for the detection of bleeding. There is evidence in the literature that its accuracy is good, mediocre, or poor. The discrepancy in the published literature can be explained and attributed to several factors [2]. First, there is the problem of a gold standard used in investigations. Contrast angiography that localizes the site of active bleeding is best; however, only a relatively small percentage of subjects in any reported series have this direct correlation. Surgery is also a

(untlabeled) Tc-99m is secreted by the salivary glands and stomach, then moves distally, and may be misinterpreted as bleeding. Several different radiolabeling methods have been used over the years. The in-vitro commercial kit method is preferred because of its high labeling efficiency, greater than 95%.

The test is used primarily for lower gastrointestinal bleeding. Its sensitivity for the detection of active bleeding is high. Bleeding rates of 0.1 mL/min can be detected (Figure 150.10). This compares favorably to contrast angiography which detects bleeding rates of 1.0 mL/min, a 10-fold difference. Scintigraphic images are routinely obtained at a framing rate of 0.5–1 min/frame for 60–90 min and delayed imaging obtained as needed for up to 24 h.

Bleeding is typically intermittent and bleeding has often ceased when the symptoms of gastrointestinal bleeding manifest. Angiographers often request that the radionuclide gastrointestinal bleeding study be performed prior to contrast angiography, for two reasons. First, if the radionuclide study is negative, a contrast study is likely to be negative. Second, if the radionuclide study is positive, it can guide the angiographer to the approximate bleeding site, saving time and contrast media.

There has been some controversy over the years regarding the accuracy of the radionuclide method for the detection of bleeding. There is evidence in the literature that its accuracy is good, mediocre, or poor. The discrepancy in the published literature can be explained and attributed to several factors [2]. First, there is the problem of a gold standard used in investigations. Contrast angiography that localizes the site of active bleeding is best; however, only a relatively small percentage of subjects in any reported series have this direct correlation. Surgery is also a

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**Figure 150.9** Delayed liquid gastric emptying. The patient had a normal solid gastric emptying study. After drinking 300 mL of water with Tc-99m sulfur colloid (SC) images were acquired every minute for 30 min. A region of interest (ROI) was drawn around the stomach and time-activity curve generated, showing delayed emptying. The emptying half-time was 45 min (normal <23 min).
appropriate therapy. This approach does not preclude stabilizing the patient and prepping them for colonoscopy the next day. A past concern was false-positive studies. This is much less of a problem because of the present day methodology and interpretative criteria. Previously, the presence of blood on delayed imaging at a site was sometimes called positive. Today, it is better appreciated that a single static image only reveals evidence of blood, but where it originated from cannot be ascertained. Continuous short framing rate is now standard. The scintigraphic criteria to diagnose active bleeding are: new onset of radioactivity where there was none initially, increasing activity with time, and movement in a pattern consistent with bowel anatomy. The images should be obtained for a long enough time that the pattern of movement can determine with certainty its origin (e.g., distinguish small from large intestine). Images are routinely viewed on computer in movie mode. If delayed images are performed, the acquisition method (e.g., continuous 0.5–1 min framing rate) is similar to the initial methodology and the diagnostic criteria should be the same. Finally, radiolabeling is superior today than good standard, but these correlations are usually limited to a small minority of patients. Colonoscopy, cannot easily be performed during active bleeding, and the finding of polyps, ulcers, arteriovenous malformations, angiodysplasia, etc., do not ensure that they were the source of bleeding unless active bleeding is seen at the time of the procedure. A good investigational research study is challenging and many published ones are not optimal.

Also, the radionuclide study is most likely to be positive soon after the patient arrives in the emergency room or is admitted to the hospital. A too common clinical approach is to admit a patient to the hospital, put them to rest, stabilize them with fluids and transfusion, and cleanse the colon for colonoscopy the following day. Then if that is negative, consider a radionuclide study. The problem with this approach is that the gastrointestinal bleeding study is most likely to be positive early after the onset of bleeding. Using this approach, the gastrointestinal bleeding study will have a low sensitivity. A bleeding study is much more likely to be positive soon after onset and prompt imaging of this can lead to successful angiography and appropriate therapy. This approach does not preclude stabilizing the patient and prepping them for colonoscopy the next day.

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previously, minimizing the problem of free Tc-99m pertechnetate as described above.

Using modern methodology and interpretative criteria and prompt performance of the test when the patient presents clinically will assure a reliable test for detecting active bleeding and localization of the site of bleeding.

**Meckel's diverticulum and ectopic gastric mucosa**

Tc-99m pertechnetate is taken up by the gastric mucosa, both in the stomach and ectopic mucosa, e.g., Meckel's diverticulum. For decades, the Tc-99m pertechnetate Meckel's scan has been an accurate and accepted methodology to preoperatively confirm the diagnosis. The sensitivity is approximately 85% [40]. Cimetidine or raniditine administered for 2 days prior to the study can increase diagnostic yield by inhibiting Tc-99m pertechnetate release from the gastric mucosa, making detection more likely. Focal uptake, usually in the right lower quadrant, is diagnostic. Ectopic uptake occurs at a rate similar to stomach uptake.

The most common cause for a false-positive study is urinary tract activity, a normal excretory route of the radiotracer, misinterpreted as ectopic gastric mucosa. False positives are occasionally seen due to gastrointestinal duplications or local intestinal inflammatory hyperemia, increased permeability, or obstruction, e.g., regional enteritis.

**Inflammatory bowel disease – Fluorine-18 fluorodeoxyglucose**

Increasing published data suggests that F-18 fluorodeoxyglucose (FDG) is a valuable noninvasive imaging modality for the diagnosis, follow-up, and care of patients with inflammatory bowel disease. F-18 FDG is transported into cells proportional to the metabolic cell activity. Neutrophils and macrophages accumulate FDG.

Fluorodeoxyglucose PET can be potentially useful in patients with suspected inflammatory bowel disease where endoscopic evaluation is not feasible due to patient safety or patient fear of an endoscopic examination. In patients with proven diagnosis, the study can provide evidence of disease activity and location. It can evaluate treatment efficacy and suggest disease complications. In patients with clinical remission, but with symptoms of active disease, FDG PET can provide evidence of clinical relapse [41].

Studies in adult and pediatric patients have found a sensitivity ranging from 85% to 98% for detecting bowel segments of active Crohn's disease. A recent prospective study of 43 patients with Crohn's disease and 241 bowel segments were analyzed with ileocolonoscopy and hydromagnetic resonance imaging as reference standards. FDG PET was able to detect mucosal inflammation with high sensitivity and specificity (90%, 93%) and specificity compared to hydro-MRI (66%, 99%). FDG PET has shown utility for the assessment of inflammatory activity vs stenosis [42].

**Somatostatin receptor imaging of neuroendocrine tumors – octreoscan**

Somatostatin receptor imaging is valuable for imaging neuroendocrine tumors, e.g., gastroenteropancreatic neuroendocrine and carcinoid tumors. Somatostatin receptors are integral membrane glycoproteins located on the normal cells of neuroendocrine origin, e.g., pancreatic islet cells. Somatostatin receptors are also found in neuroendocrine tumors derived from neural crest cells belonging to the amine precursor uptake and decarboxylation (APUD) system.

Indium-111 pentetreotide (octreoscan) is a somatostatin analog that binds to high affinity type 2 receptors. Whole-body and SPECT imaging is routinely performed 24 h after injection. Uptake with octreoscan is usually quite good with well-differentiated tumors. With poorly differentiated tumors, uptake may be poor. In these cases F-18 FDG PET imaging is often positive. Scintigraphy is particularly useful for the detection of metastases. In-111 octreoscan imaging substantially impacts patient management in 25%–45% of patients [43]. PET somatostatin receptor radiopharmaceuticals labeled with Gallium citrate-68 (Ga-68), a positron emitter, are under investigation.

**Gastroenteropancreatic neuroendocrine tumors** are highly differentiated, slow growing, and often small. Most have high concentrations of somatostatin receptors [44]. Symptoms are often secondary to the hormone expressed, e.g., hypoglycemia, gastric ulcers, severe diarrhea, and flushing (Figure 150.11). Frequently,
Radionuclide imaging in the gastrointestinal tract

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is unable to be metabolized further and therefore trapped intracellularly. Most malignant tumor cells have increased glucose metabolism compared to normal tissue cells and thus have increased uptake of F-18 FDG. Patients must be fasting for 6–8 h prior to injection. If not, the radiopharmaceutical will distribute primarily to muscle and soft tissue and not to tumor. This is due to competition with serum glucose and the effect of insulin. This is a particular problem in diabetics. Insulin should not be injected within 2 h of the study. Images are acquired 1 h after injection.

Most PET scanners are hybrid PET-CT cameras. Whole-body cross-sectional imaging is performed. The PET and CT images are obtained sequentially with the patient lying on a table that moves between the two adjacent scanners, and then the images are registered and fused (overlayed) for functional and anatomical correlation. The CT is used for attenuation correction of the FDG images and anatomical localization.

Colorectal cancer

Although FDG PET presently has a lesser role in initial tumor staging, it is routinely used for restaging, preoperative evaluation prior to hepatic tumor resection, and for evaluating response to therapy (Figure 150.13) [45].

the tumors have metastasized by the time of diagnosis, to liver, lymph nodes, bone, lungs, and skin. Gastrointestinal carcinoid tumors are derived from the foregut, midgut, or hindgut. The midgut carcinoids with liver metastases cause the carcinoid syndrome with symptoms and signs of flushing, diarrhea, wheezing, and valvular right heart disease (Figure 150.12).

Many of these tumors are quite small and difficult to detect with conventional imaging (e.g., ultrasonography, MRI, and CT) and thus have considerably lower tumor detection rates than somatostatin receptor imaging. Sensitivity for the detection of carcinoid tumors and gastrinomas is high, 80%–90%, but somewhat lower for tumors that produce vasoactive intestinal peptides (VIPomas) and glucagonomas (75%), and lowest for insulinomas (50%).

Fluorine-18 fluorodeoxyglucose PET/CT imaging of gastrointestinal malignancies

Fluorine-18 fluorodeoxyglucose PET-CT increasingly plays an important role in the diagnosis, staging, restaging, and evaluating response to therapy of various gastrointestinal malignancies. F-18 FDG is a radiolabeled glucose analog. It is transported into the cell and phosphorylated by the same mechanism as glucose but is unable to be metabolized further and therefore trapped intracellularly. Most malignant tumor cells have increased glucose metabolism compared to normal tissue cells and thus have increased uptake of F-18 FDG. Patients must be fasting for 6–8 h prior to injection. If not, the radiopharmaceutical will distribute primarily to muscle and soft tissue and not to tumor. This is due to competition with serum glucose and the effect of insulin. This is a particular problem in diabetics. Insulin should not be injected within 2 h of the study. Images are acquired 1 h after injection.

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of patients who are thought to be resectable with curative intent at the time of surgery, have recurrence within 2 years. Serial serum carcinoembryonic antigen (CEA) levels diagnose recurrent disease with a sensitivity of less than 60% and provide no localizing information. Conversely, patients may have a rising CEA but negative conventional imaging including CT. The sensitivity of FDG PET for detecting recurrence is approximately 95% compared to CT sensitivity of 70% [46a].

Twenty percent of colorectal recurrences occur in the liver. Patients with single liver metastasis are potentially curable. However, prior to FDG PET, only 25% of patients were cured, because of the presence of unknown extrahepatic metastases. Preoperative detection of distant metastases is poor by conventional methods. However, this is one of PET’s strengths. FDG PET is very useful in selecting patients for surgical resection. FDG PET has an overall accuracy in the liver of 92%, compared to 78% for CT [46b].

Fluorodeoxyglucose PET changes patient management. It is reported to have a clinical impact in 30%–40% of patients, often helping avoid unnecessary surgery. FDG PET can determine the effectiveness of therapy. With successful therapy, FDG uptake markedly decreases. FDG PET can differentiate postsurgical changes of necrosis and fibrosis, from recurrent tumor with high accuracy, often not possible with CT or MRI.

**Cancer of the esophagus**

Early-stage disease is potentially curable with surgery. However, up to 80% of patients have local metastases and 50% have distant metastases at initial diagnosis. Prognosis depends on the extent of the primary tumor (TNM classification). Regional metastases may occur anywhere from the cervical chain to mediastinal, gastrohepatic, and celiac nodes.

Fluorodeoxyglucose uptake is high in primary esophageal cancer with detection sensitivity greater than 95%. However, FDG PET cannot provide staging information on the depth of invasion and periesophageal tissue invasion (T staging) and has relatively poor sensitivity (50%–75%) for determining nodal involvement (N stage) [46c]. The important role of FDG PET in primary staging is detection of distant metastases, commonly found in the liver and lung. Sensitivity for distant metastases is 80%–90% compared to CT, 50%–75%. FDG PET imaging upstages as many as 15% of patients. A major impact of FDG PET is improved detection of occult stage IV disease.

Fluorodeoxyglucose PET can be used to monitor the effectiveness of therapy [47]. Resolution of uptake is seen with a complete response, reduced uptake with partial response, and persistent uptake with no response. FDG PET has high accuracy for detection of recurrence and can differentiate posttherapy changes from residual tumor.

**Pancreatic carcinoma**

Early diagnosis and resection is potentially curative, although in most patients pancreatic cancer is unresectable at the time of diagnosis. Sensitivity for primary tumor detection is greater
Both CT and FDG PET have high sensitivity and specificity for primary tumor detection, greater than 90%. In approximately 25% of patients, FDG PET can detect a good response to therapy earlier than CT [51]. In 5% of patients, CT will detect the response first. FDG PET correctly characterizes response to therapy at 1 month in 95% of patients, and 100% at 3 and 6 months [52].

References are available at www.yamadagastro.com/textbook

Further reading


Gastrointestinal stromal tumors

Thirty percent of these rare mesenchymal gastrointestinal tract tumors are malignant and the rest are benign. The malignant tumors tend to recur and metastasize to the liver and peritoneum, less commonly to the lungs, pleura, retroperitoneum, bone, and subcutaneous tissue. Previously, tumors were found to be generally resistant to chemotherapy and radiation therapy; however, many patients have a dramatic response to the tyrosine kinase inhibitor, imatinib mesylate (Gleevac).
Since the introduction of the newer imaging modalities, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), catheter-based angiography has been used less frequently in the evaluation of the visceral arteries and gastrointestinal (GI) disease. It is currently used to establish a specific diagnosis of mesenteric vascular disease, localize GI bleeding, evaluate portal hypertension, demonstrate traumatic arterial injury, and obtain the necessary vascular information before percutaneous or surgical intervention. This chapter reviews the equipment and technique used in catheterization of the visceral arteries and portal venous system, vascular anatomy, and the role of angiography in the diagnosis and treatment of visceral vascular and GI diseases.

### Technical considerations

Intraarterial digital subtraction angiography (IA-DSA) is used in GI angiography. DSA requires a smaller amount of dilute contrast medium, causes less discomfort to patients, and reduces the risks of renal toxicity and fluid overload. DSA images may be viewed on a video monitor during and after injection of contrast material. Intravenous DSA (IV-DSA) is an angiographic technique for imaging the aorta and its branches after an intravenous administration of contrast medium into the superior vena cava or right atrium. IV-DSA is useful in the pediatric patient who is at high risk for developing arterial spasm and thrombosis at the puncture site.

Two types of iodinated contrast material have been used for angiography: the conventional, high-osmolar (ionic) contrast agent has been replaced by the low-osmolar (nonionic) or isoosmolar (iodixanol, Visipaque, GE Healthcare, Princeton, NJ, USA) contrast agent. The nonionic contrast agents are more expensive but cause less pain and burning sensation. Patients with a history of contrast media allergy and renal failure will benefit from the use of low-osmolar contrast media [1–3].

Gadolinium-based contrast agent has been used as an alternative in patients with contrast allergy and chronic renal failure [4]. Nephrogenic systemic fibrosis has been reported in patients with renal insufficiency and exposed to gadolinium-based contrast agent [5].

Carbon dioxide (CO\textsubscript{2}) gas is used as an alternative contrast agent in both the arterial and venous circulations [6,7]. CO\textsubscript{2} is approximately 20 times more soluble than air, allowing intravascular injection of the gas without causing clinically significant gas embolism. CO\textsubscript{2} angiography is useful for patients with a history of contrast allergy or renal failure [6]. CO\textsubscript{2} can be used as a contrast agent for visualization of the abdominal aorta and renal, mesenteric, and peripheral arteries. CO\textsubscript{2} is used as a contrast agent for the diagnosis of GI bleeding, and traumatic...
hepatic and splenic bleeding. Because of the buoyancy of the gas, CO₂ is useful in visualizing the origins of the celiac and superior mesenteric arteries that arise from the ventral surface of the abdominal aorta in patients suspected of having median arcuate ligament compression syndrome, comprising acute and chronic mesenteric ischemia. CO₂ is a safe contrast agent in the venous circulation. An injection of 30–50mL of the gas into a peripheral or central vein causes no significant changes in vital signs. Because of its low viscosity, CO₂ is the preferred contrast agent for wedged hepatic venography to demonstrate the portal vein. CO₂ can be used as a contrast agent for splenoportography [8]. CO₂ is also used as a contrast agent to guide a variety of vascular interventions including angioplasty, placement of stent in the celiac and superior mesenteric arteries when stenosis causes abdominal angina and transjugular intrahepatic porto-systemic shunt (TIPS).

**Percutaneous catheterization**

Gastrointestinal angiography is performed using the technique described by Seldinger in 1953 [9]. The arteries used for catheterization of the visceral arteries are the femoral, axillary, and brachial arteries. Of these, the femoral approach is preferable. When the needle is introduced into the artery, the guidewire is inserted through the needle into the abdominal aorta and a diagnostic catheter is introduced over the guidewire. The technique used for femoral and jugular vein catheterization is similar to that used for arterial introduction. The guidewire is inserted into the inferior vena cava (IVC) and the catheter is advanced over the guidewire. If thrombosis has occurred in the femoral veins or IVC, the catheter is introduced by way of an antecubital, brachial, or jugular vein.

Three different sizes of needle have been used for both arterial and venous puncture by the Seldinger technique: an 18G needle with an outer, blunt cannula and an inner pointed trocar (double-wall puncture needle), a 19G single-wall puncture needle and a 21G micropuncture needle. Both the 18 and 19G needles will accept a 0.035-inch (0.89-mm) guidewire. The 21G needle will accept a 0.018-inch (0.46-mm) guidewire. When a 0.018-inch guidewire is introduced through the 21G needle, a 4 or 5 Fr introducer is inserted into the vessel over the guidewire. The outer 4 or 5 Fr introducer allows passage of a 0.035-inch standard angiographic guidewire. The use of a 0.018-inch guidewire and the inner 3 Fr dilator facilitates catheterization of a tortuous, small vessel. Ultrasound-guided arterial and venous catheter placement is increasingly used as it decreases discomfort as well as puncture site complications.

After insertion of an introducer sheath in the femoral artery, a 4 or 5 Fr pigtail or Omni Flush catheter is introduced through the sheath and advanced above the origin of the celiac axis for an abdominal aortogram in the anteroposterior and lateral projections to visualize the aorta and its branches. If median arcuate ligament compression syndrome is clinically suspected, lateral aortograms are obtained in full expiration and inspiration to evaluate the compression of the celiac axis by the ligament. Most angiographers today use a 4 or 5 Fr catheters that have been preshaped by the manufacturer. The most commonly used, commercially produced catheter configurations are the simple curve, double curve (cobra shape), or reverse curve (sidewinder, shepherd hook, or Simmons-shaped catheter).

Superselective catheterization is usually used for the diagnosis and transcatheter treatment of hepatic tumors, gastrointestinal bleeding, arterial bleeding associated with splenic or hepatic laceration, and visceral artery pseudoaneurysms. Celiac and superior mesenteric angiograms should always be done prior to the superselective injections. They provide a “road map” of the visceral arteries and their branches, facilitating the superselective catheterization procedure. Superselective visceral angiograms are done using the coaxial catheterization method in which a 3 Fr microcatheter is advanced through the 5 Fr diagnostic catheter positioned in the celiac, superior mesenteric, splenic, or hepatic artery. The microcatheter with an inner diameter of 0.027 inch (0.69 mm) allows the injection of contrast medium in the volume sufficient for diagnostic angiograms.

**General angiographic approach**

Gastrointestinal angiography can be performed as an outpatient procedure. On the day of the procedure, the patient is allowed to take fluids by mouth. Patients usually receive conscious sedation with a narcotic analgesic (fentanyl) and a benzodiazepine central nervous system depressant (midazolam) immediately before and during the procedure. For the evaluation of mesenteric ischemia and median arcuate ligament compression, lateral aortography is performed in both full inspiration and expiration. Otherwise, visceral angiography begins with catheterization of the celiac and superior mesenteric arteries. Selective catheterization of the branches of the visceral arteries is performed as needed: splenic, dorsal pancreatic, and gastroduodenal arterial catheterization for evaluation of pancreatic disease; left gastric and gastroduodenal arterial catheterization for gastric and duodenal bleeding; superior mesenteric branch catheterization for small bowel and right-sided colonic bleeding; and inferior mesenteric artery catheterization for left-sided colonic and rectosigmoidal bleeding.

Visualization of the portal venous system is essential in angiographic study for evaluating intraabdominal masses, mesenteric and portal vein thrombosis, and portal hypertension. The presence or absence of a venous abnormality plays an important role in determining whether the arterial abnormality is neoplastic or arteriosclerotic in nature. Arterial involvement by a neoplasm is usually associated with narrowing or occlusion of the adjacent vein. Visualization of the portal vein at indirect portography requires the injection of a large volume of contrast medium into the superior mesenteric or splenic artery. Portal vein visualization can be enhanced by the intraarterial injection of a vasodilator (nitroglycerin 150μg) before the injection of contrast medium.
Under normal conditions, puncture site hemostasis can be achieved with manual compression for 5–10 min following GI angiography. The patient may resume a normal diet after the procedure and ambulate after 4h of bed rest. A puncture site closure device can be used to reduce the duration of the postprocedure bed rest and observation. No pressure dressing is required.

**Wedged hepatic venography and manometry**

Wedged hepatic venography and manometry is frequently useful in the evaluation of patients with cirrhosis and portal hypertension, intractable ascites, abnormal liver function tests, graft dysfunction after liver transplantation, suspected portal vein thrombosis, and portal vein visualization for targeting in a TIPS procedure. The combination of wedged hepatic venography and manometry with transjugular liver biopsy provides information on hepatic–portal anatomy, hepatic hemodynamics, and liver histology.

Wedged hepatic venous pressure is a direct reflection of sinusoidal pressure and, in the absence of portal vein occlusion, of portal pressure. Additional pressure measurements in the right atrium, IVC, and hepatic vein can provide information about the level of obstruction in portal hypertension. Wedged hepatic venography can be performed with iodinated contrast medium or CO₂. When injected into the catheter wedged in the hepatic vein, contrast medium fills the sinusoids and peripheral portal vein branches. In the presence of reversed portal blood flow in the patient with advanced cirrhosis, the wedged injection will fill the portal vein. In contrast, the injection of CO₂ will poorly fill the sinusoids but usually reflux into the portal vein.

Wedged hepatic venography can be done with a slightly curved end-hole catheter or with a balloon catheter. The catheter can be introduced from a femoral vein or from an internal jugular vein. When the catheter is wedged in a hepatic vein, 4–6 mL of contrast medium is injected at the rate of 1 mL/s. When the balloon occlusion method is used, a total volume of contrast medium of 10–20 mL (4–5 mL/s) or 20–30 mL of CO₂ is injected by hand. When the portal vein is not seen after either wedged hepatic or balloon occlusion venography, CO₂ (20–30 mL) is injected into the liver parenchyma using a 21G needle, and images are acquired using the DSA technique. This will usually visualize the portal venous system.

**Transhepatic portal vein catheterization**

The indications for transhepatic portal vein catheterization include: evaluation of portal hemodynamics with manometry; venous sampling to localize islet cell tumor; coronary vein embolization for control of variceal bleeding; portal vein embolization prior to hepatic resection [10]; catheter-directed thrombolysis and thrombectomy in acute mesenteric vein thrombosis; and recanalization of stenotic or occluded portal vein [11]. Ultrasound, CT, or magnetic resonance angiography (MRA) is used to verify portal vein patency prior to the procedure. The venous phase of a celiac or superior mesenteric angiogram is also useful in visualizing the portal vein. Wedged hepatic venography with CO₂ may be performed from the jugular or femoral vein to visualize the portal vein. CO₂ (20–30 mL) may be injected into the liver parenchyma using a 22G needle to fill the portal vein. After the procedure has been completed, the catheter track is sealed near the hepatic capsule with a gelatin sponge or coil to arrest bleeding from the puncture site.

**Transjugular portal vein catheterization**

The transjugular approach to the portal venous system remains one of the most important techniques for the evaluation of patients with cirrhosis and portal hypertension, to diagnose and treat portal vein stenosis or occlusion and mesenteric vein thrombosis [12], to embolize the coronary vein in a patient with bleeding varices, and to create a TIPS [13,14]. The right or left internal jugular vein is punctured under ultrasound guidance. A 10Fr vascular sheath is advanced into the right atrium. After visualization of the central portal veins with the injection of CO₂ into a wedged hepatic vein or hepatic parenchyma, a 16G Colapinto-type needle is used to puncture the right portal vein near the portal vein bifurcation under fluoroscopic control. When the portal vein is entered, a guidewire is introduced into the portal vein. Over the guidewire a 5 Fr catheter is advanced into the portal vein and manometry is performed to determine a pressure gradient between the right atrium and the portal vein. The gradient is usually greater than 12 mmHg in portal hypertension. A splenoportogram is performed to demonstrate portal vein anatomy and portosystemic collateral veins. For a TIPS procedure, the parenchymal tract is dilated with an 8-mm angioplasty balloon catheter and covered with 10-mm metallic stents, such as Wallstent, or covered stents, such as VIATORR. Any competitive internal shunts such as spontaneous splenorenal shunt, gastrorenal shunt, and recanalized paraumbilic vein, and bleeding gastric varices that continue to fill after creation of a TIPS, are occluded with embolization with coils or Amplatzer vascular plugs. The endpoint pressure gradient should be less than 12 mmHg following creation of a TIPS.

**Splenoportography and percutaneous transsplenic portal vein catheterization**

Since the advent of the imaging modalities and the development of indirect portography (arterial portography), splenoportography is rarely performed. CO₂ is a useful contrast agent for splenoportography. Because of its low viscosity, the gas can be injected into the splenic parenchyma using a 22G or 25G needle. The relative safety of the small needle and the lack of nephrotoxicity of CO₂ make CO₂ splenoportography suitable for pediatric patients [8,15]. Percutaneous transsplenic portal vein catheterization is a safe and useful access for endovascular portal vein intervention in patients without transhepatic or transjugular access to the portal vein [16].
Risks and contraindications

The overall complication rates of transfemoral and transaxillary angiography are 1.73% and 3.29%, respectively [17]. The complications of transfemoral angiography include puncture site complications, complications related to catheter manipulation, contrast material reactions, contrast material toxicity (renal failure), and systemic complications (cardiac and neurological). Brachial nerve injury is the most serious complication of transaxillary arterial catheterization. Nerve injury is less likely to occur with a brachial artery puncture because the brachial plexus is not as close to the brachial artery as it is to the axillary artery. The use of intraarterial nitroglycerin and calcium channel blocking drugs is helpful in preventing arterial spasm. Mortality related to angiographic procedures other than reactions to contrast agents is extremely rare.

The overall mortality associated with the intravenous use of ionic contrast agents is 1 in 40 000 [18]. The risk factors involved in the use of contrast material are renal failure, a history of previous reactions (major and minor), and allergic diathesis. Before the administration of contrast medium for angiography, risk factors for contrast nephropathy should be identified. These include preexisting renal insufficiency, diabetes mellitus, intravascular volume depletion, congestive heart failure, repeat contrast procedures, and multiple myeloma [19]. Recommendations for prevention of contrast nephropathy include use of alternative contrast such as CO₂, discontinuation of potential nephrotoxic agents 48–72 h before the procedure, adequate hydration before and after the procedure, use of low-osmolar or isosmolar contrast material, and use of minimal volume of contrast material. Pretreatment with prednisone 50 mg at 13, 7, and 1 h before contrast administration has been advocated to prevent reaction to contrast agents for patients with a history of hypersensitivity to iodinated contrast medium. Before the procedure, Benadryl 50 mg is administered. For emergency cases, hydrocortisone 100 mg is administered intravenously before the procedure.

There are no absolute contraindications to GI angiography. Relative contraindications include severe coagulopathy, recent myocardial infarction, congestive heart failure, renal failure, and pregnancy. Patients undergoing brachial or axillary artery puncture or a percutaneous transhepatic procedure are at increased risk for hemorrhagic complications in the presence of coagulopathy or hypertension. Depending on the urgency and nature of the procedure, coagulopathy should be reversed with appropriate treatment. International normalized ratio (INR) should be corrected to less than 1.5 for percutaneous arterial puncture. Platelets should be greater than 50,000/mL. In heparinized patients, heparin should be discontinued at least 2 h before the arterial puncture. In patients on warfarin, the warfarin should be stopped several days before any arterial puncture. If urgent GI angiography is needed, the patient should be treated with fresh-frozen plasma and vitamin K 25–50 mg i.m. Aspirin and clopidogrel should be held for 5 days before arterial puncture.

Gastrointestinal angiography cannot be performed if the patient is unable to lie flat on the bed.

Vascular anatomy of the abdominal viscera

A thorough knowledge of vascular anatomy of the abdominal viscera is essential in performing and interpreting an angiogram and in planning therapeutic intervention for GI disease.

Arterial vasculature

The abdominal viscera receive their blood supply from the celiac, superior, and inferior mesenteric arteries. The superior mesenteric artery arises from the ventral aspect of the abdominal aorta 1–2 cm below the celiac axis and above the renal artery. It courses anterior to the third portion of the duodenum and the left renal vein into the mesentery. The celiac artery gives off the left gastric, splenic, and common hepatic arteries (Figure 151.1). Occasionally, the inferior phrenic or dorsal pancreatic artery originates from the celiac axis. The inferior phrenic artery may arise from the left gastric artery or renal artery, or directly from the aorta. One or more branches of the celiac artery may originate from sources other than the celiac axis: the left gastric artery from the aorta, the splenic artery from the superior mesenteric artery, and the hepatic artery from the aorta, superior mesenteric artery, gastroduodenal artery, or left gastric artery.

The common hepatic artery divides into the proper hepatic and gastroduodenal arteries. The proper hepatic artery ascends in the hepatoduodenal ligament for a variable distance and divides into a right and a left hepatic artery. The right hepatic artery usually courses behind the common hepatic duct and divides into an anterior and posterior segmental artery. Each of the segmental arteries gives off arterial branches to the superior and inferior subsegments of the liver. The left hepatic artery divides into a medial segmental (middle hepatic) and a lateral segmental artery. Each segmental artery gives rise to superior and inferior subsegmental branches. The middle hepatic artery may arise from the right hepatic, a left hepatic, or a proper hepatic artery. The proper hepatic artery also gives off arterial branches to the bile duct (peribiliary artery), the portal vein (vasa vasorum), and the subcapsular branches. In 14.2% of individuals, an accessory left gastric artery may arise from the left hepatic artery. It follows a course similar to an intrhepatic artery inferior to the inferior margin of the left hepatic lobe and a contrast injection into the artery will produce a gastric wall stain. Recognition of the accessory left gastric artery during the angiographic evaluation of a patient with hepatic malignancy who is a candidate for radioembolization is important because unrecognized extrahepatic branches with infusion of radioactive microspheres can result in gastric ulceration [20]. In about half of cases, one or more branches of the hepatic artery arise from sources other than the celiac/hepatic artery. Two types of aberrant hepatic artery may occur: replaced (the origin of the
artery is “replaced” and the aberrant artery serves as a substitute) or accessory (additive to the celiac/hepatic artery). According to Michels’ dissection of 200 cadavers [21], aberrant right hepatic arteries occur in 26% of patients (18% replaced, 8% accessory), most frequently originating from the superior mesenteric artery (17%); aberrant left hepatic arteries occur in 27% of patients (15.5% replaced, 11.5% accessory), most frequently from the left gastric artery (13%).

The gastroduodenal artery usually originates from the common hepatic artery. In 25% of the population, it may have an aberrant origin. The three main branches originating from the gastroduodenal artery are the posterior superior pancreaticoduodenal (posterior arcade), anterior superior pancreaticoduodenal (anterior arcade), and right gastroepiploic arteries. The posterior and anterior arcade arteries join inferomedially and anastomose with the inferior pancreaticoduodenal artery, a branch of the superior mesenteric artery. The gastroduodenal artery supplies arterial blood to the stomach, duodenum, pancreas, and bile duct. In the presence of a celiac artery occlusion, the pancreaticoduodenal arcade arteries function as the major collateral pathway to the liver from the superior mesenteric artery. Normally, the gastroduodenal blood flows away from the liver, but with stenosis or occlusion in the celiac or common hepatic artery the blood flow is reversed. Recognition of flow reversal in the gastroduodenal artery is important in planning resection of pancreatic head tumors, for placement of a hepatic artery infusion catheter for chemotherapy, and for intraarterial stimulation with calcium or secretin for the localization of occult insulinoma or gastrinoma, respectively.

The superior mesenteric artery supplies the pancreas, duodenum, small intestine, cecum, ascending colon, and the proximal half of the transverse colon. The inferior pancreaticoduodenal and occasionally the dorsal pancreatic arteries originate from the proximal portion of the superior mesenteric artery. The other branches of the superior mesenteric artery are the middle colic, jejunal, ileal, right colic, and ileocolic arteries (Figure 151.2). A true right colic artery is an inconstant branch (present in 13% of people), and the ascending colon often receives its blood supply from a paracolic arcade fed from the middle and ileocolic arteries [22]. However, Michels asserted that any branch proximal to the paracolic arcade that supplies the ascending colon is a right colic artery [23]. With this definition, the right colic artery arises from the superior mesenteric artery in 38%, from a common right colic/middle colic trunk in 52%, and from an ileocolic/right colic trunk in 8% of individuals. The right colic artery is absent in 2% and an accessory right colic artery is present in 8% of individuals.

The inferior mesenteric artery arises from the anterolateral aspect of the aorta near the level of the L3–4 interspace, and courses caudally and to the left for up to 5 cm before giving off the left colic artery (see Figure 151.2). The ascending branch of the left colic artery supplies the descending colon and a variable amount of the splenic flexure. The inferior mesenteric artery gives off several additional branches to the descending and sigmoid colon before terminating in the superior hemorrhoidal artery. The inferior mesenteric artery communicates through the left colic/middle colic anastomosis to the superior mesenteric artery. It also communicates through the superior hemorrhoidal/
middle and inferior hemorrhoidal arterial anastomoses to the internal iliac artery. They function as collaterals in mesenteric arterial or distal aortic occlusion and following endovascular repair of abdominal aortic aneurysm (EVAR). The superior mesenteric/middle colic to the inferior mesenteric anastomosis often accounts for retrograde flow of blood into the excluded aneurysm sac (type I1 endoleak) following EVAR.

**Portal venous system**

The portal vein is formed by the junction of the splenic and superior mesenteric veins behind the head of the pancreas (Figure 151.3) and ascends toward the hepatic hilus in the hepatoduodenal ligament, dorsal to the left of the bile duct, and to the right of the hepatic artery. The portal vein is joined by the left gastric, right gastric, posterior superior pancreaticoduodenal, and cystic veins. These tributaries provide the portosystemic collaterals in patients with cirrhosis and portal hypertension. They also provide portal–portal collateral veins in splenic, superior mesenteric, or portal vein occlusion. The right branch of the portal vein divides into the anterior and posterior segmental branches. The left portal branch divides into the superior and inferior subsegmental branches after giving off branches to the caudate and quadrate lobes. The umbilical vein joins the left portal vein at its bifurcation into the subsegmental branches. It is normally obliterated but may be recanalized in the presence of portal hypertension, providing collateral veins to the systemic circulation. Percutaneous ultrasound-guided paraumbilical vein cannulation can be safely performed for localization of the portal vein to facilitate portal vein puncture during TIPS placement.

The inferior mesenteric vein joins the splenic vein or, less frequently, the superior mesenteric vein. Portosystemic collaterals develop from the inferior mesenteric vein via the superior hemorrhoidal vein to the branches of the internal iliac vein and via the retroperitoneal vein to the IVC. The portosystemic collateral vein via the superior hemorrhoidal vein leads to the formation of rectal varices. Bleeding from the rectal varices in the patient with portal hypertension can be controlled with variceal embolization or sclerotherapy from the jugular or transhepatic approach. TIPS placement may be required for recurrent variceal bleeding following the embolization or sclerotherapy.

The portal venous system receives venous blood from the GI tract, the pancreas, the spleen, the gallbladder, and the omentum. Normally the portal vein blood flows toward the liver (hepato-petal). Reversal in flow (hepato-fugal) in any tributaries of the portal venous system indicates the presence of portal hypertension; visualization of the coronary vein or inferior mesenteric vein in the portal venous phase of a superior mesenteric angiogram indicates reversal in flow of these veins functioning as portosystemic collaterals. Reversal of portal vein flow may be partial or complete. Partial reversal of portal flow may occur in
hepatic artery blood leaves the liver through the portal vein. Blood flow direction in the intrahepatic and extrahepatic portal veins can be assessed by Doppler ultrasound, transhepatic portal vein catheterization, superior mesenteric and celiac angiography, and wedged hepatic venography. When the main portosystemic collateral develops from the umbilical vein, the extrahepatic portal blood flow can be hepatopetal in the presence of hepatofugal intrahepatic portal flow.

CT, ultrasound, and magnetic resonance venography (MRV) can be used to accurately visualize the portal venous system \[24-26\]. Portal and hepatic venous imaging can be obtained immediately following MRA with gadolinium enhancement for arterial examination (see Figure 151.3). The method is useful when a TIPS procedure, liver transplantation, or resection of intraabdominal tumors is contemplated. CO\(_2\) wedged hepatic venography is used to visualize the portal vein during TIPS or transjugular liver biopsy, or when hepatic vein outflow obstruction is suspected (Figure 151.4).

**Hepatic veins**

The hepatic veins begin in the center of the hepatic lobules as intralobular veins. These veins join together to form sublobular veins. The hepatic veins are intersegmental or interlobar in course: the right hepatic vein lies in the intersegmental fissure of the right hepatic lobe, dividing it into the anterior and posterior segments; the middle hepatic vein lies in the interlobar fissure; and the left hepatic vein lies between the medial and lateral segments of the left hepatic lobe. The hepatic veins converge posteriorly and run near the hepatic capsule before emptying into the IVC (see Figure 151.3).

The accessory hepatic veins, which originate from the right hepatic and caudate lobes, are small and empty into the IVC.
between the main hepatic and renal veins. They function as collaterals in hepatic vein occlusion, draining into the infrahepatic portion of the IVC. If the hepatic portion of the IVC is occluded, collateral circulation develops between the accessory hepatic vein and main hepatic vein draining into the patent suprahepatic IVC. Diagnostic imaging of the hepatic veins may be obtained by spiral CT [27], ultrasound [28], or MRA [29].

**Arterial disease**

Arteriography remains the gold standard in the diagnosis of visceral arterial disease. It can provide a specific diagnosis, and the necessary information on the vascular anatomy and arterial hemodynamics before endovascular intervention, hepatic artery chemoembolization, hepatic artery radioembolization, or surgery.

**Acute mesenteric ischemia**

Early angiography in patients with suspected acute mesenteric ischemia permits early differentiation between occlusive (thrombotic or embolic) and nonocclusive types that allows appropriate treatment [30,31] (Figure 151.5). In clinical practice, contrast-enhanced CT is frequently performed in patients with acute abdomen. It can demonstrate the signs of acute mesenteric ischemia, mesenteric arterial or venous thrombosis, intramural gas, portal vein gas, and focal lack of bowel-wall enhancement [32]. In the patient with superior mesenteric artery branch occlusion causing partial jejunal ischemia, CT demonstrates an abnormal jejunal segment with reduced contrast enhancement. However, catheter-based arteriography (DSA) will reveal an occlusion of a jejunal branch originating from the superior mesenteric artery with collateral circulation from the adjacent proximal jejunal artery.

After percutaneous catheterization of the femoral artery, a lateral aortogram is performed to demonstrate the origin of the celiac and superior mesenteric arteries. Occlusion of the celiac and superior mesenteric arteries with poor collateral circulation indicates acute occlusive mesenteric ischemia, and urgent surgery should be performed (Figure 151.6). When colonic ischemia is suspected, an inferior mesenteric arteriogram is performed. When the celiac, superior, and inferior mesenteric
arteries are occluded, the collateral blood supply to these arteries comes primarily from the pelvic branches of the internal iliac arteries through the inferior and middle hemorrhoidal/superior hemorrhoidal arterial anastomoses. The collaterals to the superior hemorrhoidal artery and branches of the superior mesenteric artery can be demonstrated by injecting contrast medium into the distal abdominal aorta or internal iliac arteries.

Acute mesenteric ischemia may be occlusive or nonocclusive in type. Occlusive lesions include embolism, atherosclerotic plaques, aortic dissection, neoplasms, and vasculitis. Arteriography can accurately identify the level of occlusion and evaluate collateral circulation. In superior mesenteric artery embolism, the occlusion may be proximal or distal to the middle colic artery. Arteriosclerosis usually involves the origin of the superior mesenteric artery, allowing collateral development through the left colic and middle colic anastomosis, and through the posterior and anterior pancreaticoduodenal arcades and the gastroduodenal artery. Inferior mesenteric artery stenosis or occlusion causes collaterals to develop through the middle colic/left colic anastomosis. If both superior mesenteric and inferior mesenteric arteries are occluded, collaterals develop from the middle and inferior hemorrhoidal arteries of the internal iliac arteries.

Nonocclusive mesenteric ischemia is caused by severe and prolonged intestinal vasconstriction from various causes, including systemic shock usually secondary to reduced cardiac output or sepsis, cocaine ingestion, ergot poisoning, and digoxin toxicity. The typical angiographic findings include diffuse mesenteric arterial constriction, slowing of mesenteric arterial flow, and decreased intestinal mucosal staining. When mesenteric vasospasm is identified, intraarterial infusion of papaverine (30–60 mg/h) is used to relieve mesenteric vasospasm. In patients with occlusive mesenteric ischemia and positive peritoneal signs, the infusion of papaverine may be continued before, during, and even after surgical intervention.

**Colonic ischemia**

Ischemic colitis is the most common form of mesenteric ischemia, frequently affecting the elderly. In most patients, colonic ischemia is transient and resolves without sequelae. Only some patients develop bowel necrosis or persistent ischemia that results in a stricture. The common causes of colonic ischemia are ligation of the inferior mesenteric artery during surgery [33] and low flow after cardiopulmonary bypass, myocardial ischemia, or sepsis. The other etiological factors include idiopathic, shock, colonic obstruction, digitalis, cocaine abuse, mesenteric artery thrombosis or embolism, vasculitis, radiation injury, certain medications, and hematological disorders [34].

CT is a useful tool for the diagnosis of ischemic colitis [35]. The CT findings for colonic ischemia include mural thickening, luminal narrowing, polypoid defect, decreased mucosal perfusion, pneumatosis, and pneumoperitoneum. Colonoscopy is the most sensitive examination for colonic ischemia and can demonstrate the mucosal changes. Biopsies can be obtained if necessary. The angiographic findings may be nonspecific. In the early stage, the mesenteric arteries are constricted and blood flow is slowed with decreased parenchymal vascularity. In the late stage, the colon may appear hypervascular with prominent intramural arteries and increased accumulation of contrast material in the wall of the bowel. Treatment depends on the severity of colonic ischemia and includes medical therapy and surgical intervention.

**Intestinal angina**

Intestinal angina, also called chronic mesenteric ischemia, is characterized clinically by a postprandial abdominal pain associated with weight loss, nausea, vomiting, or diarrhea. The abdominal pain usually begins 15 to 30 min after a meal. The most common cause is atherosclerosis involving the proximal portions of the celiac, superior mesenteric, or inferior mesenteric artery. Less common causes include aortic dissection extending to the splanchnic arteries, vasculitis, fibromuscular dysplasia, radiation, and cocaine abuse. The risk factors for splanchnic artery stenosis are smoking, hypertension, diabetes mellitus, and hypercholesterolemia.

At least two of the three splanchnic arteries (celiac artery, superior, and inferior mesenteric arteries) usually have significant occlusive disease before the syndrome of intestinal angina occurs [36]. Duplex ultrasound with spectral analysis is used for screening patients thought to have chronic mesenteric artery occlusive disease. Multidetector row CT angiography plays a primary role in the evaluation of patients suspected of having visceral artery occlusive disease [37]. Multidetector row CTA will adequately demonstrate the degree of stenosis in the celiac trunk and superior mesenteric artery, and the associated collateral circulation. It also allows visualization of the vessel wall, bowel wall thickening, and the other pathologies that may cause abdominal pain. It may not accurately assess patency of heavily calcified vessels. In patients with renal failure or contrast allergy, gadolinium-enhanced three-dimensional MRA should be used as a primary diagnostic tool in the evaluation of the origins of the celiac and superior mesenteric arteries, but its resolution is inadequate for evaluation of mesenteric artery branch stenosis [38]. Angiography provides information regarding the hemodynamic significance of mesenteric artery stenosis and the circulation distal to the stenosis necessary for endolumenal intervention (usually angioplasty and stent placement) [39] or surgical revascularization. Demonstration of collateral circulation distal to a superior mesenteric artery stenosis indicates that the stenosis is hemodynamically significant. Pressure measurement across the stenosis can help assess the hemodynamic significance of the stenosis prior to endovascular intervention.

**Celiac axis compression**

Celiac axis compression syndrome (median arcuate compression syndrome) is controversial as a cause of abdominal pain.
The celiac axis may be narrowed or, in severe cases, occluded by the median arcuate ligament of the diaphragm. Surgical correction of the lesion by decompression or reconstruction of the vessel usually ameliorates the pain [40]. Because balloon dilation is not helpful in eliminating the extrinsic compression, stent placement is required [41]. Without prior releasing of the extrinsic compression, stenting may be ineffective due to compression of the stent by the ligament. Celiac axis stenosis is frequently an incidental finding, with a reported prevalence of 12%–49% [42,43]. CTA and MRA can demonstrate celiac trunk narrowing by median arcuate ligament compression. A lateral aortogram with CO$_2$ or contrast medium demonstrates a concave impression on the cranial aspect of the celiac axis just distal to the celiac axis origin. The compression is usually accentuated during deep expiration and decreased in severity or completely relieved during deep inspiration. A superior mesenteric angiogram will demonstrate collateral circulation to the hepatic and splenic arteries through the gastroduodenal and pancreatic arcade arteries from the superior mesenteric artery.

**Superior mesenteric artery syndrome**

When the aortomesenteric angle is reduced from a normal angle of 25° to 60° to an angle of 6° to 15°, the superior mesenteric artery (SMA) can compress the third portion of the duodenum, causing duodenal obstruction. Such compression is most often found in patients with chronic immobilization with weight loss and a body cast [44,45]. The upper GI barium examination shows a characteristic oblique indentation toward the right lower quadrant on the third portion of the duodenum, corresponding to the course of the superior mesenteric artery. The second portion of the duodenum is usually dilated. CTA or MRA can demonstrate vascular compression of the duodenum and enable measurement of the aortomesenteric angle. A narrow aortomesenteric angle corresponding to the site of obstruction can be seen on a lateral aortogram. The treatment of superior mesenteric artery syndrome is conservative with nasogastric decompression, hyperalimentation followed by frequent small meals, and posturing maneuvers. Surgical bypass may be considered if conservative treatment fails.

**Vasculitis**

Vasculitis of the mesenteric arteries is usually part of a systemic process. The causes include Wegener granulomatosis, systemic lupus erythematosus (SLE), polyarteritis nodosa, Henoch–Schönlein purpura, Buerger disease, giant cell arteritis, and infection. Mesenteric vasculitis may cause acute or chronic mesenteric ischemia. The gastrointestinal symptoms of mesenteric vasculitis include abdominal pain, gastrointestinal bleeding, peritonitis, intestinal infarction, pancreatitis, duodenal ulcer, and cholecystitis. CTA or MRA can demonstrate vessel wall thickening/irregularity and aneurysms. Arteriographic studies should include an aortogram, celiac, superior, and inferior mesenteric angiograms. The angiographic findings vary with the type of vasculitis. In polyarteritis nodosa, celiac and superior mesenteric angiograms demonstrate occluded small- and medium-sized arteries with or without microaneurysms (Figure 151.7). In ergot or digitalis toxicity, the mesenteric artery branches are narrowed or occluded with collaterals. In SLE, angiography demonstrates diffusely decreased small bowel vascularity. Angiography is the most sensitive method of visualizing microaneurysms. The angiographic examination should include the renal, celiac, and mesenteric arteries.

**Splanchnic artery aneurysms and pseudoaneurysms**

Splanchnic artery aneurysms and pseudoaneurysms are rare. They often found incidentally during angiographic studies for other indications or in patients with abdominal pain, gastrointestinal or abdominal bleeding, or pancreatitis. Angiography is usually necessary to identify the exact site of the aneurysm and its relationship to adjacent vascular structures, as well as to plan surgical resection or embolization to prevent catastrophic hemorrhage [46,47]. Aneurysms occur in virtually all splanchnic arteries.

Splenic artery aneurysms account for 60% of all visceral artery aneurysms [48]. They occur four times more frequently in women than in men and are multiple in 20% of patients. Causes include atherosclerosis, medial fibrodysplasia, multiple pregnancies, pancreatitis, portal hypertension, polyarteritis nodosa, Ehlers–Danlos syndrome, and trauma. In portal hypertension, aneurysms tend to occur at the bifurcation of the intrasplenic branches of the splenic artery [49]. Most
atherosclerotic splenic artery aneurysms are asymptomatic, and calcified aneurysms less than 2 cm in diameter require no treatment. In contrast, aneurysms occurring in pregnant women and those associated with pancreatitis require treatment because of their propensity to bleed. Splenic artery aneurysms can be treated with embolization or percutaneous puncture with thrombin injection or covered stents [50]. The hepatic artery is the second most common site for splanchic aneurysms, accounting for 20% of all splanchic aneurysms [48]. Most hepatic pseudoaneurysms are traumatic in origin and are secondary to blunt or penetrating abdominal trauma, liver biopsy, liver surgery, liver transplantation, pancreaticoduodenectomy (Whipple procedure), biliary stent placement, pancreatitis, or placement of a hepatic arterial infusion catheter. Most spontaneous aneurysms occur in the common hepatic or right hepatic artery. Clinical presentations include right upper quadrant pain, hemobilia, GI bleeding, or obstructive jaundice. Rarely, hepatic artery aneurysms rupture into the peritoneal cavity, portal vein, or pancreatic pseudocyst. The diagnosis can be made by ultrasound, contrast-enhanced CT, MRA, or arteriography. Treatment includes embolization by transcatheter approach or percutaneous puncture with thrombin injection or placement of covered stents [51].

Mesenteric aneurysms are arteriosclerotic and may cause GI bleeding or mesenteric ischemia. The other causes include pancreatitis, dissection, mycotic aneurysm, and Ehlers–Danlos syndrome type 4. Celiac axis aneurysms account for 4% of all visceral aneurysms and should be differentiated from pseudocysts when encountered during ultrasound or unenhanced CT scanning. A lateral aortogram is necessary to confirm the diagnosis of aneurysms arising from the origins of the celiac and superior mesenteric arteries. Treatment includes surgical ligation, embolization, and use of covered stents [52].

Gastroduodenal (GDA) and pancreatic arterial aneurysms are usually associated with pancreatitis and pseudocysts. Other causes include blunt trauma, autoimmune disorders, vascular intervention, and surgery. They may cause GI and intraperitoneal hemorrhage. Rarely, aneurysms rupture into the pancreatic duct or a pseudocyst. Ultrasound and contrast-enhanced CT usually differentiates pseudocysts and aneurysms. Angiography is required to delineate the vascular anatomy and the exact origin of the aneurysm before surgical treatment or transcatheter embolotherapy. If a GDA aneurysm is associated with celiac stenosis or occlusion, patency of the GDA should be maintained during surgical revascularization, vessel ligation or aneurysmal sac exclusion. If celiac and hepatic arteries are patent, transcatheter embolization is preferable. It involves isolation or exclusion of the aneurysm with coil occlusion of the feeding artery proximal and distal to the aneurysm.

Abdominal trauma Abdominal trauma can be due to penetrating or blunt injuries. Most traumatized patients require radiological studies to assess the extent of the injury. Contrast-enhanced CT should be the first imaging modality for the evaluation of abdominal trauma. Angiography is indicated when CT shows a high-grade injury of solid organs, contrast extravasation, pseudoaneurysm, or vascular injuries.

Venous disease Occlusion of the portal, mesenteric, splenic, and hepatic veins may be asymptomatic or associated with ascites, hepatic failure, intestinal ischemia, or GI hemorrhage. Contrast-enhanced CT and MRV can diagnose occlusion of the portal and splenic vein by demonstrating intraabdominal varices and thrombus in the portal venous system [25]. Duplex scanning is useful in the assessment of patency and direction of blood flow of the portal vein and portosystemic shunts [53]. The portal venous phases of the celiac, superior mesenteric, and splenic angiograms are used to evaluate the patency of the splenic, mesenteric, and portal veins, respectively. An inferior vena cavogram and hepatic venogram are performed in patients with suspected Budd–Chiari syndrome. Transjugular or transelectic portal vein cannulation is used in direct splenoportography with portal venous pressure measurement, and portal venous interventions including angioplasty, stenting or a TIPS procedure.

Portal vein occlusion The pattern of portal vein occlusion usually varies with its etiology [54]. Idiopathic intrahepatic portal vein occlusion (hepatoporal sclerosis) usually occurs in children. Occlusion of the main portal vein is the most common type and is probably of congenital etiology. Thrombosis of the main and superior mesenteric veins may be caused by intraabdominal sepsis, portal hypertension, and hypercoagulable states.

Angiographic findings include large collateral veins originating from the superior mesenteric vein, ascending in the hepato-duodenal ligament in the venous phase of the superior mesenteric angiogram (Figure 151.8). The collateral vessels reconstitute the patent intrahepatic portal vein. If the intrahepatic portal venous branches are occluded, the collateral vessels continue to run along the intrahepatic bile ducts, giving the appearance of railroad tracks [55]. In mesenteric vein thrombosis, numerous tiny collateral veins are demonstrated throughout the mesentery without visualization of the superior mesenteric vein in the venous phase of the superior mesenteric angiogram.

The angiographic abnormality of portal vein occlusion due to neoplasms varies with the type of neoplasm. Pancreatic and biliary cancers cause localized narrowing or occlusion of the portal vein without associated tumor vessels. In contrast, portal vein invasion by hepatocellular carcinoma has a characteristic appearance, with abnormal vascular channels coursing within the portal vein branches in the vicinity of the tumors. Arteriovenous shunting is often associated with portal vein invasion by tumors [56].
Venous pressure from right heart failure may produce a contrast-enhancement pattern similar to that of Budd–Chiari syndrome. MRI is useful in identifying the underlying lesions, such as hepatic and vena caval thrombi, and congenital membrane [60].

Angiography is the most important procedure for the diagnosis of Budd–Chiari syndrome. Superior mesenteric and celiac angiograms are obtained to visualize the portal vein and exclude hepatic neoplasms. An inferior vena cavogram is obtained to exclude occlusion of, or membrane in, the hepatic portion of the IVC. Demonstration of hepatic vein patency excludes the diagnosis of Budd–Chiari syndrome. When the hepatic vein is occluded, the catheter is wedged into the occluded hepatic vein, and contrast medium is injected to visualize the collateral channels (Figure 151.9). If the right hepatic vein cannot be entered, catheterization of the accessory hepatic vein should be performed. If any of the hepatic veins cannot be catheterized, a 22G needle is inserted into the liver parenchyma using the same technique used for percutaneous transhepatic portal vein catheterization. Injection of iodinated contrast medium or CO₂ usually demonstrates hepatic vein occlusion and collateral veins [61].

**Splenic vein occlusion**

Splenic vein occlusion is usually clinically silent but may cause hypersplenism or gastric variceal bleeding [57,58]. The causes include pancreatitis, pancreatic cancer, and hypercoagulable states. The diagnosis can be made by dynamic CT, duplex ultrasound, and three-dimensional contrast MRV. Angiography should be performed when noninvasive studies are inconclusive or when additional vascular information is needed. A celiac or splenic arteriogram is performed for the diagnosis; the angiographic findings include splenportal collaterals through the short gastric/coronary and gastroepiploic veins, as well as nonopacification of the splenic vein during the venous phase. The treatment of choice for bleeding gastric varices associated with splenic vein occlusion is splenectomy. If surgical intervention is contraindicated, partial splenic artery embolization by transcatheter approach is an effective alternative treatment [59]. Localized splenic vein occlusion or stenosis can be treated by transhepatic splenic vein balloon dilation and stent placement.

**Budd–Chiari syndrome**

In Budd–Chiari syndrome, a significant portion of the hepatic venous system is obstructed. CT is usually used as the initial test and may reveal nonuniform contrast enhancement of the liver parenchyma and enlarged caudate lobe. Increased central venous pressure from right heart failure may produce a contrast-enhancement pattern similar to that of Budd–Chiari syndrome. MRI is useful in identifying the underlying lesions, such as hepatic and vena caval thrombi, and congenital membrane [60].

Angiography is the most important procedure for the diagnosis of Budd–Chiari syndrome. Superior mesenteric and celiac angiograms are obtained to visualize the portal vein and exclude hepatic neoplasms. An inferior vena cavogram is obtained to exclude occlusion of, or membrane in, the hepatic portion of the IVC. Demonstration of hepatic vein patency excludes the diagnosis of Budd–Chiari syndrome. When the hepatic vein is occluded, the catheter is wedged into the occluded hepatic vein, and contrast medium is injected to visualize the collateral channels (Figure 151.9). If the right hepatic vein cannot be entered, catheterization of the accessory hepatic vein should be performed. If any of the hepatic veins cannot be catheterized, a 22G needle is inserted into the liver parenchyma using the same technique used for percutaneous transhepatic portal vein catheterization. Injection of iodinated contrast medium or CO₂ usually demonstrates hepatic vein occlusion and collateral veins [61].
Percutaneous transluminal angioplasty and stent placement has been used to treat Budd–Chiari syndrome caused by obstruction of the hepatic vein and hepatic segment of the IVC [62,63]. Restenosis or reocclusion occurs frequently at the angioplasty site. Patency of the vein may be improved with use of metallic stents after unsuccessful angioplasty. The transjugular or transhepatic approach is used for angioplasty and stent placement for right hepatic vein occlusion causing Budd–Chiari syndrome [64,65]. The TIPS procedure is used to treat intractable ascites and bleeding varices from hepatic venous occlusive disease and as an effective bridge to transplantation for hepatic failure associated with Budd–Chiari syndrome [66,67].

**Gastrointestinal disease**

When evaluating GI disease, angiography is indicated for the diagnosis of vascular disease, visualization of vascular anatomy, and diagnosis and treatment of GI bleeding. If active GI bleeding is diagnosed, angiography can be urgently performed for localization of the bleeding site as well as control of the bleeding. The rate of bleeding should be at least 0.5 mL/min to be detected by angiography. Angiography is insensitive in detecting capillary or venous bleeding because of the dilution of the contrast material. Helical CT angiography with intraarterial or intravenous injection of contrast medium is useful in detecting active GI bleeding as well as GI bleeding of obscure origin, and facilitates angiographic localization of the bleeding [68–70]. CO₂ is a sensitive contrast agent in detecting active bleeding that may not be seen with contrast medium. Once the bleeding site has been identified by CO₂, contrast medium is injected for a vascular “roadmap” before superselective catheterization of the bleeding artery for embolotherapy. Angiography is useful for identifying vascular malformations and vascular neoplasms. A catheter may be placed in the mesenteric branch supplying a vascular malformation preoperatively to facilitate intraoperative localization of the lesion.

**Upper gastrointestinal bleeding**

Endoscopy is the primary procedure for the diagnosis and treatment of upper GI bleeding. If endoscopy has failed to localize or control the bleeding, angiography is performed for the diagnosis and treatment. After percutaneous catheterization of the femoral artery, celiac and superior mesenteric angiograms are obtained with CO₂ and contrast medium. Because of its lower viscosity, CO₂ is a useful contrast agent in detecting GI bleeding (Figure 151.10). If a bleeding site is identified, the bleeding artery is selectively catheterized to control the bleeding by embolization [71]. If a bleeding site has not been demonstrated, left gastric and gastroduodenal arteriograms are obtained. If the source of bleeding has still not been identified and nasogastric aspiration reveals dark blood, a catheter may be placed in the left gastric artery for the next 6–12 h. The bleeding may be precipitated by intraarterial administration of heparin, vasodilators, or thrombolytic agents, allowing accurate localization of the bleeding site and prompt treatment [72,73]. Prophylactic embolization (left gastric artery embolization for gastric bleeding and gastroduodenal artery embolization for duodenal bleeding) is an acceptable alternative when the massive bleeding has ceased at the time of angiography [74,75].

Angiography is usually not helpful in determining the cause of upper GI hemorrhage. Hemorrhagic gastritis is the most common cause of capillary bleeding and imaging may demonstrate a hypervascular stomach with dilated gastric arteries and increased parenchymal staining. Peptic ulceration is the most common cause of arterial bleeding and usually produces no angiographic abnormality. Gastric bleeding usually arises from the left gastric artery and occasionally from the short gastric, right gastric, or gastroepiploic artery. Duodenal bleeding may originate from the celiac or superior mesenteric artery or from both arteries. Angiographically the arterial bleeding appears as a localized accumulation of contrast material extravasation.
coaxial catheter system with minimal risk for intestinal necrosis [80–82].

Angiodysplasia

Angiodysplasia may occur in a variety of pathological types: vascular ectasia, arteriovenous malformations, and capillary telangiectasia [83]. Clinical presentation and angiography allow identification of each type of angiodysplasia.

Vascular ectasia usually occurs in the cecum and ascending colon. Most patients are older than 60 years of age. The angiographic findings include a small vascular cluster and blush in the wall of the colon and early dense opacification of the draining vein (Figure 151.12) [84]. Normal mesenteric angiography is usually accepted for exclusion of vascular ectasia, although data supporting this assumption are not available. Two or more vascular ectasias are frequently present at microscopic examination of the injected specimen, although most patients demonstrate a single vascular lesion at angiography. Endoscopy is superior to angiography in identifying vascular ectasia. If active extravasation is demonstrated, selective arterial embolization is an effective treatment. Arteriovenous malformations are of

Lower gastrointestinal bleeding

Once lower GI bleeding is diagnosed by clinical presentation (hematochezia) and colonoscopy, a superior mesenteric angiogram is performed to detect the bleeding from the small intestine and the right side of the colon. If no bleeding site is seen, a celiac arteriogram is obtained because massive gastroduodenal bleeding may present as lower GI bleeding. If a radionuclide scan has localized the bleeding to the left side of colon, inferior mesenteric arteriograms are obtained with coverage from the rectum to the splenic flexure of the colon. Active bleeding shows a localized accumulation of escaped contrast material during the arterial phase of the mesenteric angiogram, which usually persists through the venous phase (Figure 151.11). CO₂ should be used as a contrast agent for the superior and inferior mesenteric angiograms if contrast angiograms have failed to demonstrate the bleeding site.

Selective infusion of vasopressin is usually effective in controlling the bleeding in up to 80% of patients, but the recurrence rate is as high as 50% [79]. Patients with coronary artery disease should not be treated with vasopressin because of the risk for myocardial infarction. Selective embolization is the therapeutic procedure of choice. Superselective catheterization and embolization of the bleeding artery can be achieved with use of the 3 Fr coaxial catheter system with minimal risk for intestinal necrosis [80–82].
vasopressin into the inferior mesenteric artery is effective in controlling the bleeding. If the patient has coronary artery disease or if vasopressin fails, selective embolization is performed with Gelfoam, Ivalon particles, or microcoils [89].

**Intestinal varices**

Intestinal varices represent varices at an unusual site in patients with cirrhosis and portal hypertension. Contrast-enhanced CT and MRV are used to diagnose intestinal varices. Angiography provides the necessary information about the location and extent of the varices, and the status of the portal venous system. The varices are demonstrated in the portal venous phase of a superior mesenteric angiogram. Percutaneous transhepatic or transjugular portal vein catheterization may be necessary for evaluation of portal hemodynamics and embolization of intestinal varices. TIPS is effective in treating stomal or rectal varices unresponsive to conservative treatment, injection sclerotherapy, or embolization [90–92].

**Neoplasms of the small intestine**

**Gastrointestinal stromal tumor**

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract, previously called as leiomyoma and leiomyosarcoma. CT is the primary imaging modality for the detection of GI stromal tumors [93]. Angiography is useful in diagnosing small bowel stromal tumors. The tumors are usually hypervascular with abundant tumor vessels and dense blush (Figure 151.13). The draining vein usually is densely opacified. Angiographic differentiation between benign and malignant tumors is not possible unless venous invasion or metastasis is demonstrated [94]. When active bleeding occurs from the tumor, a radionuclide bleeding scan or enhanced CT is performed to localize the bleeding site. Angiography is then performed to localize and control the bleeding with superselective arterial embolization. Once the bleeding has been controlled by embolization, the tumor should be resected.

**Carcinoid tumor**

Carcinoid tumors arise from enterochromaffin cells that are present in the GI tract, lung, ovary, pancreas, and other organs. They produce various hormones, including serotonin, histamine, dopamine, and tachykinins. The imaging modalities (including CT, MRA, and radionuclide scan) play an important role in the evaluation of mesenteric extension of carcinoid tumors and liver metastases [95]. Angiography may be used for diagnosis and staging of carcinoid tumors. The angiographic findings include retraction, kinking, and occlusion of the mesenteric arteries. Carcinoid tumors metastatic to the liver are usually hypervascular with abundant tumor vessels. Venous sampling with hormone assay may be necessary for localizing occult carcinoid tumors, especially those occurring in the ovary and lungs. When the patient with liver involvement has severe carcinoid syndrome, hepatic artery embolization is an
Abdominal angiography

CHAPTER 15

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... and to assess the extent of the lesion before surgery. Newer imaging modalities are now used to both diagnose and stage the lesion [100]. Angiography is performed to obtain a specific diagnosis, to determine the extent of the tumor, and to demonstrate vascular anatomy. In patients with pancreatitis, pseudocysts, or vascular lesions, angiography is necessary when surgery or endovascular therapy is contemplated for the treatment of visceral artery pseudoaneurysms. Selective angiography and hepatic venous sampling with the intraarterial injection of secretin for gastrinoma and of calcium gluconate for insulinoma continue to play a role in the localization of occult pancreatic endocrine tumors.

Adenocarcinoma

Current imaging techniques, including helical CT, multidetector CT, MRI, endoscopic ultrasound (EUS), and positron emission tomography are important in early diagnosis and staging of pancreatic cancer [101,102]. Angiography is performed to evaluate vascular anatomy and involvement of any major peripancreatic artery (splenic, hepatic, or superior mesenteric artery) or vein (superior mesenteric, splenic, or portal vein). When any major peripancreatic artery or vein is involved, the tumor may be unresectable (Figure 151.14). If pancreatic cancer is confined within the pancreas, surgical resection offers the only potential cure. Irreversible electroporation, a newer ablative treatment modality, has demonstrated some potential benefit in the treatment of unresectable locally advanced pancreatic cancer [103,104].

Cystic tumors

Cystic lesions may be found on imaging studies of patients without symptoms. A wide variety of cystic lesions occurs in the pancreas, including cystic neoplasms and pseudocysts. CT, EUS, and MRI should be used to diagnose cystic lesions of the pancreas [105,106]. Angiography is reserved for determining the extent of the tumor and vascular anatomy before surgical resection. Angiographically, microcystic adenomas are usually hypervascular with abundant tumor vessels and blush, whereas mucinous cystic tumors are hypovascular with sparse tumor vessels mimicking a pseudocyst.

Pancreatic endocrine tumors

CT, MRI, and EUS have all been used to demonstrate endocrine tumors of the pancreas with varying success. Angiography is infrequently used for localization of islet cell adenomas. Angiographic technique in the examination of the pancreas requires meticulous catheterization of the superior mesenteric artery and celiac artery, and its branches. Angiographically, islet cell tumors appear as a localized area of contrast material accumulation (tumor blush) with or without tumor vessels (Figure 151.15). Malignant islet cell tumors may grow into the portal vein [107]. Most hepatic metastases from islet cell carcinomas are hypervascular and are readily detected by hepatic angiography.
angiography. Angiography is sensitive in localizing insulinomas (accuracy 60%–90%) but is less sensitive in detecting gastrin-producing tumors. Other endocrine tumors, such as vasoactive intestinal peptide producing tumors (VIPoma), glucagonoma, and somatostatinoma, are usually hypervascular with abundant tumor vessels.

Percutaneous transhepatic venous sampling with hormone assay is a useful method for localizing occult islet cell tumors. This method may be used to localize the source of abnormal hormone secretion to the head, body, and tail of the pancreas, as well as to the liver. This is helpful in avoiding blind resection of the pancreas [108]. Simultaneous arterial and venous sampling from the splenic, superior mesenteric, and portal veins can detect localized elevation of hormones near the tumor site; adenomas of the body and tail of the pancreas produce increased hormone concentrations in the splenic vein, and those of the pancreatic head produce increased hormone concentrations in the superior mesenteric and portal veins. Simultaneous blood sampling from the hepatic and portal veins helps to determine the presence of hepatic metastases from gastrinomas [109].

Selective intraarterial injection of secretin with assay of hepatic venous gastrin has been useful in localizing gastrinomas and hepatic metastases [110,111]. It involves injection of 30 units of secretin into the splenic, gastroduodenal, proper hepatic, and superior mesenteric arteries, as well as blood sampling from the hepatic vein to measure the changes in gastrin concentration. An increase in hepatic venous gastrin concentration of at least 50% at 30–40 s after selective arterial injection of secretin indicates a positive response, localizing the tumor to

Figure 151.14 Unresectable pancreatic cancer. (a) Hepatic arteriogram (magnification technique). The common hepatic (a) and proximal gastroepiploic (b) arteries are encased by a tumor in the head of the pancreas. (b) Portal venous phase of a superior mesenteric angiogram (oblique view). The junction of the superior mesenteric and portal veins is invaded by the tumor (arrow). PV, portal vein; SMV, superior mesenteric vein. Source: Shields et al. 1981 [178]. Reproduced with permission of Elsevier.

Figure 151.15 Islet cell adenoma in a patient with hyperinsulinism. Parenchymal phase of a splenic angiogram (digital subtraction technique) demonstrates a 1-cm diameter tumor blush (arrow) in the distal body of the pancreas. S, splenic parenchymal staining.
the part of the pancreas supplied by the artery injected: the gastroduodenal and superior mesenteric arteries for the head of the pancreas and the splenic artery for the body or tail. The selective arterial secretin injection test is more sensitive than transhepatic portal venous sampling for localizing occult gastrinomas [112]. An increase in hepatic venous gastrin concentration of at least 25% at 20 s or 50% at 30 s after hepatic arterial injection of secretin indicates the presence of hepatic metastases [113].

In patients with suspected insulinomas, calcium gluconate is injected intraarterially and the level of insulin is measured in the hepatic vein for localization of insulinomas [114]. The patient is admitted the night before the procedure to stabilize the glucose level with intravenous administration of 10% dextrose. Blood samples are obtained from the hepatic vein before and at 30, 60, 90, and 120 s after the injection of calcium gluconate (Ca\(^{2+}\) 0.015 mEq/kg body weight) into the superior mesenteric, gastroduodenal, splenic, and hepatic arteries, respectively. Calcium injection should be separated by 20–30 min to allow the insulin level to return to baseline. A 1.5–2.0-fold rise in insulin level in the hepatic vein at 30 and 60 s after intraarterial injection of calcium localizes the source of insulin to the region of the pancreas supplied by the artery stimulated.

**Pancreatic arteriovenous malformations**

These rare vascular lesions may bleed directly into the intestine, the pancreatic duct, or the bile duct [115–117]. Portal hypertension and varices resulting from arteriovenous shunting in the malformation may be the cause of the bleeding. Angiography is important in the preoperative diagnosis and localization of the lesion (Figure 151.16). The lesion may mimic chronic pancreatitis or a vascular tumor. Surgical resection of the involved portion of the pancreas can be curative. Transcatheter embolization may be used as treatment for control of hemorrhage [118].

**Vascular lesions associated with pancreatitis**

Angiography has little diagnostic use in patients with pancreatitis because the diagnosis is well established clinically. When vascular complications occur, angiography is necessary for the diagnosis of vascular involvement and treatment. In about half of cases of pseudocyst, peripancreatic venous narrowing or occlusion is found. Bleeding associated with pancreatitis may be venous or arterial in origin. Venous bleeding usually results from gastric varices associated with splenic or portal vein occlusion. Venous bleeding rarely results from duodenal varices caused by superior mesenteric or portal vein occlusion. Arterial hemorrhage is a rare but life-threatening complication of pancreatitis, usually secondary to rupture of intrapancreatic or peripancreatic pseudoaneurysms. Arteriography is indicated for the diagnosis of arterial bleeding and pseudoaneurysm, and selective embolization should be used as a definitive or preoperative temporizing procedure [119–121].

**Hepatic disease**

Radionuclide scintigraphy, ultrasound, CT, and MRI have all been used for demonstration of liver masses [122–125]. Angiography still is important in evaluating liver tumors for the specific diagnosis, resectability of the tumor, and before therapeutic hepatic artery embolization.

Knowledge of the hepatic circulation is important in the performance and interpretation of hepatic angiograms and in planning for hepatic arterial chemotherapy. The liver receives a dual blood supply; about 75% of the total hepatic blood flow comes...
from the portal vein and the remaining 25% comes from the hepatic artery. The relationship between the portal vein and hepatic artery is reciprocal; a decrease in portal blood flow results in an immediate compensatory increase in hepatic arterial flow. When portal blood flow is diminished in cirrhosis or obstructive jaundice, hepatic arterial embolization for bleeding or tumors must be undertaken cautiously because the liver in these conditions depends primarily on arterial blood.

**Cavernous hemangiomas**
Cavernous hemangiomas, the most common benign hepatic tumors, are composed of large sinusoidal spaces with fibrosis and thrombosis. CT, MRI, and technetium-99m scintigraphy with the use of single photon emission computed tomography (SPECT) are useful for obtaining a specific diagnosis [126,127]. The lesions usually appear well defined and hypodense on unenhanced CT. When contrast medium is administered, the lesions initially show nodular peripheral enhancement, which becomes confluent gradually. On MRI, the lesions usually show bright signal intensity on T2-weighted images. The angiographic findings are characteristic, with normal feeding arteries and dense persistent pooling of contrast material through the venous phase of a hepatic angiogram.

**Adenoma**
Hepatic adenoma usually occurs in young women with a history of oral contraceptive use, and rarely in patients with glycogen storage disease [128,129]. Because of the risk of bleeding, hepatic adenoma should be surgically resected in almost all patients. Hepatic adenomas are nonspecific at ultrasonography, and are usually evaluated by CT or MRI [130]. Angiographically, hepatic adenomas are usually vascular, with abnormal vessels and tumor blush. Adenomas associated with bleeding may become hypovascular or avascular, making their angiographic localization difficult. The definitive diagnosis cannot be established on the basis of the angiographic abnormality. When an adenoma bleeds, angiography is necessary to evaluate the extent of bleeding and identify the tumor. Selective arterial embolization may be used for treatment of abdominal pain and bleeding from hepatic adenomas [131]. When the patient becomes stable following the embolization, resection may be considered to prevent recurrent bleeding.

**Focal nodular hyperplasia**
Focal nodular hyperplasia (FNH) is a benign liver tumor, often found incidentally on imaging studies performed for other indications. Asymptomatic FNH rarely bleeds and therefore no treatment is necessary. CT and MRI have been used to differentiate FNH from other hepatic tumors [132]. Because of the difficulty in differentiating FNH from hepatic adenoma and fibrolamellar hepatocellular carcinoma, surgical resection may still be necessary for some patients. Angiographically, FNH is usually hypervascular with abnormal vessels and granular blush. Multiple septa radiating from the central area of scar is usually demonstrated. Patients with FNH located near the capsule may present with nonspecific abdominal pain prompting resection of the tumor. Transarterial bland embolization is a safe, effective alternative treatment for FNH [133].

**Biliary cystadenoma**
Biliary cystadenomas are benign multiloculated cystic tumors arising from the intrahepatic or extrahepatic bile duct. Ultrasound and CT can demonstrate the lesions [134]. Angiography is performed to define hepatic arterial anatomy and determine the extent of the tumor before surgery. The angiographic findings are usually nonspecific and may demonstrate subtle neovascularity and rim-like staining in the wall of the tumor, mimicking a hepatic abscess, echinococcal cyst, or congenital hepatic cyst.

**Hepatocellular carcinoma**
CT and MRI are the primary imaging methods used for the diagnosis of hepatocellular carcinoma (HCC) [135–138]. Angiography is necessary to define the extent of the tumor, blood supply, and portal venous anatomy. Most hepatomas are hypervascular angiographically, with coarse tumor vessels (Figure 151.17). Involvement of the extrahepatic portal vein by HCC indicates that the tumor is unresectable. Angiography is also performed for a vascular “roadmap” before hepatic artery chemoembolization for HCC.

**Hepatocellular carcinoma**
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![Figure 151.17 Hepatoma. Hepatic arteriogram shows a hypervascular mass (arrowheads) with tumor blush. Numerous tumor vessels supplied by a dilated right hepatic artery branch (arrow) are seen. The left hepatic artery (open arrow) arises from the left gastric artery (LGA). CHA, common hepatic artery; GDA, gastroduodenal artery.](image_url)
Cholangiocarcinoma

Angiography has a limited role in the diagnosis but may be performed to provide a vascular “roadmap” and evaluation of portal vein patency when surgical resection is contemplated. The angiographic findings include encasement of the hepatic arterial branches, which may be associated with encasement of the portal vein.

Metastatic hepatic neoplasms

Hepatic metastases from renal cell carcinomas, islet cell carcinomas, carcinoid tumors, and medullary thyroid carcinomas are hypervascular, while metastases from other primary sites are less vascular. Angiography is sensitive in detecting hypervascular metastases (Figure 151.18). Angiography is performed to determine resectability of hepatic metastases and the presence of aberrant hepatic arteries before the surgical placement of a hepatic arterial catheter for chemotherapy, hepatic artery chemoebolization or Yttrium-90 radioembolization.

Panhepatic angiography

Increased resistance to the flow of portal vein blood is the principal cause of portal hypertension. The location of the blockage in portal blood flow may be intrahepatic or extrahepatic. Cirrhosis is the most common cause of intrahepatic sinusoidal block. Hepatic vein (postsinusoidal) and portal vein (presinusoidal) occlusion produce an extrahepatic block to portal vein flow. An increase in portal vein blood flow secondary to splenomegaly or arterioportal fistulae rarely causes portal hypertension (hyperkinetic) [139]. Transcatheter embolization may be used to occlude the arterioportal fistula and lower portal pressure.

The term panhepatic angiography is used for the angiographic study performed for the evaluation of portal hypertension. It includes: celiac, superior mesenteric, hepatic, and splenic angiograms; wedged hepatic venograms; and manometry. Panhepatic angiography determines hepatic arterial variations, assesses portal hemodynamics, and excludes hepatoma. Visualization of aberrant hepatic arteries is important because accidental ligation of the hepatic artery in the presence of portal hypertension may result in hepatic necrosis. A right hepatic artery that originates from the superior mesenteric artery poses technical difficulty for portacaval shunt surgery. A hepatic angiogram is necessary to exclude hepatomas and helps determine the hemodynamics of intrahepatic portal flow. In advanced cirrhosis with reversed portal flow, the portal vein may be visualized in the venous phase of the hepatic arteriogram. High-dose superior mesenteric and splenic angiograms are necessary to see the superior mesenteric, splenic, and portal veins, as well as the portosystemic collaterals. In alcoholic cirrhosis, a pressure measurement from the catheter wedged in the hepatic vein reflects portal vein pressure and is useful in determining whether the location of the obstruction is intrahepatic or extrahepatic. However, wedged hepatic vein pressure is not a useful determinant for selecting the type of shunt surgery. It is also a poor predictor of prognosis and survival after shunt surgery. In any case, the TIPS procedure has largely replaced surgical shunt in recent years. Wedged hepatic venography is the most accurate means of assessing the morphological features of the hepatic sinusoids and parenchyma. CO₂ is used as a contrast agent for most wedged hepatic venography to visualize the portal vein for its targeting during a TIPS procedure. Manometry of the right atrium, hepatic vein, and IVC helps determine the level of hepatic venous outflow obstruction. Wedged hepatic venography, manometry, and transjugular liver biopsy from the jugular vein approach are frequently used as this provides in one session hepatic–portal anatomy, hemodynamics, and liver histology. This combination study may be performed in: (1) a patient with known cirrhosis and portal hypertension; (2) a patient with a history of cirrhosis or hepatitis and intractable ascites; (3) a patient without a history of cirrhosis or hepatitis who bleeds from esophageal varices; (4) patients with hepatic failure of unknown etiology; (5) a patient with suspected Budd–Chiari syndrome; and (6) liver transplant patients with suspected hepatic outflow obstruction.

Percutaneous transcatheter therapy

Diagnostic angiography should be performed before any transcatheter intervention for hepatic–portal disease, cirrhosis and portal hypertension, and GI disorders. Interventional radiological procedures are reviewed in detail in Chapter 152.
Percutaneous transluminal angioplasty and stent placement

Balloon angioplasty and stenting have proven to be safe and effective treatment for intestinal angina resulting from atherosclerotic disease of the mesenteric artery and mesenteric arterial compression by the false lumen of an aortic dissection [140–143]. The treatment for median arcuate ligament syndrome is surgical with median arcuate ligament release or laparoscopic release of the arcuate ligament. In patients with persistent or recurrent celiac stenosis following surgical or laparoscopic intervention, celiac angioplasty and stenting are recommended [144].

Percutaneous transluminal angioplasty (PTA) and stenting have proven safe and effective for treating hepatic and IVC stenosis/web causing Budd–Chiari syndrome [145,146]. If the hepatic vein is obliterated diffusely, TIPS should be performed to relieve portal hypertension [147]. Portal vein stenosis and postoperative stricture of the portal vein complicating liver transplantation are amenable to balloon angioplasty and stenting [11,148,149].

PTA and stenting is the preferred therapeutic option for hepatic artery stenosis in liver transplant recipients because of a significant risk of thrombosis of untreated stenosis and high risk of rethrombosis following surgical repair [150].

Transcatheter embolotherapy

Transcatheter embolotherapy is an acceptable alternative to surgery in treating massive arterial GI bleeding, visceral aneurysms and pseudoaneurysms, hypersplenism, isolated gastric varices associated with splenic vein occlusion, and traumatic hepatic and splenic bleeding [46,151–155]. Occlusion of the hepatic artery by embolization for control of hepatic bleeding is usually tolerated because the hepatic sinusoidal perfusion can be maintained by collateral circulation and the portal venous blood. Hepatic arterial embolization is used for the treatment of traumatic hepatic bleeding, hemobilia, and symptomatic arterioporal fistula. However, hepatic artery embolization in patients with symptomatic hepatic arteriovenous malformations associated with hereditary hemorrhagic telangiectasia has a high risk for hepatic infarction and death [156]. The spleen receives adequate collateral blood flow through the pancreatic, left gastric/short gastric, inferior phrenic/short gastric, and gastroepiploic arteries after occlusion of the splenic artery. Superselective catheterization of the splenic artery is performed using the coaxial catheterization method using a 3 Fr microcatheter. Microcoils are the most frequently used occluding agent and produces arterial occlusion equivalent to surgical ligation. Injection of thrombin into an aneurysm promotes clot formation. A 3 Fr coaxial catheter system is extremely useful in catheterization and embolization of a mesenteric branch artery. If an aneurysm cannot be catheterized transarterially, a 22G needle is used for percutaneous puncture, and embolization of the lesion is accomplished with microcoils and thrombin.

Thrombolytic therapy

Thrombolytic therapy may be used for superior mesenteric artery embolism and portal vein thrombosis. A report of thrombolytic therapy for superior mesenteric artery embolism indicates that the method is safe and effective, with technical success in 90% and clinical success in 70% [157], but the treatment requires at least 6–8 h of infusion. A percutaneous transhepatic or transjugular approach is necessary for thrombolysis of mesenteric and portal vein thrombosis. The technique involves placement of a catheter into the embolus or thrombus, and infusion of a lytic agent. During thrombolysis, the patient should be monitored for bleeding and evidence of bowel infarction in the intensive care unit. A mechanical thrombectomy device, such as AngioJet (Bayer Co. Pittsburgh, PA) may be used for removal of thrombi from the mesenteric and portal vein thrombosis.

Hepatic arterial infusion chemotherapy

Regional delivery of antineoplastic agents through a selectively placed arterial catheter produces higher tumor response than systemic infusion [158,159]. The success of hepatic arterial chemotherapy depends on accurate evaluation of the hepatic arterial anatomy and hemodynamics, and correct catheter placement. To ensure total liver perfusion and drug delivery to the tumor site, the hepatic arterial anatomy is meticulously evaluated by celiac and superior mesenteric arteriograms. Multiple hepatic arteries can be converted to a single hepatic artery using the transcatheter embolization technique to facilitate catheter placement [160]. For example, if an aberrant left hepatic artery from the left gastric artery is embolized, the left hepatic lobe receives blood supply through intrahepatic collaterals from the right hepatic artery. If the infusion catheter cannot be placed in the proper hepatic artery, the gastroduodenal artery may be occluded by embolization to allow infusion of drugs with a catheter placed in the common hepatic artery [161]. Hepatic arterial catheters can be placed through a percutaneous approach from the femoral or brachial artery, or surgically. The introduction of the totally implantable pump has improved regional chemotherapy with surgical catheter placement [162]. Radionuclide flow study using 99mTc-labeled macroaggregated serum albumin is the most accurate means of assessing hepatic perfusion pattern after catheter placement. The complications of percutaneous catheter placement are biliary artery thrombosis, hepatic artery thrombosis, catheter displacement, and puncture-site bleeding. The complications of surgical catheter placement are hepatic artery thrombosis, incorrect catheter placement, catheter occlusion, and pump malfunction. Complications related to the toxicity of chemotherapeutic agents are chemical hepatitis, biliary sclerosis, chemical cholecystitis, and gastroduodenal inflammation and ulceration.

Hepatic tumor embolization

Transarterial chemoembolization (TACE) is used to palliate hepatic tumors including hepatoma, metastatic neuroendocrine
tumors, and metastatic colon cancer if the tumors cannot be treated by the percutaneous ablation method (Figure 15.19). Generally, TACE has been shown to be beneficial and improve survival [163–167]. TACE has also been used to prevent tumor progression or shrink the tumor while awaiting liver transplantation in order to improve clinical outcome [168–171].

CT or MRI of the liver must be reviewed for evaluation of location of tumor, extent of disease, and any associated findings (portal vein occlusion, biliary obstruction). Adequate portal venous flow should be available to maintain hepatic parenchymal vitality. If the intrahepatic portal flow is reversed (hepatofugal), embolization should not be performed or limited to the subsegment containing tumor.

Hepatic arterial embolization results in selective destruction of the tumors exclusively dependent on arterial supply while maintaining the vitality of the normal liver with portal vein blood. Small particles such as polyvinyl alcohol (Ivalon 150–250 μm) are used to occlude peripheral arteries to decrease the development of collateral blood flow. Concurrent embolization increases the effect of the drug by prolonging exposure of the tumor and producing tumor anoxia while minimizing systemic drug effects. Injection of iodized oil into the hepatic artery results in selective accumulation of the oil within most vascular hepatic tumors. This phenomenon has been exploited to selectively deliver antineoplastic agents and radioactive isotopes to hepatic cancers, with intraarterial injection of a mixture of iodized oil and antineoplastic agents or radioactive iodized oil solution. Hepatic arterial delivery of yttrium-90 microspheres (TheraSphere, SIR-Spheres) is widely used for treatment of HCC and metastatic liver tumors [172–174]. The microspheres are injected into the hepatic artery to deliver radiation directly to tumors with concurrent ischemia from microspheres. Once embolized within the tumor microcirculation, these microspheres emit beta radiation at therapeutic levels. Another new agent, DC Bead®, is used for hepatic artery chemoembolization. The DC Bead® is an embolic agent loaded with chemotherapeutic agents [174–176]. When introduced into the tumors, it eludes drug over weeks.

Hepatic artery embolization may be associated with the postembolization syndrome: abdominal pain, nausea, vomiting, and fever lasting 2–7 days. Mildly abnormal liver tests are common. Other complications include hepatic necrosis, gallbladder infarction, and gastroduodenal ulcers. Follow-up CT or MRI is obtained at 3-month intervals and repeated embolizations can be performed for recurrent tumors.

Figure 151.19 Hepatic artery chemoembolization in a 63-year-old patient with hepatitis C cirrhosis and hepatocellular carcinoma (HCC). (a) Right hepatic arteriogram. Branches of the right posterior segmental hepatic artery supply a hypervascular mass in the liver (arrow). (b) Hepatic arteriogram performed shortly after embolization showing complete devascularization of the HCC (arrow). (c) Contrast-enhanced magnetic resonance image obtained 6 weeks after chemoembolization confirmed complete necrosis of HCC (arrow).
Forthcoming advances

Noninvasive imaging modalities (CT, MRI, ultrasound, and PET) will play an increasing role in the evaluation of GI diseases, hepatic tumors, splanchnic arterial disease, and cirrhosis and portal hypertension. They now provide much of the diagnostic information that can be obtained from angiography. Therapeutic applications of angiography will continue to expand in the treatment of GI bleeding, vascular lesions, hepatic neoplasms, mesenteric vascular occlusive disease, variceal bleeding unresponsive to endoscopic therapy, intractable ascites, and hepatic–portal venous occlusion.

References are available at www.yamadagastro.com/textbook

Further reading


CHAPTER 152
Interventional radiology

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Introduction
Vascular and interventional radiology (VIR or IR) utilizes minimally invasive image-guided targeted procedures to diagnose and treat diseases in nearly every organ system. In the past decade advances in technology have combined with the skill set of interventional radiologists and resulted in significant changes in patient care. IR procedures frequently offer less risk, less pain and less recovery time compared to open surgery.

Treatment of primary and secondary liver cancer
Image-guided percutaneous therapies play an important role in the treatment of patients with primary and secondary hepatic malignancies. A variety of therapeutic modalities are available including ablative techniques such as ethanol ablation and radio-frequency ablation as well as intraarterial approaches such as transarterial chemoembolization and radioembolization. These therapies offer reduced systemic toxicity and effective local tumor control. As a result, some procedures have been included in the National Comprehensive Cancer Network (NCCN) treatment guidelines [1]. The success of percutaneous therapies has brought recognition to the field of interventional oncology, and united physicians from multiple specialties to work on multidisciplinary teams to treat liver cancer.

Ablative therapies
Background
The scientific rationale for the use of ablative techniques in patients with primary liver cancer lies in the limited resectability of some liver tumors due to a background of cirrhosis and a limited hepatic reserve. Initial trials focused on injection of ethanol [2], which resulted in 5-year survival rates comparable with surgical resection [3]. In time, different types of chemo- and thermo-ablative methods evolved and their potential to cure liver cancer paved the way for modalities such as radiofrequency ablation in the National Comprehensive Cancer Network (CCN) treatment guidelines for liver cancer.

Techniques
Initial experience with one of the first image-guided, chemo-ablative techniques was collected by Livraghi and colleagues, when 12 patients with various primary and secondary liver malignancies were treated with injections of 95% ethyl alcohol (percutaneous ethanol injection [PEI]) [2]. The injection of ethanol into a lesion induces cellular dehydration, protein...
denaturation and, as a result, leads to coagulation necrosis of the targeted tissue. PEI can achieve complete necrosis of small liver nodules and is safe in tumors near sensitive organs. However, the need for multiple treatments and frequent local tumor recurrence are significant limitations of this modality [4].

Radiofrequency ablation (RFA), the first energy-based ablation technique, uses electrical current to cause thermal injury to the tissue, producing coagulation necrosis near the electrode [5]. RFA is able to overcome some of the PEI limitations by using the “oven effect,” defined as heat retention in nodules surrounded by the tumor capsule and cirrhotic tissue [6] thus causing extensive necrosis (Figure 152.1). An important benefit of RFA induced necrosis is the ablation of a tumor-free margin, which might explain the lower frequency of local tumor recurrence as compared to PEI. However, a physical limitation of RFA is the “heat sink” effect, which can be defined as the cooling effect of blood flow through large vessels or ascites near the ablation zone [7]. This can result in insufficient tumor necrosis.

Microwave ablation (MWA), another thermo-ablative technique, is less susceptible to the physical limitations of the “heat-sink” effect [8]. This system uses high-frequency electromagnetic energy (≤900 kHz) to rapidly oscillate water molecules, resulting in coagulation necrosis through frictional heat. When compared to RFA, MWA shows higher temperatures and a shorter treatment time.

Multiple other modalities such as cryoablation, laser ablation, irreversible electroporation as well as image-guided, catheter based high-dose brachytherapy of liver tumors are gaining more attention. However, technical specifics of each method are beyond the scope of this chapter.

Clinical evidence
Several clinical trials provide evidence for significant outcome benefits in patients with early-stage primary liver cancer, treated with ablative techniques. As most of the thermal ablative methods show excellent safety profiles and tumor response rates according to imaging criteria, most of the clinical trials focus on progression-free survival (PFS) and overall survival (OS). A retrospective study reported the 20 year clinical outcome of 685 patients with early-stage hepatocellular carcinoma (HCC), treated with a total of 2147 ethanol injections [9]. The median follow-up in this large patient cohort was 51.6 months. The overall survival rate was 49% and the recurrence rate was reported as 60.8% after 20 years. This retrospective analysis confirmed the potential of PEI, when used in patients with early-stage HCC and small tumors (2.83 cm ± 1.47). However, the relatively high recurrence rate confirmed the limitations of PEI.

An important prospective trial, designed to provide long-term survival data for early-stage HCC patients treated with RFA, enrolled a total of 187 patients. Minor complications appeared in only 5% of the patients, confirming the overall safety of the technique. In this group of patients, the median survival rate was 57 months and the overall survival rate after 5 years was 48%. Local tumor recurrence was observed in only 10% after 5 years [10], showing the efficacy of RFA as compared to PEI.

The success of ablative techniques prompted the trend of combining these modalities with intraarterial therapies. A prospective, randomized controlled trial compared the impact of RFA alone versus the combination of transarterial chemoembolization (TACE) with RFA on the overall survival of 189 patients (n = 94 received RFA, and n = 95 received TACE-RFA). Patients with mostly early-stage and some with intermediate-stage disease were included; 90 patients in the study were classified as Child–Pugh A. The mean tumor size in each treatment arm was 3.47 cm and 3.39 cm for the TACE-RFA and the RFA alone group, respectively. In the TACE-RFA group, RFA followed the conventional TACE treatment within 2 weeks. As a result, patients treated with the TACE-RFA combination showed significant benefits regarding overall survival and recurrence-free survival when compared with the RFA alone group. The 4-year survival rate was reported as 61.8% and 45% for the TACE-RFA and RFA group, respectively [11]. The results of this trial are encouraging for the combination of intraarterial approaches with ablative techniques in patients with intermediate stage HCC. Additional combination studies are underway.

Figure 152.1 A patient with a 2.5 cm HCC lesion in the left lobe of the liver. (a) Baseline-MRI shows enhancement of the target lesion. (b) RFA needle placed under CT guidance. (c) Ablation zone in a follow-up MRI 1 month after treatment.

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation.
with the hope to confirm the results from this initial experience.

**Intraarterial therapies**

**Background**

Over the past 35 years, catheter-based intraarterial therapies have gained acceptance as a therapeutic option for patients with primary and metastatic hepatic malignancies [12,13]. Recently, intraarterial approaches have been utilized for downstaging bridge to orthotopic liver transplantation [14] or resection. (Figure 152.2) The scientific rationale for all intraarterial therapies lies in the fact that in contradistinction to healthy liver tissue, which is predominantly supplied by the portal vein, most liver malignancies draw their blood supply from the hepatic artery. This characteristic allows an operator to use catheter-based intraarterial approaches to deliver chemotherapy or radiation selectively to the tumor, while preserving normal hepatic parenchyma [15].

The first clinical trials that helped establish catheter-based embolotherapies of liver tumors date back to the 1970s and aimed at simply ablating the local arterial blood supply to liver tumors [16]. Although the general principles of intraarterial therapies remain unchanged, important modifications have been introduced to improve patient outcomes. The most frequently used image-guided intraarterial liver therapies performed by interventional oncologists include transarterial chemoembolization (TACE) with or without drug-eluting beads (DEBs) and radioembolization using Yttrium-90 (Y90).

![Figure 152.2](image-url) A patient with a 7 cm HCC lesion in the right lobe of the liver. (a) Baseline-MRI shows homogeneous enhancement of the target lesion. (b) Angiogram of the right hepatic artery shows a tumor blush. (c) Follow-up MRI 1 month after treatment shows a largely necrotic lesion. (d) MRI after surgical resection of the right lobe. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.
Radioembolization exploits the same concept as TACE but delivers localized radioembolics to liver tumors. The strength of radioembolization seems to lie in a slightly better quality of life in patients with late-stage liver cancer and slight survival benefits in patients with portal-venous thrombosis [17]. However, most clinical trials have been relatively small. The following paragraphs provide an overview on intraarterial therapies, techniques, complications and discuss the most recent clinical evidence.

Techniques
All intraarterial procedures share a common approach. Initially, arterial access is gained using the Seldinger technique [18], and multiple diagnostic angiograms are performed. This defines the hepatic arterial anatomy, assesses the blood supply of the tumor, determines portal venous patency and establishes the ideal location for embolization. This is particularly important for transarterial chemoembolization, where (as opposed to radioembolization) a super-selective placement of the catheter is crucial for optimal results.

Conventional TACE
The concept of conventional TACE (cTACE) (Figure 152.3) was originally introduced in 1977 by Yamada and colleagues as a palliative therapy with the goal of treating patients with resectable HCC [15]. The scientific rationale for the use of cTACE is to increase the intratumoral concentration of chemotherapeutic agents and to combine it with tumor vessels embolization [19], while reducing systemic toxicity related to chemotherapy. During the cTACE procedure, an emulsion of chemotherapeutic agents and oily contrast medium (Lipiodol™, Guerbet, USA) is selectively delivered to the tumor-feeding artery. This is followed by temporary or permanent embolization. Lipiodol is a key ingredient of TACE and has unique properties as a drug-carrier and embolizing agent. Due to the hypervascularized character of most liver tumors and the absence of Kupffer cells, Lipiodol persists within tumor nodules for several weeks [20,21]. The amount of injected Lipiodol emulsion is titrated to be proportionate to the size of the tumor [22]. Several chemotherapeutic agents can be used for cTACE; most commonly cisplatin and adriamycin/doxorubicin are utilized for injection [23]. Depending on the origin of the liver cancer, other combinations are also possible and often include epirubicin, 5-fluorouracil, or mitomycin C [24]. The subsequent administration of embolic material such as Gelfoam (Upjohn, Kalama-zoo, MI, USA), polyvinyl alcohol (PA) particles or trisacryl gelatine (TG) microspheres, serves a dual purpose: (1) causing stasis in subsegmental arterial branches; and (2) preventing washout of the previously deposited drug [25]. Embolization with Gelfoam (a biodegradable gelatin sponge) has proven safe and effective for the occlusion of larger blood vessels [26], but it has been largely replaced by nonbiodegradable TG microspheres, which to occlude very distal tumor supplying blood vessels [27].

DEB-TACE
The development of drug-eluting microspheres (drug-eluting beads, DEBs) enabled a new transarterial approach, the DEB-TACE. This system delivers a higher concentration of drugs to the tumor and reduced systemic drug exposure compared with cTACE [28,29]. This development has led to a shift away from cTACE towards DEB-TACE in the treatment of patients with HCC especially in the US and Europe. Although two different types of drug-eluting microspheres are available clinically in the US as embolic material (DC Beads and QuadSphere/Hepasphere microspheres), neither is approved as a drug-delivery microsphere by the Food and Drug Administration (FDA) [30,31]. Most of the clinical data to date has been generated by the DC Beads (Biocompatibles/ BTG, UK) that can be loaded with doxorubicin (DEBDOX) or irinotecan (DEBIRI). The DC beads are soft, compressible, spherical particles that are based on nonbiodegradable PVA microspheres and range in size from 75–900μm. The smaller bead diameters achieve a more peripheral embolization and a more extensive necrosis compared with larger beads (Figure 152.4) [32]. Drug elution occurs gradually and selectively within the targeted tissue. A histopathological study described the high efficiency of DEB-mediated drug delivery and release to the tumor tissue, thus causing local coagulative necrosis and an inflammatory-fibrotic tissue (Figure 152.5) [33]. The other type of microspheres, made by Merit Medical (USA), is based on a nonbiodegradable suprasorbent polymer (SAP). The SAP spheres have the ability to absorb fluids and thus to expand their volume to a size of up to 800μm. The few existing studies of this system show encouraging results when the spheres are loaded with doxorubicin or cisplatin [34].

Radioembolization
The high toxicity profile of external beam hepatic irradiation in patients with primary and secondary liver malignancies [35] have prompted the development of alternate approaches. One such technique is “radioembolization” which utilizes the same scientific rationale as TACE, but instead of chemotherapy delivers high-dose radiation directly to the tumor. The selective intraarterial infusion of small embolic particles loaded with the radioisotope Y90 achieves tumoricidal effects while preserving normal liver tissue. This therapy combines the benefit of effective tumor kill due to a high local radiation dose with the reduction of systemic toxicities of external beam radiation [36]. Two embolization agents are FDA-approved for clinical use; the resin-based SIR-Spheres (Sirtex Medical Ltd., Australia) and the glass-based TheraSpheres (MDS Nordion, Canada) [37]. The 20–30μm sized TheraSpheres show a high activity (2500 Bq/Sphere) and are FDA-approved for radioembolization of HCC. The 20–60μm sized SIR-Spheres show a lower activity (50 Bq/Sphere) and are FDA-approved for the treatment of colorectal metastases to the liver. Both types of microspheres deliver high cumulative doses of radiation to the tumor, which can vary from 100 Gy to more than 3000 Gy. Because of the small particle size of the microspheres and highly aggressive
Figure 152.3 A patient diagnosed with HCC presents with two new 3 cm lesions in the left lobe. (a) Baseline-MRI shows two enhancing lesions (arrow head indicates the target lesion for the initial cTACE). (b) Angiogram of the arteries supplying the target lesion (tumor blush). (c) Postprocedural CT scan shows successful deposition of embolic material. (d) Follow-up MRI shows necrotic target lesion (arrow head) next to a viable nontarget lesion. (e) Second cTACE, Angiogram of the viable lesion (tumor blush). (f) Intraprocedural Cone-beam CT showing fresh embolic material within the target lesion (big arrow head) and remaining material within the previously treated lesion (small arrow head). HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.
prior to tumor resection or as a bridge to orthotopic liver transplantation. TACE has been included in treatment guidelines and according to the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy, it can be applied as a palliative therapy in patients with intermediate stage HCC [40]. In general, TACE may be indicated in patients with liver-dominant, unresectable hepatic malignancies. This includes several groups of patients with secondary liver malignancies [41]. For instance, TACE of unresectable, hormonally active neuroendocrine tumors may reduce or eliminate hormonal symptoms [42]. TACE can be used as a salvage option in patients with unresectable colorectal metastases to the liver [43]. Until recently, there were no existing guidelines for the use of radioembolization in patients with unresectable primary and secondary liver cancer. However, potential indications for the use of radioembolization include patients with intermediate stage disease that are poor candidates for TACE as well as patients with large solitary tumors invading segmental or lobar branches of the portal vein and patients that show progression after TACE [44]. Not all liver cancer patients with unresectable liver tumors can benefit from intraarterial therapies. Patient selection must be based on the presence of adequate liver function, sufficient performance status (Karnofsky index, East Coast Oncology Group performance status [ECOG]) and the absence of extrahepatic spread [45]. The most important contraindications are similar for all intraarterial techniques. Table 152.1 provides an overview on the current contraindications for conventional TACE.

Adverse effects and complications
The overall safety of intraarterial therapies has been demonstrated in a variety of prospective clinical trials. Systemic adverse effects of cTACE can include nausea, vomiting, bone marrow aplasia, renal failure, and cardiac toxicity. The postembolization syndrome is a self-limiting reaction after TACE that can cause nausea, vomiting, fever, right upper quadrant pain and increased white blood cell count. It occurs in approximately 10% of the patients and reflects the effects of tumor necrosis, acute cytokine release and systemic exposure to chemotherapeutic agents [41,46]. Super-selective TACE has been demonstrated to decrease risks and to improve overall survival compared with nonselective TACE [47]. This approach can also reduce the rate of more severe complications such as postprocedural liver failure, abscess, cholecystitis, biloma, and hemorrhage.

The introduction of drug-eluting beads in TACE was intended to reduce the complications and toxicities observed in cTACE. Enhanced systemic pharmacokinetics of DEB-TACE has been shown both in animal models [48] and patients [49], when peak plasma concentrations of doxorubicin were measured for DEB-TACE and compared with conventional TACE. DEB-TACE demonstrated significantly lower peak plasma levels of the chemotherapeutic. Adverse effects of doxorubicin used in DEBs range from alopecia and skin discoloration to mucositis and bone marrow suppression. A multicenter, randomized, prospective phase II study, that compared the safety and toxicity of

payload radioembolization bears the risk of systemic distribution of radioactive isotopes via hepato-pulmonary shunts or nontarget delivery of Y90 to the GI tract [38]. A preprocedural angiographic evaluation with test injection of 99m-Tc-labeled macro-aggregated albumin is performed in order to evaluate vessel anatomy, exclude a high shunting fraction and to estimate the dose delivered to the tumor (Figure 152.6) [39].

Patient selection/contraindications
Intraarterial therapies can be used for palliative treatment of patients with unresectable liver tumors, as an adjunctive option
DEB-TACE and cTACE in HCC patients, demonstrated the significantly better toxicity profile of DEB-TACE compared with cTACE. The overall frequency of treatment-related adverse effects was lower in the DEB-TACE group as were the toxicity grades and the occurrence of severe adverse effects. For instance, alopecia in patients treated with doxorubicin was almost absent in the DEB-TACE group with only one patient versus 23 events in the cTACE group. Furthermore, major liver toxicities were also lower in DEB-TACE as compared to cTACE [28]. In summary, DEB-TACE is a safe, tolerable and effective technique.

The intraarterial injection of Y90 containing spheres during radioembolization can cause rare but severe toxicities [50]. The selection of proper patients and a thorough evaluation using test injection of $^{99m}$Tc-labeled macro-aggregated albumin can significantly reduce complications. Postradioembolization syndrome occurs in 20% to 50% of patients [51]. However, there
is evidence that the symptoms are less severe and the postproce-
dural quality of life is higher than after cTACE [17].

Clinical evidence
Transarterial chemoembolization
Although intraarterial therapeutic approaches have expanded over the past 30 years, TACE remains the only intraarterial therapy for which significant survival benefits have been demonstrated in patients with unresectable HCC and other liver malignancies [40].

Conventional TACE
The level one evidence for survival benefits of patients treated with conventional TACE was provided by two separate prospective phase three trials in 2002, leading to its inclusion in treatment guidelines for HCC. Subsequent additional prospective and retrospective studies confirmed survival benefits. One retrospective, single-center study, designed to assess treatment response and long-term survival outcomes in a large group of patients with unresectable HCC, included 172 mainly cirrhotic individuals (91%). In this study, 55% of the patients experienced procedure-related toxicities, most of which were minor. According to the European Association for the study of the liver criteria (EASL), 64% of the treated tumors showed response with 23% showing complete response. The median overall survival (OS) for patients with early stage disease (BCLC A) was reported as 40.0 months. In patients with intermediate and advanced stage disease, OS was 17.4 months (for BCLC B), and 6.3 months (BCLC C) [52]. A more recent retrospective multicenter analysis confirmed the effects of highly selective conventional TACE in patients with unresectable HCC. Here, a total of 199 patients were treated and followed over the course of 10 years. However, local recurrence rates for the entire collective was relatively high at 46%, 58% and 62% after 2, 3 and 5 years, respectively [53]. Another study addressed the issue of cTACE regimen and included 151 consecutive HCC patients that were treated “on demand.” Complete response was achieved in 48% of patients after the first cTACE and the rate slightly increase after additional procedures, suggesting some benefits of such a regimen [54].

TACE may represent an effective treatment of patients with unresectable intrhepatic cholangiocarcinoma (iHCC) and is increasingly used in such clinical scenarios. One of the initial prospective trials, designed to study feasibility, and safety, as well as the impact of cTACE on patient survival, included 17 patients with unresectable iHCC. cTACE procedures were well tolerated by most patients (82%). Two of the patients were bridged to successful surgical resection after cTACE. The median survival in this study was 23 months [55]. Recently, a single-center study with a total of 115 patients confirmed these results. In this trial, patients were repeatedly treated with cTACE with a mean of 7.1 sessions per patient. According to response evaluation criteria in solid tumors (RECIST criteria), 57.4% showed stable disease (SD) which can be considered a good tumor response rate given the condition of the patients. The safety profile and tolerability of cTACE was very good for the entire collective with only 15 patients showing adverse effects. The mean overall survival in this group of patients was 20.8 months with a 3-year survival of 10%, showing the benefits of cTACE in this group of patients [56].

Conventional TACE is commonly used for salvage therapy of patients with metastatic cancer to the liver. In some cases, this therapy can allow patients with unresectable cancer to become candidates for surgical resection. However, for most patients intraarterial therapy represents a palliative option with the goal to improve survival. Several studies that include patients with chemorefractory colorectal, neuroendocrine, gastric and pancreatic metastases to the liver provide clinical data for safety and efficacy of this therapy. One these studies evaluated the local tumor response and acquired survival data in a total of 56 patients with liver metastases of gastric cancer [57]. A total of 310 TACE procedures were performed and a variety of different drug combinations was tested (mitomycin, gemcitabine and cisplatin). As a result, SD was achieved in 51.8% of patients, which can be considered as an excellent result. With a survival rate of 58%, 38% and 23% after 1, 2 and 3 years, respectively, this study confirmed the potential of cTACE to provide some survival benefit. Another study evaluated the role of repetitive cTACE in the treatment of a cohort of 32 patients with liver metastases of pancreatic cancer. The analysis of tumor response and overall survival showed the efficacy and feasibility of this TACE regimen for this group of patients as 72% of the patients experienced SD and 9.4% PR [58].

DEB-TACE
Drug-eluting beads as a novel drug delivery system for TACE have been the subject of both prospective and retrospective studies. In a first, FDA-sanctioned prospective phase II pilot study in the US, a total of 20 mostly cirrhotic (80%) patients with unresectable HCC were evaluated regarding safety, efficacy as well as progression-free and overall survival. Most patients were staged as Child–Pugh A (75%), with almost two-thirds of the patients classified as BCLC stage C (60%), 64% of the patients were classified as responders according to EASL criteria and 30% achieved CR after an overall of 34 DEB-TACE sessions. After 6 months, only one patient showed disease progression according to RECIST (Figure 152.7). Only modest toxicities and a median overall survival of 26 months in a majority of advanced patients (BCLC C) confirmed the potential of DEB-TACE as an alternative to cTACE [29]. The international multicenter prospective randomized phase II trial directly compared cTACE and DEB-TACE regarding safety and efficacy. In this study, a larger collective of 212 patients were randomized 1:1 and 201 patients received treatment according to standardized protocols. The two treatment groups were stratified according to ECOG performance status and the Child–Pugh class. Patients in the DEB-TACE group showed better imaging response according to EASL criteria than those
In the cTACE group. Although at the 6 month follow-up time point (the end point of the study), the CR rate was nearly identical in both groups (26.6% and 22.2% complete response in the DEB-TACE and cTACE groups, respectively), the rate of progressive disease was significantly lower and in favor of DEB-TACE (32.3% vs. 40.7% for the cTACE group) [28]. The results of this study confirmed the previously demonstrated advantages of DEB-TACE. In another prospective multicenter study, a total of 173 unresectable HCC patients were subjected to DEB-TACE treatment. This study was designed to assess long-term clinical outcomes for DEB-TACE. Results revealed a 5-year survival of 29.4% and 12.8% for Child–Pugh class A and B, respectively [59]. The data on DEB-TACE demonstrate the potential of that therapy. However, the inclusion of DEB-TACE in the treatment guidelines will likely require a definitive randomized trial. Still, evidence indicates that DEB-TACE is better tolerated than cTACE.

DEB-TACE has also been utilized to treat patients with unresectable IHC. A first prospective trial of DEB-TACE (using irinotecan, DEBIRI) enrolled 26 consecutive patients with the purpose to assess feasibility, safety and efficacy of the modality. PFS and OS were 3.9 months and 11.7 months, respectively. When compared with an historical cTACE cohort (PFS of 1.8 months and OS 5.7 months), DEB-TACE was safe with only minor toxicities. More importantly, DEB-TACE provided a better local tumor control than the other therapies as reported in previous studies [60]. The data on the use of TACE in patients with unresectable IHC is growing and the main strength of DEB-TACE seems to lie in the ability to elicit a strong tumor response and disease control. The use of DEBs as a platform for intraarterial drug delivery to secondary liver tumors has been demonstrated in a retrospective analysis of 28 patients with metastatic colorectal cancer. Irinotecan-eluting beads (DEBIRI) were used and tumor response was assessed using modified RECIST (mRECIST) criteria in all patients. After 47 procedures, 15% of the treated patients were classified as complete responders and 30% showed PR, while 20% showed SD and 35% PD. Most importantly, a median overall survival of 13.3 months was
achieved with this treatment, again demonstrating the potential of DEB-TACE [61]. Another, prospective phase II study found encouraging results in the use of DEB-TACE in patients with neuroendocrine metastases [62]. However, further data in larger patient cohorts are needed to validate the safety of DEB-TACE in patients with metastatic liver cancer.

Radioembolization

The technical principle of tumor radioembolization has existed since the late 1960s. However, radioembolization is not a replacement for TACE as a treatment for HCC. The most recent studies concentrate on patients with HCC and portal vein invasion [63]. One of the first US studies designed to evaluate the safety and survival of HCC patients treated 80 patients with radioembolization using TheraSpheres (Nordion, Canada). In this trial, patients were mostly classified as Child–Pugh A, had unresectable noninfiltrative HCC, an ECOG performance status of 0–2 and adequate liver, pulmonary, renal and bone marrow function; 44% of the patients had bilobar disease, and 27 patients received multiple treatments with one patient receiving a maximum of four procedures. In terms of safety, 28% of the patients showed some adverse events with eight patients experiencing life-threatening and one patient a fatal event. Child–Pugh A patients showed a median overall survival of 18.6 months whereas Child–Pugh B patients achieved only a median of 8.04 months [36]. Since that study was published in 2004, multiple studies with radioembolization have been conducted and many studies are underway. One prospective, single-center study was designed to validate safety and determine efficacy of TheraSpheres radioembolization in 108 HCC patients not eligible for TACE. Fifty-one percent of the patients were classified as BCLC stage C and 77% were staged as Child–Pugh A [63]. Imaging response according to mRECIST 90 days after treatment showed CR in 6% of the patients, while 35% and 48% of the patients showed partial response (PR) and SD, respectively and only 10% showed progressive disease (PD). The overall survival rate for the entire patient cohort was 16.4 months, but significant differences in survival between Child–Pugh classes were again found. One of the few available long-term prospective outcome studies of radioembolization treated a total of 291 patients with TheraSpheres in 526 sessions over the course of 5 years [64]. There was an almost even split between Child–Pugh A (45%) and Child–Pugh B (52%) patients. Regarding the BCLC staging, 52% of the patients were classified as BCLC stage C (BCLC A 17% and BCLC B 28%). When assessed with EASL criteria, the overall response rate was 57% (CR 23% and PR 34%), while stratified response rates were significantly better for Child–Pugh A patients with 66% responders (compared to 51% in Child–Pugh B patients). The time to progression for the entire cohort was 7.9 months. The data on median overall survival reported 17.2 months for Child–Pugh A patients and 7.7 months for Child–Pugh B patients, thus demonstrating the potential of radioembolization to treat unresectable HCC patients.

The data on radioembolization for IHC is not as mature and complete as for TACE but available studies have demonstrated good results. A prospective single-center pilot study designed to show the safety and feasibility as well as efficacy for radioembolization included 24 patients with histologically proven diagnosis of IHC [65]. At the time of the procedure, 38% of the patients had imaging signs of portal vein thrombosis (PVT) and a total of 13 patients had multifocal disease. Although well tolerated, the procedure caused grade 3 toxicities in 17% of patients and one patient developed a refractory gastroduodenal ulcer. Imaging response after radioembolization yielded good tumor control with 9% of CR and 77% of PR. A follow-up study from the same center provided more data and expanded the number of patients to a total of 46 [66]. Successful downstaging to resectability was achieved in five patients. Most importantly, the overall median survival in patients without PVT was 14.4 months (5.3 months with PVT). Both studies provided robust data in support of radioembolization as a modality to treat advanced IHC. Another prospective, single-center study confirmed this potential and presented similar survival data (14.7 months for ECOG one patient) and comparable toxicity profiles in a similar, small cohort of 19 patients [67]. It appears that radioembolization can be of benefit for both, HCC and IHC patients.

There is increasing interest in studying the effects of radioembolization on chemorefractory metastatic liver cancer of various origins. The use of radioembolization to treat colorectal liver metastases has been studied in recent trials and proved to be safe and effective showing good clinical outcome and survival for asymptomatic patients with preserved liver function [68]. A multicenter phase II trial enrolled 50 consecutive patients with unresectable and chemorefractory metastatic colorectal carcinoma for treatment with SIR-Spheres [69]. Median overall survival was 12.6 months and the 2-year survival rate of 19.6% was achieved, suggesting the ability of radioembolization to stabilize end-stage liver metastases. Similar results were reported in patients with breast cancer liver metastases treated with radioembolization, demonstrating survival benefit and a high tumor response rate in patients with treatment-refractory disease [70].

Vascular interventions

Introduction

Vascular interventions of the GI (GI) tract are directed to maintain sufficient perfusion of the abdominal viscera, stop bleeding and equilibrate venous pressure. (Figure 152.8)

GI tract bleeding

GI bleeding is generally thought of as upper or lower GI in origin, and although frequently self-limiting, can be a life threatening event.

Upper GI bleed (UGIB) is defined as bleeding into the gut proximal to the ligament of Treitz. In the United States, the
annual incidence of UGIB is 102 per 100,000 persons and increases markedly with age [71]. Three major groups of causes of UGIB are: (1) primary gut pathologies; (2) transpapillary hemorrhages (involving hemobilia and transpancreatic duct hemorrhage); and (3) variceal hemorrhages secondary to portal hypertension [72]. Peptic ulcer disease is the most common cause [71].

Lower GI tract bleeding (LGIB) is less common than upper GI (UGIB) tract bleeding. The incidence of LGIB is estimated to be 20–30 cases per 100,000 adults per year in the United States, and is associated with 0%–25% with 5% 1 year mortality rate with rate greater than 5% found in older studies when patients went for emergency surgery [73].

The general management goals of GIB are resuscitation, diagnosis, hemostasis, prevention of recurrent bleeding and treatment of the etiology. In GIB, angiography with embolization can be a lifesaving procedure. Intravascular embolization, rather than surgery, has become the preferred treatment when endoscopic management fails [74–76]. Cooperation between endoscopists, interventional radiologists, and surgeons is essential to adopt the best therapeutic option for an individual patient.

A number of diagnostic strategies are available for the management of GIB. These are: upper endoscopy, colonoscopy, flexible sigmoidoscopy, angiography, radionuclide scintigraphy (tagged red blood cell scanning), and multidetector computed tomography (MDCT). Early endoscopy is the preferred diagnostic and therapeutic strategy for most patients with GIB, due to the ability to make the diagnosis and achieve hemostasis [77]. Radiographic modalities are reserved for patients who cannot undergo endoscopy or in whom endoscopy fails to control the bleeding.

The imaging modality chosen to evaluate the GIB should be based on the patients’ clinical presentation and status. Identifying the site of bleeding requires the patient to be actively bleeding at the time of the imaging study. Successful localization of bleeding is highly dependent on the rate of bleeding at the time of the examination [78,79]. Computed tomography angiography (CTA) is a noninvasive rapid way to document and localize active bleeding – showing extravasation of contrast with a bleeding rates as low as 0.3–0.5 mL/min [80]. In addition, it offers all the diagnostic benefits of cross-sectional imaging. The technetium-labeled erythrocyte scintigraphy (tagged red blood cell [t-RBC] scan) has a higher sensitivity for detecting GIB than CTA or angiography. It is noninvasive and the most sensitive examination – identifying bleeding at a rate of ≥ 0.05–0.1 mL/min) [81]. Nonselective angiography requires bleeding rates of at least 0.5 mL/min in order to be detectable [82]. The advantage of angiography is that it offers both diagnostic and therapeutic options. Clinically, a systolic blood pressure of 90 mmHg or less and a requirement of transfusion of at least 5 units of packed red blood cells within a 24-hour period have been shown to predict a positive angiographic study [83]. Although, angiography is useful in active LGIB, it is not as useful in chronic low-grade bleeding, frequently failing to yield the diagnosis.
[84]. However, if the bleeding can be localized to a vascular distribution by radionuclide scintigraphy, then super-selective angiography may be beneficial to the patient.

**Technical aspects**

In general, the femoral artery is accessed utilizing the Seldinger technique. Various angiographic catheters, with a large variety of shapes, are available to catheterize and select the mesenteric vessels, such as the Simmons catheter (Cook, Bloomington, IN, USA), or the Cobra catheter (Terumo, Tokyo, Japan). These catheters allow diagnostic angiography by contrast injection with digital subtraction imaging. Super-selective angiograms of small vascular territories with microcatheter systems are often necessary to demonstrate active bleeding – particularly when the vascular distribution of bleeding is known, yet not identified on flush aortogram.

**Upper GI**

The primary arterial supply to the upper GI tract is from the celiac trunk and collateral vessels off the SMA. The extensive collateral UGI vascular supply makes embolization at lower risk of ischemia than for LGIB, yet these collaterals make hemostasis more difficult. Empiric embolization in UGIB is an option, when there is no angiographic abnormality and/or the endoscopist has marked the site of bleeding by deploying clip-landmark [76]. The choice of embolic agent depends on the abnormality being treated, the vascular anatomy, the achievable catheter position, and the operator preference. (Figure 152.9).

![Figure 152.9](a) A 68-year-old male with a lower GI bleeding documented on Tc-99m RBC imaging in the right upper quadrant (a). The SMA was selected by a catheter and SMA angiography was performed. (b) A large pseudoaneurysm was noted with rapid extravasation of contrast into the jejunum in the right upper quadrant on fluoroscopy images. (c) These finding were better visualized on DSA than on fluoroscopy. (d) A super selective catheterization was performed with a microcatheter to a small jejunal branch vessel feeding the pseudoaneurysm. Coils were used to occlude the feeding vessel including. Selective then global SMA angiographies were performed postcoiling and confirmed the occlusion of the pseudoaneurysm and the absence of persistent bleeding. DSA, digital subtraction angiography; GI, GI; RBC, red blood cell; SMA, superior mesenteric artery.
Microcoils can be combined with other embolic agents to achieve thrombosis.

**Lower GI**
The primary arterial supply to the lower GI tract is from the superior mesenteric artery (SMA) and inferior mesenteric artery (IMA) (Figure 152.10). In most patients, the SMA supplies the entire small bowel as well as the cecum, ascending colon, and a variable length of the transverse colon. The descending colon to the rectum is commonly supplied by the IMA. When bleeding is seen at angiography, microcoil embolization is the most utilized embolic agent at the authors’ institution. Because the origin of the bleeding is located at the periphery of the vessel mesenteric arteries, a microcatheter introduced coaxially through the parent catheter is used to select arteries at the level of the vasa recta. This approach offers the ability to perform super-selective catheterization and improves the safety of embolization. In addition to microcoils, a variety of embolic agents are available including gelatin sponge (Gelfoam), polyvinyl alcohol (PVA) particles, autologous clot, and glue n-butyl cyanoacrylate (NBCA) (Cordis Corporation, Miami Lakes, FL). When embolization is not feasible, infusion of a vasoconstrictor into the main trunk of the artery of concern is another therapeutic option. This can temporally stabilize the patient when waiting for a definitive surgical procedure [78,79].

*Figure 152.10* An 80-year-old male with diverticulosis presents with episodic bleeding from the right colon requiring blood transfusions. Initially controlled with endoscopically placed clips the bleeding reoccurred – angiography was requested. (a) On a late phase of a SMA angiography though a catheter, extravasation of contrast into the bowel, bowel folds outlined active bleeding was seen in the region of the cecum, close to the clips. (b) A selective DSA of the terminal cecal branch of the ileocecal artery though a microcatheter inserted coaxially to the catheter confirmed the location of the bleed. (c) Coils were deployed through the microcatheter to the terminal cecal branch. Selective angiography and then global DSA though the SMA (d) confirmed the absence of bleeding. DSA, digital substraction angiography; SMA, superior mesenteric artery.
Complications
Patients undergoing GI tract embolization are exposed to the usual complications associated with angiography including puncture site hematomas, or pseudoaneurysm, arterial occlusion, arterial dissection, contrast reactions, and contrast induced renal failure. Specific complications related to successful embolization depend on the site and local anatomy. Possible complications include splenic or hepatic infarctions, gastric, duodenal or colonic ischemia, resulting in strictures, ulceration, and necrosis, but these are limited [85–89]. Bowel infarction is the complication of most concern. By using super-selective embolization, the possibility of ischemic complications may be decreased considerably [85–89].

Acute mesenteric ischemia
Acute mesenteric ischemia (AMI) is a life-threatening vascular emergency that requires rapid diagnosis and treatment to restore mesenteric blood flow and prevent bowel necrosis and death. It occurs when blood supply is interrupted and perfusing blood flow is insufficient to meet bowel needs. Acute mesenteric ischemia arises primarily from vascular disorders in the SMA circulation or its venous outflow. Disruption in the IMA is often being less morbid because of pelvic collateral circulation. Among all visceral arteries, the SMA is the most susceptible to emboli (90%) with the IMA a distant second [90]. The major groups of causes arterial occlusion are embolus (50%), thrombosis (25%), nonobstructive causes (10%–15%), aortic dissection (5%), venous obstruction (5%–15%), and extra-vascular sources [91,92]. Regardless of the etiology the mortality is high [93].

On clinical exam, when abdominal pain out of proportion to peritoneal signs is encountered, laboratory (including lactic acid levels) and imaging evaluation should be obtained. When emergent surgical exploration is not indicated, definitive diagnosis with CTA or angiography should be performed without delay to avoid any irreversible ischemic change. Although angiography remains the gold standard, CTA has proved to be a valuable tool for diagnosis and treatment planning of AMI. When mesenteric occlusion is present, given the frequency of occurrence, an echocardiogram is necessary to exclude an intracardiac thrombus as a possible source.

Indications
Although surgical treatment is still considered the standard of care, even in the absence of peritoneal signs mortality rates remain as high as 50% [94–96]. Percutaneous techniques appear to be valuable alternatives to surgical treatment in selected cases [97,98]. Endovascular management of AMI should be considered in patients without clinical or imaging signs of bowel infarction, or poor surgical candidates. Patients after successful endovascular treatment may still require surgery in cases with absence of symptom regression. Overall mortality of AMI remains high after surgery (60%–80%) [99]. A multidisciplinary approach is mandatory, including gastroenterologists, anesthetists, surgeons, and interventional radiologists working together [94].

Arterial thromboembolism
Standard treatment for patients with obstructive mesenteric arterial syndromes is a surgical embolectomy or/and revascularization and potentially resection of infarcted bowel. Progression of bowel ischemia to bowel infarction may be prevented by initiation of intraarterial thrombolytic administration, within a few hours after the onset of symptoms [100]. Angioplasty with or without stenting is performed on an underlying stenosis, should arterial recanalization be insufficient [101]. Despite limited data, percutaneous treatment (lytic therapy, angioplasty or stenting or both) of arterial obstructions is reasonable given the high mortality associated with the standard operative approach [101–103].

Nonocclusive causes
Arteriography and endovascular therapy are indicated in patients suspected of having nonocclusive mesenteric ischemia whose condition does not improve rapidly with the treatment of their underlying disease. Arteriography can demonstrate arterial vasospasm, and endovascular therapy with a direct intraarterial infusion of a vasodilator can be performed. Intraarterial vasodilators are considered valuable supportive therapeutic treatment option by reducing vasospasm [104].

Venous thrombosis
The mainstay of therapy for patients with mesenteric venous thrombosis is anticoagulation with surgical resection of affected bowel. Thrombolytic therapy is reserved for mildly symptomatic thromboses diagnosed early. Post thrombolysis patients should continue anticoagulation for 3–6 months [104] and select patients should undergo a hypercoagulability evaluation.

Technique
The appropriate technique used for endovascular treatment of acute mesenteric artery depends on the etiology [105]. Intrarhegious infusion can be done using vasodilator medications such as papaverine, infused through the angiogram catheter after diagnostic angiography is performed, and adjusted depending on clinical outcomes for at least 24 hours. Thrombolytic agents such as recombinant tissue plasminogen activator (r-tPA), can be infused through angiographic catheters [105] and are typically accompanied by heparin administration for anticoagulation. Combined techniques for arterial recanalization with angioplasty and stenting, to treat underlying stenosis, may be necessary after thrombolysis of an occluded artery. Venous recanalization in the absence of any clinical evidence of bowel infarction can be performed using intravascular thrombolytic agents combined with balloon venoplasty to treat venous mesenteric thrombosis [106,107].

Complications
Common complications of mesenteric vascular intervention are similar to those of all vascular procedures including vessel injury, bleeding, and contrast media complications. The main
Chronic mesenteric ischemia (CMI) is the most common vascular disorder involving the intestines [109] (Figure 152.11). Atherosclerosis is by far the most common cause of CMI, whereas other less common etiologies include fibromuscular dysplasia, Buerger disease, and aortic dissection [110]. Open surgical repair is the standard treatment for CMI treatment, and for clinically significant stenosis of the celiac and superior mesenteric arteries. However, open repair is associated with significant morbidity and mortality [111,112]. Percutaneous transluminal balloon angioplasty and stenting is a safe and

**Figure 152.11** A 79-year-old female with history of chronic epigastric pain and weight loss. Abdomen MRA demonstrated severe stenosis of the proximal SMA and mild to moderate stenosis of the origin of the celiac trunk. (a) An abdominal aortic aortogram (lateral position) was performed and evidenced a proximal narrowing of the celiac trunk. (b) The SMA was selected using a catheter and the arteriography was performed in lateral and oblique positions. A significant short segment stenosis within the proximal superior mesenteric artery approximately 1–2 cm distal to the SMA origin was seen. (c) This finding was consistent with the duplex Doppler ultrasound demonstrated hemodynamically significant stenosis of the proximal SMA. (d) A PTA was performed in the region of significant stenosis for predilatation. A bare metal stent was deployed across the stenosis and a balloon dilatation of the stent was performed. A final angiogram of the SMA demonstrated significantly improved flow through the SMA. MRA, magnetic resonance angiography; PTA, percutaneous transluminal angioplasty; SMA, superior mesenteric artery.
effective alternative to surgical treatment for patients with chronic mesenteric ischemia caused by calcified ostial stenoses, high-grade eccentric stenoses, chronic occlusions, and flow-limiting dissection of mesenteric arteries [95,111,113]. If the diagnosis is overlooked or missed, AMI can occur with a mortality rate approaching 90% [114]. High clinical suspicion and positive screening Doppler study of the mesenteric arteries should prompt noninvasive cross sectional imaging. In addition to an accurate diagnosis, pretreatment cross-sectional arteriogram will facilitate treatment planning and lead to optimal clinical outcomes. The natural history of sub-clinical mesenteric arterial disease is not well characterized.

Indication
The most common clinical indication for treatment of stenosis or occlusions of the mesenteric vessels is the presence of ischemic symptoms such as “intestinal angina.” Given the three vessel blood supply to the bowel, typically two of the three vessels will have a hemodynamically limiting stenosis before symptoms occur. Endovascular therapy is commonly considered as a primary choice of treatment for stenotic lesions of the mesenteric arteries [110,115]. Endovascular revascularization for treatment of CMI is technically successful in 80% to 100% of patients [91,95,116]. The primary patency rates after angioplasty and/or stenting has been reported to be lower than open surgery [117]. However, 30-day morbid-mortality are similar after angioplasty/stenting when compared with surgery, in large part owing to postoperative cardiopulmonary and renovascular complications seen with open surgical repair [111]. Primary patency after angioplasty and/or stenting assisted success approaches 90% at 5 years, with 5-year survival rates of 76% [95]. For some patients, initial treatment with stenting may provide a bridge to surgical therapy, by improving the patients’ nutritional and performance status [110,118]. Neither angioplasty nor stent placement has been demonstrated to be effective in treating celiac stenosis caused by median arcuate ligament compression [95].

Techniques
Patients can be treated from a femoral artery or the brachial artery approach. Mesenteric artery angioplasty and stenting for CMI is a technically challenging procedure, because it can lead to complications such as acute mesenteric ischemia. Before the procedure, selective mesenteric arteriograms are performed to evaluate the arterial lesions and visceral arterial circulation. Various catheter types are available for selective catheterization, percutaneous transluminal angioplasty and stent placement of the variant abdominal vascular anatomy. Balloon angioplasty dilates the stenosis and stenting is traditionally reserved for residual stenosis after angioplasty of 30% vessel diameter or greater [95]. Pressure transducers for translesion pressure gradient measurements can be used to monitor intraprocedural treatment success.

Complications
The most common complications are related to arterial access. Brachial access is associated with median nerve injury as well as higher incidence of pseudoaneurysm formation. In severe and long-standing CMI, the revascularization syndrome may result in a reperfusion injury. Patients who have severe atherosomatous disease of the aorta are at risk for cholesterol embolization during an endovascular procedure. Emboli to the bowel may turn CMI into AMI. Failure of angioplasty and stenting is another complication; however, it does not exclude surgery as a therapeutic option.

Abdominal visceral artery aneurysm
Abdominal visceral aneurysms (VAAs) are classically divided into true and false aneurysms (Figure 152.12). A true aneurysm involves all three layers of the arterial wall and has a localized dilatation more than 1.5 times the expected arterial diameter [119]. The prevalence of true VAAs is 0.1%–2% [120]. True aneurysms are associated with underlying arterial pathologies such as atherosclerosis, fibromuscular dysplasia, or arteritis. False aneurysms, or pseudoaneurysms, are effectively contained ruptures of the artery that are lined by adventitia or by the perivascular tissues. False aneurysms may occur as a result of inflammation, infection, or trauma [121,122], visceral artery aneurysms are most commonly found in the splenic (60%) and hepatic arteries (20%), and the remaining elsewhere in the visceral vessels [123]. The natural history of these aneurysms is that of expansion, rupture, or thrombosis [123].

Indications
The risk of rupture of a true aneurysm is difficult to predict, but does appear size dependent. Traditional management strategies have been debated between surveillance and surgical repair. Treatment is recommended when the true aneurysm is large (>2 cm), symptomatic, rapidly expanding, or found in a patient who is or could become pregnant. VAA in pregnant women are especially prone to rupture. When treatment of the aneurysm is not indicated, routine surveillance should be initiated. Mortality after elective surgical repair is approximately 5% but increases substantially after aneurysm rupture [124,125]. Surgery was originally recommended in most cases; however, endovascular treatments are now replacing some surgeries [119,125–127]. Transcatheter embolization is the treatment of choice for most intrahepatic and splenic artery pseudoaneurysms. Selective arterial embolization is safe and effective in treating visceral arterial aneurysms in patients who are a poor surgical risk, particularly those with pancreatitis-associated aneurysms and pseudoaneurysms [128]. The technical success of endovascular repair of visceral aneurysm reaches 98% with low-morbid-mortality [125,126]. While the decision to intervene on a true aneurysm may depend on a size threshold above which the potential for rupture increases, in general all pseudoaneurysms should be promptly treated, whatever their size or location [121–123,125].
Figure 152.12 A 29-year-old gentleman with a history of intravenous drug abuse and endocarditis. (a) A CTA of the abdomen revealed large pseudoaneurysms within the liver and in the SMA distribution, as shown on the coronal view of the figure. (b) The patient was presented for angiography and potential embolization. An angiogram was performed though a catheter placed in the SMA and showed the pseudoaneurysm. A microcatheter was used to select a proximal ileal branch of the left lower quadrant off the SMA and confirmed the location of the pseudoaneurysm. The pseudoaneurysm was embolized with coils. (c) A nonselective angiogram of the SMA evidenced the occlusion of pseudoaneurysm. (d) The catheter was then placed into the celiac trunk and an angiogram was performed showing a pseudoaneurysm arising from the right hepatic artery. (e) A microcatheter was advanced to the pseudoaneurysm and enabled his embolization with a liquid embolic agent (Onyx), until the absence of residual contrast filling of the aneurysm of the pseudoaneurysm evidenced on the hepatic arteriography. (f) CTA, computed tomography angiography; SMA, superior mesenteric artery.

Techniques
Patients can be treated from a femoral artery or the brachial artery approach. Celiac and superior mesenteric arteriograms are performed to evaluate the lesion and arterial anatomy. A catheter with coaxil microcatheter system is often used to gain proximal and distal control of the artery. Coil packing of the artery and/or aneurysm is commonly used [119,126,129]. Embolization across the aneurysm neck is important to prevent retrograde flow into the aneurysm through collateral vessels feeding the distal artery. A covered stent to exclude the aneurysm is an effective therapeutic option and preserves function of the artery [128].

Complications
Access site complications tend to be the most frequent. Rupture of the aneurysm during treatment is another potential complication. Most endovascular vascular complications such as artery occlusion from which the aneurysm takes off, coil migration, infarction of the downstream viscera, dissection or rupture can be management by endovascular team. An experienced team may reduce or avert these complications.

Inferior vena cava disorders
Inferior vena cava (IVC) disorders result from these etiologies: thrombosis (extension of iliac vein thrombus, hypercoagulability disorders of IVC filter, indwelling catheter, aneurysm, inflammation, or infection), intraluminal tumor extension (intraluminal growth, direct invasion), and extrinsic compression (right common iliac artery, right renal artery, hepatic masses, ascites, hepatomegaly, and retroperitoneal masses) [130–132]. The most common of these problems are extension of clot from the iliac veins, transvenous spread of tumor thrombus and filter related IVC thrombus. Bilateral lower extremity swelling is a frequent clinical manifestation of these problems. The diagnosis is usually made by MDCT [133]. The management of vena cava disorders is based on the etiology and symptomatology.
Indications
The endovascular therapeutic options for IVC disorders include mechanical thrombectomy, catheter directed thrombolytic therapy alone or a combination of both, permanent or temporary IVC filter placement, endoluminal recanalization, and stent placement. Endovascular therapy catheter-directed thrombolysis (CDT) is used to treat acute IVC thrombosis and augment the treatment of chronic IVC thrombosis. Thrombolysis should be considered in patients with symptoms and in those who fail to respond to anticoagulant therapy [134,135]. These methods have emerged as an effective treatment for caval stenosis, and occlusions and venous lower limb occlusion [136–141]. All these methods have been shown to have intermediate-term outcome success in patients who have symptoms or who do not show an adequate clinical response to pharmacological therapy [142]. Figure 152.13, shows stenting of IVC stenosis caused mass extrinsic mass effect in a patient whose symptomatic bilateral leg swelling resolved within 24 hours after intervention.

Techniques
The access for endovascular management of IVC disorders is mainly femoral venous but may be through internal jugular vein or both. Catheter directed cavograms can distinguish among IVC compromise caused by stenosis, obstruction, and thrombosis. It confirms the initial diagnosis and helps direct treatment methods.

Catheter directed thrombolysis
A catheter is placed in contact with the thrombus, and used for pharmacological thrombolysis [143]. Prior to initiating thrombolysis, patients should be assessed for contraindications to tPA such as recent hemorrhage, stroke, brain mass, and recent surgery. Anticoagulation is used to maintain patency of vessels after successful thrombolysis reestablishes flow. Patients at risk of bleeding and those who have had a previous adverse reaction to heparin or warfarin [144] may not benefit from thrombolysis. After initiation of CDT patients are closely monitored, to detect bleeding complications at an early stage. Follow-up cavography is carried out in 8–24 hour intervals to evaluate the progress of thrombolysis and to adjust the catheter position. Thrombolysis should continue until the thrombus is resolved completely, a major complication has occurred, or no progress is evident over a period of 24 hours [145].

Figure 152.13 A 56-year-old woman with advanced liposarcoma presented with subcutaneous abdominal edema and lower extremity edema. (a) A venogram of the IVC was performed through a catheter and demonstrated a prominent IVC with abrupt narrowing at the level if the intrahepatic IVC. (b) A catheter was advanced into the right atrium. A concurrent SVC/IVC venogram through the catheter showed an approximately 4 cm near occlusion of the intrahepatic IVC. (c) Two consecutive stents were deployed successfully at the level of the intrahepatic IVC stenosis and were angioplastied by a balloon. The poststents angiogram was performed and showed a widely patent IVC with prompt flow into the right atrium consistent with good technical success. IVC, inferior vena cava; SVC, superior vena cava.
Mechanical endovascular thrombectomy

Mechanical endovascular thrombectomy may be performed with catheter-directed thrombolysis. This technique offers an opportunity for a faster clearance of obstructing thrombus. This method is usually restricted to patients with severe symptoms, long-segment thrombosis, patients with large clot burden or in cases of prolonged thrombolysis, such as more than 36 hours. A variety of motorized thrombectomy devices with different principal mechanisms, mainly rotational or hydrodynamic, are available.

Angioplasty balloons and various sizes of catheters used for direct aspiration are an alternative for mechanical fragmentation of thrombi [146]. In such cases, placement of a suprarenal IVC filter may be appropriate [141].

Insertion of an IVC filter is performed to prevent clinically relevant pulmonary embolism in patients with documented venous thrombosis of the legs or pelvis or as prophylaxis in selected patients at high-risk for the disease [141]. IVC filters should not replace standard medical therapy for lower extremity venous thrombosis or documented pulmonary embolism in patients who are reasonable candidates for anticoagulant therapy [141]. Typically, filters are deployed in the infra-renal IVC unless a thrombus is present in this segment. For the IVC placement, various permanent or temporary filters are available [72,141]. Indications for retrievable filter placements are mainly: young patient, IVC thrombosis during lower extremity, deep vein thrombolysis and contraindication to systemic anticoagulation [141]. Angioplasty and venous stent placement has been reported to be an effective palliative procedure for IVC stenosis or obstruction [136,140,142,147–149].

Complications

The complications of the IVC disorders endovascular treatment depend on the treatment type. Thrombolysis may cause bleeding at different body sites. The use of thrombectomy devices may damage the intimal layer and the venous valves. IVC reconstruction, angioplasty and filter removal can induce IVC perforation, and retroperitoneal bleeding. An IVC filter placement may be complicated by migration, thrombosis or filter fracture.

Transjugular intrahepatic portosystemic shunt and portal vein interventions

Introduction

According to the most recent report of the Center for Disease Control and Prevention [150], chronic liver disease represents the 12th leading cause of death in the United States and a significant cause of morbidity, accounting for a substantial portion of health-care utilization [151]. It is also the most common cause of sinusoidal portal hypertension, the most frequent cause of portal hypertension worldwide [152].

A treatable sequelae of chronic liver disease is portal hypertension, such as increased portal pressure gradient (PPG), above its normal upper limit of 5 mmHg [153]. PPG is measured as the hepatic venous pressure gradient, which represents the perfusion pressure of the liver with portal blood [152]. The increase in portal pressure can be viewed as a compensatory mechanism allowing portal perfusion to be maintained [154]. When PPG exceeds 12 mmHg, portal hypertension may become clinically significant [153]. Sequelae of portal hypertension include formation of portosystemic collaterals with varices, portal hypertensive gastropathy, upper GI bleeding usually secondary to ruptured gastroesophageal varices, ascites, hepatic encephalopathy, and spontaneous bacterial peritonitis [152,155].

Any condition that interferes with portal blood flow may cause portal hypertension. Classification of portal hypertension can be organized by anatomic site of obstruction: (a) prehepatic (involving the splenic, mesenteric, or portal veins); (b) intrahepatic (parenchymal liver diseases), and (c) posthepatic (diseases involving the hepatic venous outflow). Portal vein thrombosis and Budd–Chiari syndrome (BCS) are the most frequent causes of pre and posthepatic portal hypertension, respectively. Intrahepatic portal hypertension can be further classified as presinusoidal, sinusoidal and postsinusoidal portal hypertension depending on relative pressures obtained via hepatic vein catheterization [155].

Transjugular intrahepatic portosystemic shunt (TIPS)

First introduced in 1989 by Richter and colleagues [156], TIPS is a relatively noninvasive method of diverting blood from the portal circulation to systemic circulation via an artificial conduit between the intrahepatic portal and hepatic veins. Successful TIPS placement is often defined as reduction in PPG less than 12 mmHg [157], reducing the likelihood variceal hemorrhage and intractable ascites [153]. These complications of portal hypertension (i.e., variceal hemorrhage and ascites) are the most common indications for TIPS. Several studies have shown the benefit of TIPS in controlling portal hypertensive gastropathy, hepatic hydrothorax, hepatic venoocclusive disease, BCS and hepatorenal /hepatopulmonary syndromes [158].

Absolute contraindications for TIPS placement include primary prevention of variceal bleeding, congestive heart failure, severe pulmonary hypertension (mean pulmonary pressure > 45 mmHg), uncontrolled sepsis, multiple hepatic cysts, unrelieved biliary obstruction and severe tricuspid regurgitation. Relative contraindications include anatomic variants that technically complicate shunt placement, including portal or hepatic vein thrombosis, hepatic masses (especially those in a central location), thrombocytopenia (cell count < 20 cells/cm$^3$) masses, congestive and moderate pulmonary hypertension [159]. Factors which significantly predict a worse outcome are also considered relative contraindications [160]; these include bilirubin levels above 3 mg/dL, serum sodium level of 130 or lower [161]. Some experts also consider pre-TIPS hepatic encephalopathy a relative contraindication for TIPS procedure due to evidences that it is a predictor of mortality in cirrhotic
patients, even though a recent metaanalysis [161] has not confirmed this data.

Procedure-related mortality rates range from 0.6% to 4.3%, varying from 1.4% to 3.0% depending on the amount of experience in institutions. Fatal complications include intraabdominal hemorrhage due to laceration of the hepatic artery or portal vein and right heart failure [162]. Major procedural complications should occur in no more than 3% of cases [163]. The post-TIPS mortality can be best predicted by the model for end-stage liver disease (MELD) score, comparing with other models created to access prognosis of chronic liver disease [164,165]. However, the value of the MELD score as an independent predictor of mortality and the cut off value to mortality prediction has been inconsistent among studies [161,164–166]. MELD scores greater than 15 [166], 18 [158] [164,165], or 25 [167] have been considered to predict a significantly higher mortality compared to lower MELD scores. A recent metaanalysis did not find that the MELD score was an independent predictor of mortality [161]. Long-term survival rates are lower when the indication is ascites rather than bleeding varices, 48% to 76% versus 48 to 90%, respectively [159].

TIPS seems to be more effective than paracentesis for the treatment of ascites with tense ascites recurring in 42% of the TIPS patients versus 89% of the paracentesis patients. The actuarial probability of transplant-free survival is also significantly better in TIPS patients than in paracentesis patients: the average transplant-free survival at 6, 12, 24, and 36 months of follow-up is 75.1%, 63.1%, 49.0%, and 38.1% versus 65.3%, 52.5%, 35.2%, and 28.7% for TIPS and paracentesis patients, respectively. However, the average number of hepatic encephalopathy episodes is significantly higher in the TIPS patients, although the cumulative probability of developing the first episode of hepatic encephalopathy is similar between TIPS and paracentesis patients [161].

TIPS also seems to be associated with significant reductions in treatment failure and in mortality when comparing early TIPS and drug therapy/endoscopic band ligation in the treatment of variceal bleeding in patients first managed with vasoactive drugs plus endoscopic therapy. A recent randomized trial found a significantly higher 1 year actuarial probability of remaining free of failure to control bleeding and of variceal rebleeding in the early-TIPS patients than in the drug therapy/endoscopic band ligation patients (97% versus 50%, respectively; \( P < 0.001 \)). The 1 year actuarial survival was 86% in the early-TIPS group versus 61% in the pharmacotherapy/ endoscopic band ligation group (\( P < 0.001 \)) [168].

Morbidity following TIPS placement is most often related to deterioration of hepatic function, hepatic encephalopathy, liver capsular perforation, and stent migration and/or misplacement [158]. Diversion of portal venous flow through the shunt diminishes liver perfusion [160] and the metabolic filtering effect of the hepatic parenchyma, leading to deterioration of hepatic function in approximately 10% of patients and new or worsened encephalopathy in 30% to 46% of patients [158]. Capsular perforation may occur in as many as 33% of patients, which can result in significant intraperitoneal hemorrhage in 1% to 2% of individuals [158]. Before the introduction of Viatorr polytetrafluoroethylene (PTFE)-covered stent-grafts (Gore Medical & Associates, Flagstaff, AZ, USA), the only type of stent exclusively designed for TIPS, hemolysis due to damage to the red cells by the stent was also a common complication, occurring up in 13% [169] of cases. Stent misplacement or migration is becoming rare since the advent of modern stents [160]. Other possible complications include gall bladder perforation [157], hemobilia, fistulae, and TIPS infection and sepsis [158]. Occasionally hepatorenal syndrome and hepatic infarction [158] may also develop.

Guidelines regarding TIPS follow-up continue to evolve. In managing patients whose TIPS was placed to treat intractable ascites, follow-up evaluation can often wait until symptoms of portal hypertension recur. In contrast, patients receiving TIPS to treat chronic variceal bleeding require close follow-up as the first clinical sign of TIPS dysfunction might be fatal exsanguination. Currently, venography and pressure measurements are the reference standards for TIPS dysfunction diagnosis. Doppler ultrasound findings indicating TIPS stenosis generally require venographic evaluation [170]. Doppler ultrasound showing a post-TIPS portal vein flow velocity of less than 30 cm/sec suggests shunt insufficiency [160]. However, because some ultrasound examinations are falsely negative, venography is also warranted in patients with a negative ultrasound who demonstrate symptomatology of portal hypertension [170]. In general, TIPS dysfunction can be addressed with balloon dilatation or stent extension in the setting of persistent pressure gradient elevation. Technically difficult cases may require other advanced approaches, including parallel TIPS placement and percutaneous transhepatic recanalization [171]. The introduction of the Viatorr PTFE-covered stents, has yielded significant improvement in long-term shunt patency [157].

**Conventional TIPS technique**

To ensure proper patient selection for a TIPS procedure, a detailed clinical history, focused physical exam and proper laboratory and imaging studies are required. Hepatic functional insufficiency and clinically overt hepatic encephalopathy should be excluded. An echocardiography should be performed to exclude significant diastolic or systolic cardiac failure [160], or pulmonary hypertension in patients with suspected or known cardiac disease [158]. Within 24 hours of the procedure, significant thrombocytopenia (platelet count, <50,000 cells/mL), anemia (hematocrit, <25%), or coagulopathy (INR, >1.5) should be corrected and a doppler ultrasound evaluation of the hepatic vasculature should be performed to confirm portal vein patency [158]. In the setting of refractory ascites and/or hydrothorax, paracentesis and/or thoracentesis should be performed in order to facilitate portal puncture and improve fluoroscopic imaging quality [160].
Interventional radiology CHAPTER 152

12 mmHg should be achieved [157]. Excessive reduction of the PPG along with severe liver dysfunction has been shown to be associated with increased risk of mortality after TIPS creation in patients presenting with refractory ascites [167].

A 10 mm stent diameter is typically chosen for adult patients, whereas smaller stents are more often used in the pediatric population [158]. However, stents with 10 mm should be employed but dilated only to 8 mm to avoid shunt related complications. This may result in more limited pressure reduction, not always achieving the recommended threshold of 12 mmHg, but possibly reducing the rate of TIPS-induced hepatic encephalopathy. In case of insufficient response, further pressure reduction can be achieved by a second intervention [160].

When clinically indicated a TIPS stent Doppler may be obtained. If stent flow is sonographically difficult to obtain (common in PTFE-covered stents soon after placement due to small air overlap - ping stents of the same diameter are often used to achieve the desired shunt length and to reduce severe angulation within the shunt [158].

Once stents are deployed, trans-TIPS portal venography and PPG measurements in the main portal vein and the right atrium are repeated [158,160]. As noted above, a post-TIPS PPG under 12 mmHg should be achieved [157]. Excessive reduction of the PPG along with severe liver dysfunction has been shown to be associated with increased risk of mortality after TIPS creation in patients presenting with refractory ascites [167].

TIPS placement can be performed under conscious sedation or general anesthesia [158] (Figure 152.14). A needle is passed from the hepatic vein through liver parenchyma to the portal vein utilizing image guidance. Subsequently, Seldinger technique [18] is used to secure shunt access.

When using PTFE-covered stents, care is taken to leave the uncovered caudal portion of the stent in the portal vein, whereas the covered portion of the stent should be in the parenchymal tract and in the hepatic vein. The cranial end of the stent should extend to the junction of the hepatic vein and the IVC. Overlapping stents of the same diameter are often used to achieve the desired shunt length and to reduce severe angulation within the shunt [158].

Figure 152.14 (a) TIPS hepatic vein access: access is achieved into the right internal jugular vein under ultrasound guidance, using a micropuncture set. A Bentson wire is advanced down into the IVC and a 10 Fr 40 cm vascular sheath is advanced into the right atrium. The right hepatic vein is then accessed. (b) CO₂ Portovenogram: after pressure measurements confirm PPG, a CO₂ portovenogram is performed, to portal patency and map the portal vein for transhepatic puncture. (c) Stent mapping: after portal vein access is achieved simultaneous hepatic and portal venograms are performed, to delineate stent size and relative anatomy. (d) Post-TIPS stent placement venogram; after stent deployment and angioplasty a portal venogram confirms stent placement and decompression of gastric and esophageal varices. IVC, inferior vena cava; PPG, portal pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.
Because there are no normal hepatic veins to use as a starting point for the puncture. However, the point of origin or stump of an occluded hepatic vein can often be found or a direct puncture through the caval wall straight into the liver can be made [174]. Once the puncture needle is inside the liver the conventional TIPS technique can be employed [174]. In contrast to patients receiving a transjugular shunt for variceal bleeding, where a graded reduction of the portal pressure may be advisable, in BCS patients a larger diameter of the shunt may be recommended to allow decompression of both the sinusoidal and splanchnic beds and to facilitate arterial perfusion [160].

The use of Viatorr PTFE-covered stent-grafts affords marked overall improvement in shunt patency [172,174]. This is particularly useful in BCS patients with a coagulopathy. Overall, the results of TIPS procedures in patients with BCS have been encouraging, with a technical success rate of more than 90% and a clinical success rate of more than 75% reported [173].

**Portal vein interventions**

Since Richter and collaborators [156] reported good results of TIPS, several innovative portal interventions have been developed [175].

**Portal vein thrombolysis**

Portal vein thrombosis (PVT) is a relatively common complication of cirrhosis, occurring in up to 35% of patients with decompensated liver disease [176]. Other important risk factors include thrombophilic states (inherited or acquired), portal vein injury, abdominal inflammatory lesions, hepatocellular and pancreatic carcinomas, contraceptive use, pregnancy, cytomegalovirus and bacteroides fragilis infections and liver transplantation. PVT has acute or chronic presentation. Chronic PVT coexists with portal hypertension, thus, its treatment consists of managing portal hypertension and its related complications. Acute PVT treatment involves anticoagulation and thrombolytic therapy [176]. Techniques of thrombolytic therapy differ in method of infusion. A catheter is positioned in the SMA to achieve indirect lysis of portal vein thrombus or in the portal vein itself [177] with a catheter introduced transhepatically or through transjugular approach [176]. Response rate of site-directed venous thrombolysis ranges from 75% to 100% partial to complete recanalization. Arterial infusion has been shown to result in longer infusion times, delayed time to resolution of thrombus, and inefficient thrombus resolution compared to portal venous thrombolysis [178]. Regardless of thrombolysis strategy employed (i.e., portal venous or arterial), there is a reduction in thrombus burden and more efficient restoration of portal flow as compared to systemic anticoagulation therapy alone. In patients in whom anticoagulation is contraindicated, site-directed thrombolytic therapy may provide a viable alternative [177].

**Direct intrahepatic portocaval shunt (DIPS)**

DIPS, a modification of the conventional TIPS procedure, was first described in 2001 by Petersen and collaborators [179] and

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**Figure 152.15** Hepatic venogram showing the classic "cob web" appearance of chronically occluded hepatic veins.
uses the caudate lobe as the parenchymal tract to create a side-to-side shunt between the IVC and the portal vein. The conventional DIPS method relies on direct needle guidance using intravascular ultrasound introduced via the femoral vein [180]. A TIPS needle, introduced from the jugular approach, is visualized sonographically as it passes from the IVC into the portal vein. The remainder of the procedure is similar to that of conventional TIPS [158]. The shunt is completed with a PTFE-covered stent graft [181]. DIPS is particularly useful in patients with Budd–Chiari disease and other conditions where access to the hepatic veins is not feasible [175]. Results of the procedure are comparable to those of TIPS [175].

Embolization of ectopic and stomal varices
Portosystemic venous collaterals as a complication of portal hypertension can lead to the development of stoma varices in patients with ileostomy or colostomy. Superselective catheterization of mesenteric venous branches supplying stoma varices can be done through percutaneous transhepatic or transjugular access to the portal vein [175]. Embolization can be performed using coils or a sclerosing agent. The results of treatment are generally positive; bleeding episodes cease and stomal function is preserved [175].

Indirect interventions for treatment of portal hypertension and portal vein interventions for other indications
Other treatments for portal hypertension include partial splenic embolization, angioplasty of hepatic veins/IVC stenoses, and embolization of arterioportal shunts. Detailed discussion of portal vein interventions performed for purposes other than portal hypertension are beyond the scope of this chapter. These include preoperative portal embolization facilitating growth of the liver parenchyma, transportal pancreatic islet cell transplantation to the liver in the treatment of diabetes mellitus, closure of portobiliary and portovenous fistulas, and portal vein recanalization for stenosis or chronic occlusion [176].

Biliary interventions in interventional radiology

Introduction
When dealing with a potential biliary tract pathology, all patients should be evaluated clinically, biochemically and by imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Although a definitive pathologic diagnosis cannot be established by imaging, cross-sectional imaging is invariably helpful. Indeed it provides accurate information about the anatomy and, usually, the probable cause of the bile duct obstruction, or the presence of a bile leakage. When further diagnostic information or a specific treatment is required, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and percutaneous transhepatic biliary drainage (PTBD) are indicated. Advances in diagnostic imaging and ERCP techniques have decreased the need for PTC and/or PTBD, however invasive percutaneous biliary interventions continue to play a major role in the management of some patients. A multidisciplinary evaluation, made by a gastroenterologist, oncologist, surgeon and radiologist, is mandatory for optimal patient care.

Percutaneous transhepatic cholangiography and biliary drainage
Percutaneous transhepatic cholangiography
Careful review of existing imaging studies, notably CT and MRI ± cholangiopancreatography sequences, should be performed before considering PTC for diagnostic purposes only. In most patients the PTC is performed to evaluate ductal anatomy as a first step before PTBD (Boxes 152.1 and 152.2).

Preoperative drainage is considered an indication of PTBD by some authors but is much debated in the literature; further evidence is needed [188–190]. PTBD to decrease total serum bilirubin level to permit administration of chemotherapy may be considered. Thornton and colleagues found that only 31% of patients attained a normal serum bilirubin level by 100 days and

<table>
<thead>
<tr>
<th>Box 152.1</th>
<th>Indications for percutaneous transhepatic cholangiography (PTC).</th>
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</thead>
<tbody>
<tr>
<td><strong>Main indications for PTC [182–186]</strong></td>
<td>Identify and evaluate ductal obstruction Differentiate obstructive from nonobstructive jaundice Evaluate suspected bile duct inflammatory disorders Localize the site of bile leakage Evaluate suspected bile duct stones</td>
</tr>
<tr>
<td><strong>Main contraindications of PTC</strong></td>
<td>Uncorrectable coagulopathy Unfavorable anatomy (e.g. interposed bowel) Severe ascites Severe reaction to iodinated contrast agents (may be managed with premedication)</td>
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<th>Box 152.2</th>
<th>Indications for percutaneous transhepatic biliary drainage (PTBD).</th>
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<tbody>
<tr>
<td><strong>Main indications for PTBD [187]</strong></td>
<td>Manage bile duct related infections such as cholangitis and biliary sepsis Relieve obstructive jaundice when ERCP failed or is indicated Treat benign biliary strictures Treat malignant lesions Remove intrahepatic or common bile duct stones when ERCP failed or is not indicated Divert the bile to treat biliary leaks or fistulae Perform endobiliary tissue sample Perform brachytherapy/phototherapy</td>
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</table>
thus careful patient selection is warranted for this indication [191]. Main contraindications of PTBD are the same as listed above for PTC. In patients with multiple isolated and obstructed biliary segments (e.g., metastatic liver disease), careful review of therapeutic objectives is important since PTBD is usually ineffective in relieving symptoms and should therefore usually be avoided. Ascites constitutes a relative contraindication. When severe, it displaces the liver from the abdominal wall making the PTC/PTBD technically more challenging. Moreover this displacement impedes effective tamponade of bile and blood, and carries a risk of chronic leakage of ascites through a peritoneal-cutaneous fistulous tract (access site). A left approach may be considered as there is less fluid anterior to the left lobe than around the right liver. Thus endoscopic approach should be favored in these patients and, when contraindicated, paracentesis before PTBD should be performed.

**Preprocedure work-up**

History, current medication and clinical examination should be obtained. The imaging studies should be reviewed for diagnostic evaluation and intervention planning. Blood tests including complete blood count, coagulation tests, and liver and renal function tests should be obtained. Any underlying coagulation abnormality should be corrected before proceeding using vitamin K, fresh frozen plasma and platelets depending on the lab results and timing for the procedure. At the author’s institution an INR (international normalized ratio) of less 1.7 and a platelet count of more than 50 × 10^9/L are used as cutoffs. Because of the high incidence of bacterial colonization of the biliary tree in patients with biliary obstruction, prophylactic broad-spectrum intravenous antibiotics covering both gram-positive and gram-negative organisms should be given within 1 hour of the start of the procedure (e.g., cefotetan, ciprofloxacin, ertapenem).

**Outcomes and complications**

PTC and PTBD are safe and effective procedures for evaluating and for primary or palliative treatment of many biliary pathologies. The technical success rate is high (97%–100%) and clinical success is >75% in all major series [192,193]. Technical success is lower (70%) in nondilated biliary systems [182]. Complications include sepsis, cholangitis, hemorrhage, bile leakage, peritonitis, pneumothorax and death. Reported rates of major complications for PTC is 2% and for PTBD are 0.5%–2% [187]. The majority of complications can be treated conservatively. The procedure-related mortality ranges from 0% to 3% in most series and 30-day mortality ranges from 2% to 20% in patient with malignant obstruction and is usually related to the underlying disease. Recurrence of obstructive jaundice after PTBD ranges from 5% to 25% [193].

**Postprocedure care**

PTC requires a postprocedure bed rest for 3 hours in the recovery area. Afterwards the patient may ambulate as tolerated. PTBD requires a bed rest for 6 hours and the patient should be admitted (e.g., if procedure done in an outpatient clinic) post-procedure for clinical monitoring for signs of bleeding or sepsis. Depending on the patient’s condition, antibiotics may be continued. The biliary drainage catheter should be left to external gravity drainage via drainage bag for 24 hours. After 24 hours, the tube should be capped and be flushed twice daily with 10 cc of normal saline to prevent bile clogging. Patients should be instructed about catheter care and to uncap the catheter and set it for external drainage should they develop any signs of cholangitis.

**Percutaneous transhepatic management of malignant biliary obstruction**

Most cancers causing bile duct obstruction, such as pancreatic cancer, cholangiocarcinoma and gallbladder carcinoma, have a dismal prognosis. At the time of diagnosis the majority of these tumors are unresectable and palliative treatment is the only option. The goal of palliative treatment is symptomatic relief and restoration of bile flow to prevent cholangitis and sepsis. The treatment depends on patient’s specifics and local expertise, and should be made by a multidisciplinary team. PTDB and stenting are the two main radiologic treatment modalities.

Biliary endoprosthesis or internal stents are of two types: plastic stents and self-expandable metallic stents (SEMS). Advantages of internal stents are a better quality of life and no risk of inadvertent tube removal. Disadvantages are a low patency rate and a loss of percutaneous transhepatic access.

SEMS have higher patency rates than plastic stent [194–196]. A review and metaanalysis of Moss and colleagues [196] showed a mean duration of stent patency of 111–273 days with SEMS compared to 62–165 days with plastic stents. The major cause of SEMS dysfunction is tumor ingrowth whereas sludge deposition is the main cause of plastic stent dysfunction. Despite the higher cost of SEMS compared to plastic stent, initial placement of a SEMS showed to be cost-effective in decreasing reintervention rates [194–196]. Uncovered SEMS (bare stent) were developed first. Subsequently covered SEMS were designed to overcome tumor ingrowth through the stent mesh. Results of randomized controlled studies have been controversial regarding potential benefit in patency rate of covered over uncovered SEMS [197–201]; thus more evidence is needed. Uncovered SEMS are permanent and are generally not indicated in benign biliary stricture or in patients who are surgical candidates. If the diagnosis is uncertain, the procedure should be postponed until pathologically proven.

Stents can be placed endoscopically, percutaneously and as part of combined procedure (rendezvous procedure). In most centers the endoscopic route is usually attempted first, with the percutaneous route being reserved for endoscopic failures. Plastic stent are mainly placed endoscopically.

Malignant, distal bile duct obstruction should be addressed separately from a proximal obstruction. In current practice, distal bile duct obstruction is treated first by ERCP, with PTBD
being reserved when ERCP fails, or is not indicated. In such cases, PTBD is usually technically successful. Proximal bile duct (hilar) obstruction treatment is controversial and either ERCP or PTBD may be used as primary drainage treatment, depending on patient's specifics and local expertise [202,203] (Figure 152.16).

In a prospective randomized clinical trial by Piñol and colleagues [204] comparing PTBD with SEMS versus conventional endoscopic polyethylene endoprosthesis for treatment of malignant biliary obstruction, the technical success rates of both procedures were similar (PTBD, 75%; ERCP, 58%; \( P = 0.29 \)), whereas therapeutic success was higher in the PTBD group (71% vs 42%; \( P = 0.03 \)). Major complications were more common in the PTBD group (61% vs 35%; \( P = 0.09 \)) but did not account for differences in 30-day mortality rates (PTBD, 36%; ERCP, 42%; \( P = 0.83 \)).

The most common complications of transhepatic stent placement are cholangitis, hemorrhage, and bile leakage [204–207].

**Percutaneous transhepatic management of benign biliary strictures**

Benign biliary strictures are less frequent than malignant stricture. Common causes are iatrogenic (bile duct injury or stenosed biliary enteric anastomosis), inflammatory disease

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*Figure 152.16* A 49-year-old female with pancreatic cancer. (a) Coronal T1-weighted fat-suppressed spoiled gradient-recalled echo image after injection of gadolinium showed a hypoenhancing mass in the pancreatic head encasing the distal common bile duct (arrowheads) and a left-sided 16 Fr locking biliary drainage catheter (arrow). (b) After removal of the existing tube over, an 0.035-inch Amplatz Super Stiff guidewire (Boston Scientific, USA) (arrow), deployment of a 10 mm \( \times \) 8 cm self-expanding endoprosthesis (Gore Viabil, USA) in the common bile duct (arrowheads). (c) Completed deployment of the stent (arrowheads) and placement of foreshortened 18 Fr silastic biliary tube (Heyer-Schulte, Bentec, USA) to keep access (arrow). (d) 24 hours after, tube cholangiogram showed a patent common bile duct stent (arrowheads) with no intrahepatic biliary duct dilatation and free passage of contrast into the bowel (*). The foreshortened tube was removed.
Transhepatic access is most common, but the procedure may be done percutaneously via existing T-tube tracts or specially created jejunal loops (i.e., Roux-en-Y bowel loop used to drain the biliary system tacked to the anterior abdominal wall). Once the lesion has been crossed, the stricture may be dilated using a high-pressure balloon catheter. A 10–15 mm balloon is usually used in the biliary-enteric anastomosis, 10 mm and 6–8 mm

Pancreatitis, primary sclerosing cholangitis, biliary calculi, biliary tract infection, stenosis of the sphincter of Oddi and following liver transplant. Postsurgical strictures are by far the most frequent. Unrecognized or insufficiently treated stricture may lead to serious complications such as cholangitis, biliary cirrhosis and portal hypertension [208,209].

Depending on the etiology, the site and the patient’s condition, benign biliary strictures may be treated by surgical, endoscopic or interventional radiologic procedures [209,210], Box 152.3.

The overall success rate of postoperative benign biliary strictures treated with surgical reconstruction (Roux-en-Y hepaticojejunostomy) has been reported by Lillemoe and colleagues [209] to be 90.8% at 5 years follow-up. However, postsurgical hepaticojejunostomy benign ischemic strictures do occur (Figure 152.17).

Main contraindications for interventional radiologic treatment are the same as those listed for PTC/PTBD, see Box 152.2.

Figure 152.17 A 65-year-old female status post-Whipple procedure for pancreatic cancer with hepatojejunal anastomosis stricture and symptomatic jaundice. (a) Anteroposterior view. (b) Lateral oblique views. After gaining access through the left-sided biliary system, contrast was injected through a micropuncture sheath (arrow) and the dilated biliary system was opacified. (c) A Brite Tip sheath (Cordis Corporation, USA) was inserted over the wire and the tip was advanced just proximal to the stricture (arrow). A combination of guidewire (not shown) and 5 Fr catheter (arrowhead) were used to cross the stricture. Contrast injection confirmed good positioning into the small bowel (*). (d) Placement of a 10 Fr biliary drainage catheter (arrow) across the hepatojejunal stricture and opacification of the small bowel with contrast (*).
biliary strictures and previous surgery (e.g., Roux-en-Y, Billroth peripherally impacted stones not accessible endoscopically, frequently fails due to challenging anatomy with angulated ducts, in most cases [222]. When ERCP fails patients are referred for and has replaced surgical exploration of the common bile duct patients with extrahepatic stones, ERCP is the main technique in most cases [222]. When ERCP fails patients are referred for percutaneous approach. For intrahepatic stones, ERCP frequently fails due to challenging anatomy with angulated ducts, peripherally impacted stones not accessible endoscopically, biliary strictures and previous surgery (e.g., Roux-en-Y, Billroth II). In contrast, percutaneous procedures can be easily performed through a transhepatic access or a T-tube tract for residual stones after surgery [223,224].

The main absolute contraindication is uncorrectable coagulopathy. Relative contraindications are ongoing infection, chronically collapsed gallbladder, and severe reaction to iodinated contrast agents.

Percutaneous gallstones treatment

The procedure consists of initial percutaneous cholecystostomy, tract up-size with sheath placement, stone removal, tract and biliary tree evaluation, and tube removal. A stone basket is usually used to grasp and extract most stones through the sheath. When stones are too large to be removed with a basket, they can be fragmented using a snare guidewire technique [225]. Other techniques such as intracorporeal electrohydraulic lithotripsy (IEHL) can be used [226]. The complete stone clearance rate is high (94%–97%) [225,227]. Complications include cholangitis, hemorrhage, bile leakage, gallbladder perforation and death. Reported rate of major complications for is 7%–9% [226, 227]. The 30-day mortality is 3% [227]. Gallstones recurrence rate is 22–41% [228,229].

Percutaneous intra/extrahepatic biliary stones treatment

Patient with retained stones postcholecystectomy may be referred shortly after surgery with a T-tube in place. For patients seen later after cholecystectomy (i.e., without T-tube), or with stones related to biloenteric anastomosis, or primary biliary abnormalities, initial access is similar to PTBD.

The usual technique consists in dilating the papilla with an angioplasty catheter and pushing the stone into the bowel with an occlusion balloon [230–232]. Larger or more complex stones can be removed using a basket, IEHL and laser lithotripsy using cholangioscopy [226,232–235]. The complete stone clearance rate is high whatever the technique employed (90%–100%) [231,234,236]. Complications include cholangitis, hemobilia, pancreatitis and death. Reported rate of major complications for sphincteroplasty/occlusion balloon stone removal is 0%–4.7% [231,232]. The procedure related mortality is 0%–1.4% [231,234].

Percutaneous cholecystostomy

Percutaneous cholecystostomy (PC) is a therapeutic procedure that involves the placement of a tube for external drainage of gallbladder contents.

Main indications for PC are acute cholecystitis in high-risk patients who are not surgical candidates and possible cholecystitis with unexplained sepsis, particularly in intensive care patients [236]. It can also be used for imaging or to access the biliary system when ERCP and PTC/PTBD have failed [187]. As PC is commonly performed in critically ill patients, there are few absolute contraindications: severe intractable coagulopathy or interposed bowel may preclude safe access. Relative contraindications include a perforated and decompressed gallbladder,
Technique

The gallbladder may be accessed under ultrasound guidance by a transhepatic or a transperitoneal route (Figure 152.18). In patients with distorted anatomy, CT may be necessary. The transhepatic route is usually preferred. It creates a stable tract and, as the gallbladder has a tendency to collapse toward the tube, it prevents any bile leakage with subsequent peritoneal irritation. Advantages of transperitoneal access include avoidance of the potential hemorrhagic complications associated with the transhepatic route and pain from intercostal catheter passage. Disadvantages include accidental perforation of interposed bowel (especially the colon) and peritoneal bile leakage if the gallbladder fundus is not adherent to the abdominal wall. PC can be performed using the Seldinger technique or the trocar technique. The Seldinger technique is preferred when visualization and/or access to the gallbladder is difficult and in small/decompressed gallbladders. The trocar technique may be used in distended gallbladder with good visualization and access [238].

Outcomes and complications

PC is an effective method for managing cholecystitis either definitively or as a bridge before cholecystectomy. The technical success rate is 98%–100% [239,240]. Complications include sepsis, hemorrhage, bile leakage, transgression of adjacent structures (colon, pleura, small bowel), pneumothorax and death. Reported rate of major complications is 1.6%–2.9% [6,60,187,241]. The vast majority of 30-day mortality cases are related to patient comorbidities rather than the procedure itself and ranges widely from 3.1%–36% [239–242]. Among patients with acute cholecystitis, PC tubes are placed in older patients with increased comorbidities compared to cholecystectomy. Mortality rates after PCT decreased over time [243]. A systematic literature review reported mortality resulting from PC as 0.36% [244].
Postprocedure care
Regardless of the access route, the PC drain should be left in place for at least 4–6 weeks to allow formation of a mature fibrous tract around the catheter shaft and prevent bile leakage. Once a mature tract has formed, additional procedures such as percutaneous stone extraction or lithotripsy can be performed if indicated. A tube cholangiogram/cholangiography should be performed in all patients as well as a clinical trial with tube capping before any tube removal to assess the patency of the cystic duct and CBD, and the maturity of the tract. PC is generally followed by elective cholecystectomy. However, it may be a definitive treatment, especially in patients with acalculous cholecystitis [240].

Percutaneous management of bile leakage
Because there are no clear definitions of bile leakage a consensus definition was suggested by an international study group of hepatobiliary and pancreatic surgeons [245]. Bile leakage is defined as fluid with an increased bilirubin concentration (at least three times greater than the serum bilirubin concentration measured at the same time) in the abdominal drain, or in the intraabdominal fluid on, or after postoperative day 3, or as the need for radiologic intervention (i.e., interventional drainage) because of biliary collections or relaparotomy resulting from bile peritonitis [245]. Bile leakage is a common complication after hepatobiliary and pancreatic surgery, and liver transplant. The incidence of bile leakage after liver resection without biliary reconstruction ranges from 3.6% to 12% [246], and after hepaticojejunostomy ranges from 0.4% to 8% [247]. Less frequent etiologies are trauma and necrotizing pancreatitis [248–250]. Small leaks may be treated conservatively with maintenance of perioperatively placed drains and antibiotics [247]. Patients with a bile leakage requiring a change in patients’ clinical management but which can be treated without reoperation (defined as Grade B) often undergo radiologic or endoscopic procedures. Besides percutaneous intraabdominal drainage of fluid collections, additional invasive therapy may include ERCP with placement of an intrahepatic stent and PTBD to control bile leakage from the cut surface or a bile duct injury and biliary enteric anastomosis, respectively [245]. Main indications for an interventional radiologic treatment are shown in Box 152.4.

Box 152.4 Percutaneous management of bile leakage.

Main indications for an interventional radiologic treatment
Failure of previous surgical repair(s)
Patient with a contraindication to surgery or refusing surgery
Failure of previous endoscopic repair(s) or not indicated

Main contraindications for interventional radiologic treatment are the same as listed for PTC/PTBD.

Technique
PTBD for bile leakage is performed in a similar fashion as for biliary obstruction (Figure 152.19). However, nondilated bile duct are present in 82%–92% of the cases [247,250], hence more difficult to access. A single-puncture or a double-puncture technique may be performed [251].

Outcomes and complications
PTBD decompresses efficiently the biliary system and redirect the bile flow bypassing the bile duct wall defect. Relaparotomy is seldom necessary when PTBD is performed [247]. The technical success rate is 90%–100%. Leak healing rate is 81%–90%. Complications include sepsis, hemorrhage, bile leakage, pneumothorax, and death. Reported overall rate of complications are 0%–12.5%, with major complication rate of 4%. Procedure-related mortality is 0%–6% [247,250,251].

Postprocedure care
Biliary drainage may be required for weeks or months. At the author’s institution, routine catheter change is performed every 8 weeks. If no further bile leakage is present on repeated over-the-wire cholangiogram and the patient is asymptomatic, a fore-shortened nondraining catheter is left in place to keep access. The tube is capped for at least 2 weeks. After successful trial, the catheter may be removed.

Percutaneous gastric, gastrojejunostomy and jejunostomy feeding tubes

Introduction
For hundreds of years, medical practice has included efforts to bypass segments of the enteric system [252]. Nutritional support may be administered enterally or parenterally. When it is clinically appropriate, the enteral route is preferred. Interventional radiology allows for the minimally invasive placement of feeding and decompressing tubes in all segments of the GI tract.

Enteric tubes have traditionally been placed by surgical or endoscopic techniques. The first percutaneous radiologic gastrostomy under fluoroscopic guidance was placed by Preshaw in 1981 [253]. Percutaneous image guided enteric tube placement is a minimally invasive procedure that overlaps and fills a clinical demand between endoscopically and surgically placed tubes.

Indications
The indications for Interventional radiology placed percutaneous enteric and colonic tubes are similar to those described elsewhere.

Oral or nasal enteric tubes
Tubes placed through a natural orifice particularly those connected with the airway are only recommended for short-term use (generally less than six weeks) or as a bridge to more
permanent access. The advantage of placement by radiology is image guidance during tube placement.

**Gastric tube**

The more common subgroups of population for which interventional radiology places gastrostomy tubes includes patients in which an enteroscopic approach is not feasible due to inability to transilluminate or pass the scope through the oral pharyngeal, or esophageal route. Indications include gastric feedings for calorie and/or hydration support, impaired swallowing resulting in aspiration, and decompression of a gastric outlet obstruction.

**Small bowel feeding**

Patients who are unable to tolerate gastric feeding include patients with gastroparesis, gastric outlet or duodenal obstruction. Patients with gastric or duodenal fistulas may benefit from proximal decompression as well as feeding distal to the fistulous tract. In addition, patients with severe gastroesophageal reflux may benefit from feeding distal to the ligament of Treitz. Studies suggest that feeding beyond the ligament of Treitz helps reduce the incidence of pneumonia in hospitalized patients [254–256].

**GI decompression**

Placement of a decompression gastric or enteric tube for diversion away from a downstream obstruction or fistula may be indicated in the appropriate patient. Palliative decompression and downstream obstruction is often requested by patients that do not wish to go to hospice with a nasogastric tube.

**Gastric access for biliary procedures**

Patients with postsurgical anatomy such as a Roux-en-Y anastomosis who require retrograde access into the biliary system may need gastric tube placement to allow for enteroscopic procedures.

**Cecostomy tube**

Cecostomy tubes may be used in patients who need long-term cleansing enemas or gas decompression of the colon. Patients with neurologic disease resulting in fecal incontinence and patients with chronic constipation may use the cecostomy tube for cleansing enemas. Patients with colonic pseudoobstruction may benefit from using this tube for gas decompression.

**Contraindications**

Contraindications to image guided GI access include anatomic factors, bleeding and infection. The interposition of liver or spleen between the ventral abdominal wall and bowel precludes direct puncture – in these patients often the only option is a surgical option. Downstream obstruction is an absolute contraindication to feeding but an indication for decompression. Absolute contraindications include uncorrectable coagulopathy or placement of the tube into ischemic bowel. Relative contraindications are managed on a patient by patient basis. The
complications related to the relative contraindication can sometimes be mitigated through diligent management of the procedure and postprocedural care. For example, the risk of ascites causing peritonitis or nonhealing stoma track may be mitigated in some patients by paracentesis and gastropexy. There is some evidence showing that patients receive gastrostomy tubes in the presence of ventriculoperitoneal shunt’s are at increased risk for ascending meningitis [257]. Similarly patients with peritoneal dialysis may be at risk for peritoneal dialysis catheter infection.

**Preprocedure**

As bleeding is one of the most important complications, preprocedure evaluation for bleeding should be undertaken in all patients receiving enteral access. In general, anticoagulation and antiplatelet management should be based on local practice patterns. At the authors’ institution, the INR should be less than 1.5, platelets should be greater than $50 \times 10^9/L$, clopidogrel is held for 5 days prior to the procedure and dose of low molecular weight heparin prior to the scheduled procedure time is held.

Patients are NPO (nothing by mouth) after midnight before the procedure, or when clinically appropriate NPO, except for clear liquids up to 2 hours prior to the procedure. Although not frequently practiced at the authors’ institution, 300 mL of oral barium is given the evening prior to the procedure to help outline the colon when fluoroscopic guidance is used.

**Technique**

After the preprocedure evaluation is complete the patient is brought into the interventional radiology (IR) suite. The steps followed for all new enteral tubes are similar, but tailored for the particular tube and patient. At the authors’ institution, a limited ultrasound of the abdominal area of tube placement is performed to delineate solid organs and vasculature. Then, the patient is prepped and draped in normal sterile fashion. A tube used to insufflate the bowel of interest is placed through a natural orifice. Next, the bowel is secured using ‘t-tacks’, which are short metal bars attached to suture and when placed under tension fix the bowel wall to the abdominal wall (Figure 152.20).

**Outcomes**

Frequency of technical success for placement of gastrostomy tubes is high regardless of the modality chosen for placement – 95% for percutaneous placement and near 100% for surgical placement [258].

**Complications**

Complications include bleeding, infection and injury to adjacent structures are reported to be 6% with 30-day mortality of 0.3% [258]. Surgical and endoscopically placed feeding tubes have slightly higher short term complication and mortality rates [258]. Bleeding is often self-limited, but if it continues, should be evaluated with arteriography. Peritonitis is uncommon, but if suspected, after discontinuing the use of the tube, a radiograph to look for increasing pneumoperitoneum as well as contrast tube studies and/or abdominal CTs should be performed to evaluate tube position. Conversion of a gastrostomy to a gastrojejunostomy tube, to prevent aspiration pneumonia should be considered in the appropriate patient. “Buried bumper” syndrome and skin infections should be treated with barrier protection and antimicrobials as needed.

**Postprocedural and follow-up care**

Care for IR placed feeding tubes is the same as for all feeding tube with one exception. The t-tacks placed should be removed based on the proceduralist’s recommendation. Although most t-tacks can be removed between 2 days and 2 weeks, some need to be left in longer depending on the clinical situation.

**Percutaneous image-guided biopsy**

Percutaneous image-guided biopsy is a widely accepted technique used to characterize and identify superficial and deep abdominal masses and collections. Transjugular liver biopsy indications and outcomes will be reviewed later in this section. Indications and contraindications for percutaneous image-guided biopsy are listed in Box 152.6.

**Preprocedure**

The evaluation of the patient should include a thorough history, medication review and physical exam with focus on complicating factors and contraindications. Complete review of recent laboratory values should be made including coagulation profile. Recent and previous imaging should be reviewed, and new imaging obtained as needed. Although almost all biopsies can be performed percutaneously, this route is sometimes not optimal for the patient. Endoscopic biopsies may provide a less invasive and safer alternative to the percutaneous rout in

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**Box 152.5 GI decompression.**

**Absolute contraindications**

- Active peritonitis
- Uncorrectable coagulopathy
- Bowel ischemia
- Lack of safe access route (interposed liver or colon)

**Relative contraindications**

- Postsurgical anatomy (Billroth to gastro antrostomy, partial gastrectomy and gastric pull through surgery)
- Ascites
- Presence of a ventriculoperitoneal shunt
- Morbid obesity
- Obstruction of the oral pharyngeal and or esophageal intestinal tract
- GI bleeding from unknown or peptic also disease with visible vessel or visible vessels from the gastroesophageal varices
- Neoplastic involvement of the entire gastric wall making it impossible to dilate
PART 5 Diagnostic and therapeutic modalities in gastroenterology

Box 152.6 Percutaneous image-guided biopsy.

**Indications for percutaneous image-guided biopsy**
- Diagnosis of primary tumor or suspected metastasis
- Cancer staging
- Diagnosis of benign mass (cyst, infection, inflammation)
- Sampling of collection for culture
- Assess response to treatment

**Contraindications to percutaneous image-guided biopsy**
- Uncorrectable coagulopathy
- Lack of safe access route
- Patient refusal after informed consent

Percutaneous image-guided biopsy.

**Indications for percutaneous image-guided biopsy**
- Diagnosis of primary tumor or suspected metastasis
- Cancer staging
- Diagnosis of benign mass (cyst, infection, inflammation)
- Sampling of collection for culture
- Assess response to treatment

**Contraindications to percutaneous image-guided biopsy**
- Uncorrectable coagulopathy
- Lack of safe access route
- Patient refusal after informed consent

some instances. If a percutaneous biopsy in not feasible or of exceedingly high risk to the patient, perhaps the patient should be referred for a surgical biopsy.

As bleeding can be a source of morbidity post biopsy, review of patients history, medications and laboratory tests to evaluate hemostasis should be undertaken. History of bleeding and physical signs of bleeding should prompt additional evaluation. Diseases such as cirrhosis, drugs such as aspirin and warfarin as well as conditions such as uremia should be assessed. Laboratory values should be evaluated in the context of any underlying conditions and biopsy technique. Typically PTT should be $<1.5 \times$ control, platelet count should be $>100,000/\text{mL}$ and INR should be $<1.5$. If the location or coagulation profile precludes the percutaneous approach then alternative techniques should be considered.

**Postprocedure care**
Standard postprocedure care should be focused on monitoring for bleeding, infection and biopsy specific complications including damage to structures adjacent the biopsy site.

**Outcomes**
Successful biopsy results should be returned in 80% to 95% of procedures [259].

**Complications**
Overall major complication rate should be less than 2%, with the most common complications being bleeding and infection. Other complications include pneumothorax, vascular injury, pancreatitis, injury to hollow viscus as well as needle-tract tumor seeding. Tumor seeding and mortality are exceedingly rare [260].

**Transjugular liver biopsy**
Transjugular liver biopsy does not traverse the liver capsule, thereby preventing bleeding into the peritoneum and rupture of
Indications and contraindications are shown in Box 152.8.

**Preprocedure**

Patient preparation is similar to that of percutaneous biopsy, although, drainages are usually preferred as an urgent/emergent procedure in contrast to biopsies which are typically elective.

**Outcomes**

The cure rate of percutaneous drainage with concurrent medical therapy can be greater than 90% for simple collections and approximately 70% for complex collections [264,265]. Failure rates tend to less than 20% and are related to premature removal of the drain, untreated fistula, or tumor [259,264,266].
Complications

Complications include bleeding, organ perforation (e.g., normal bowel, normal solid organ), and rupture of collection with seeding. Overall complication rate is less than 5% [264,267,268].

References are available at www.yamadagastro.com/textbook

Further reading


CHAPTER 153
Confocal laser microscopy

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Introduction

In recent years, the development of advanced endoscopic imaging techniques have enabled increasingly detailed analysis of mucosal and submucosal structures. These novel imaging techniques include dye-based chromoendoscopy (i.e., application of dye agents to the mucosal surface via spraying catheters) and dye-less chromoendoscopy (e.g., narrow band imaging [NBI]; Fuji Intelligent Chromo Endoscopy [FICE], Fujinon, Tokyo, Japan; i-scan, SPIES, Pentax, Tokyo, Japan) [1]. Chromoendoscopy is used as a red flag technique, highlighting subtle lesions and improving detection and diagnosis of various luminal gastrointestinal diseases [2]. Nevertheless, the final diagnosis still rests on the histopathological results. So-called optical biopsy techniques have been introduced recently to provide in vivo histopathology. These include confocal laser endomicroscopy, endocytoscopy, and the WavSTAT system (Spectra Science, San Diego USA) [3–5]. In this review, we focus on the technological details and clinical applications of confocal laser endomicroscopy and provide an outlook on future developments.

Technical aspects

Three types of endomicroscopy systems are available [6] (Figure 153.1). One system consists of a microscope that is integrated into the distal tip of a standard, high-resolution gastroscope or colonoscope (iCLE, integrated confocal laser endomicroscopy; Pentax, Tokyo, Japan). The confocal lens of the iCLE system is visible at the 7 o'clock position of the distal tip of the endoscope and is used to macroscopically guide microscopic imaging. The second endomicroscopy system comprises handheld confocal probes (pCLE, probe-based confocal laser endomicroscopy; Mauna Kea Technologies, Paris, France). The probes are advanced through the working channel of a standard endoscope and gently applied under macroscopic guidance to the mucosal surface [7]. More recently, the armamentarium of CLE was expanded to include small probes that can be advanced through a 19-gauge puncture needle (nCLE, needle-based confocal laser endomicroscopy; Mauna Kea Technologies, Paris, France), thereby enabling confocal imaging of cysts and mass lesions [8]. Technical details of the various systems have been reviewed in detail elsewhere [4–8]. All endomicroscopy systems use an incident blue laser light with a wavelength of 488 nm and allow for a magnification of up to 1000-fold, thereby providing optical biopsies during endoscopy. The handheld confocal probes use a fixed imaging plane depth, which varies between different probe types, while the iCLE system allows incremental adjustment up to 250 μm in depth.

As autofluorescence of tissue is not strong enough for imaging, exogenous fluorescence agents are necessary for confocal imaging. These fluorescence agents can either be applied systemically (i.e., intravenous injection) or can be directly sprayed onto the mucosal surface using standard spraying catheters. The most common agent for confocal imaging is 10% fluorescein sodium. The dye allows confocal imaging within approximately 5–10 s after intravenous injection. The dye
Confocal laser microscopy CHAPTER 153

2945

patients with early squamous cell cancer [11]. The overall accuracy was 95%, and the sensitivity and specificity were calculated as 100% and 87%, respectively. Interobserver and intraobserver agreement were calculated as substantial to almost perfect.

Multiple studies have evaluated the value of CLE for in vivo diagnosis of Barrett esophagus [12–14]. These have found that CLE can distinguish between different types of epithelial cells and detected cellular and vascular changes in Barrett epithelium [12]. Barrett esophagus and associated neoplasia could be predicted with a sensitivity of 98% and 93% and a specificity of 94% and 98%, respectively. In addition, confocal imaging showed good interobserver and intraobserver agreements for the prediction of the histopathological diagnosis. More recently, a large multicenter international randomized controlled trial compared high-definition white-light endoscopy alone with random biopsies and high-definition white-light endoscopy plus endomicroscopy and targeted biopsies for diagnosis of Barrett neoplasia [13]. A significantly lower number of mucosal biopsies and a higher diagnostic yield for neoplasia were found in the confocal group. The addition of CLE and targeted biopsies tripled the diagnostic yield for neoplasia and would have obviated the need for biopsy in 65% of patients. Moreover, the sensitivity for neoplasia detection was significantly increased (to 96%) in the CLE group compared to white-light endoscopy alone with random biopsies. Importantly, the treatment plan was changed in 36% of patients according to in vivo imaging.

Figure 153.1 Two different confocal endomicroscopic systems are currently available. The mini-probe (a) can be passed over the working channel of standard endoscopes (MaunaKea, France) and can even be advanced in the biliary tree. Most recently, small probes can also be advanced over a 19G needle, or the endomicroscope is embedded in an otherwise standard endoscope (Pentax, Japan). (b) The blue laser light is applied onto and into the mucosa (c). The fluorescence and reflected light is measured and grey scale images of mucosal microarchitecture are displayed on an additional monitor. The miniprobe has a fixed imaging plane depth (d) whereas the confocal endoscope can vary the imaging plane depth during imaging from the surface up to the deepest parts of the mucosal layer.

highlights the extracellular matrix but does not allow for a direct nuclear visualization. A multicenter study evaluated the safety of intravenous fluorescein sodium and found the following adverse events: transient hypotension without shock (0.5%), nausea (0.39%), injection site erythema (0.35%), self-limited diffuse rash (0.04%), and mild epigastric pain (0.09%) [9]. Fluorescence agents that are topically applied include 0.05% acriflavine hydrochloride (in saline) and 0.13% cresyl violet (in acetic acid). Acriflavine stains nuclei and cresyl violet the cytoplasm of cells. Concerns have been raised regarding the use of acriflavine as it may have mutagenic risk.

Clinical applications

Esophagus

Liu and coworkers compared endomicroscopy characteristics of cells and intrapapillary capillary loops (IPCLs) in normal and esophageal squamous cell cancer [10]. Patients with squamous cell cancer showed a significantly higher proportion of squamous epithelial cells with irregular arrangement, increased diameter of IPCLs, and irregularly shaped IPCLs compared to control patients. Massive IPCLs with tortuous vessels and long branching IPCLs were observed in patients with squamous cell cancer. Pech et al. assessed the potential of endomicroscopy for predicting histology in vivo during routine endoscopy in 21
Recently, our group has also shown that confocal imaging could be performed in an esophageal tunnel during peroral endoscopic myotomy (POEM) to visualize the neuronal network [14]. It is possible that endomicroscopy may be used to guide myotomy for optimized disease management in patients with achalasia.

Collectively, available evidence suggests that confocal imaging is reliable for in vivo diagnosis of esophageal squamous cell cancer, Barrett, and associated neoplasia and can be used to guide therapeutic decisions.

**Stomach**

Early data suggested that endomicroscopy enables diagnosis of *Helicobacter pylori* bacteria in vivo [15,16]. Various reports have also highlighted the potential of endomicroscopy to diagnose superficial gastric neoplasia with an overall accuracy for the diagnosis of adenocarcinoma of 92% compared to 85% for conventional biopsies [17,18]. Li and colleagues assessed the diagnostic value of endomicroscopy for gastric superficial cancerous lesions and found a significantly higher sensitivity, specificity, and accuracy for gastric superficial cancer compared to standard white-light endoscopy [19].

Endoscopic mucosal resection (EMR) is widely used to treat early gastric lesions. However, residual neoplastic tissue at the resection margin is common but often difficult to detect by conventional white-light endoscopy. Ji et al. aimed to investigate the ability of confocal imaging to assess resection margins after EMR [20]. Accuracy of endomicroscopy in predicting incomplete resection was 92%, with sensitivity and specificity of 100% and 90%, respectively. Another group prospectively compared endoscopic biopsies and endomicroscopy before endoscopic submucosal dissection in gastric epithelial neoplasia [21]. Overall accuracy of endomicroscopy was significantly higher than endoscopic biopsies alone, demonstrating the potential of endomicroscopy for diagnosis of gastric epithelial neoplasia. It is possible that endomicroscopy could reduce the number of biopsies and mistaken diagnoses before endoscopic submucosal dissection.

**Duodenum and small bowel**

Only limited data on the use of endomicroscopy in the small bowel are available. The value of in vivo diagnosis of celiac disease has been evaluated in three studies, which found that endomicroscopy is sensitive and specific in documenting increased numbers of intraepithelial lymphocytes and villous atrophy, but not adequate in relation to crypt hyperplasia, with a sensitivity of only 52% [22–24]. Ji et al. reported a sensitivity, specificity, and accuracy of 86%, 97%, and 93% and an interobserver agreement of 0.89 using CLE for in vivo diagnosis of gastric metaplasia in the duodenum in a cohort of 76 patients [25].

In another study, the accuracy of confocal imaging and narrow band imaging (NBI) in the classification of duodenal polyps was compared [26]. The accuracy, sensitivity, and specificity of endomicroscopy were 83%, 92%, and 78%, whereas those of NBI were 80%, 83%, and 78%, respectively. Accordingly, endomicroscopy had superior sensitivity as compared to NBI for detection of dysplasia in duodenal polyps.

Handheld confocal imaging during double-balloon endoscopy (DBE) procedures was evaluated in 16 patients [27]. The mean depth of small bowel insertion was 255 cm for antegrade and 130 cm for retrograde DBE. Technical success of endomicroscopy was achieved in almost all cases. No adverse events related to the confocal procedure were observed and confocal imaging of the small bowel mucosa was feasible in all cases. In vivo imaging revealed loss of intestinal villi, crypt hyperplasia, advanced neoplasia, or increased blood flow due to mucosal inflammation.

**Biliary and pancreatic system**

Following the development of small-caliber probes capable of passage into the biliary and pancreatic system, endomicroscopic imaging has expanded the potential application of these approaches [28]. Thus, confocal imaging was used to evaluate indeterminate biliary strictures and observations in initial studies suggest that a negative confocal imaging study of the biliary tree may be used to rule out carcinoma [29,30]. These findings were confirmed by Meining and coworkers in a large multicenter study including 102 patients [31]. The sensitivity, specificity, positive predictive value, and negative predictive value of confocal imaging for detection of cancerous strictures were 98%, 67%, 71%, and 97%, respectively, compared to 45%, 100%, 100%, and 69% for index pathology. In 2012, Meining et al. validated a standard descriptive classification of confocal imaging in the pancreaticobiliary system. Characteristics most suggestive of malignancy included thick white or thick dark bands, and dark clumps or epithelial structures [32]. Recently, it has also been shown that endomicroscopy achieves a high technical success rate in patients with primary sclerosing cholangitis and dominant biliary strictures and may have a sensitivity and negative predictive value high enough to exclude neoplasia [33]. Effective use of endomicroscopy for in vivo diagnosis of strictures requires in-depth training in confocal imaging interpretation [34].

**Cystic or solid lesions**

Needle-based endomicroscopy is compatible with an EUS needle, enabling real-time imaging after puncture of cystic or solid lesions. The feasibility of the new device was first proven in a study by Becker and coworkers in an animal model [35]. A study has also shown the potential of the technique to distinguish normal from cirrhotic liver tissue in a rat model [36]. Initial experience in patients has been reported [37]. The detection of epithelial villous structures by needle-based endomicroscopy was significantly associated with pancreatic cystic lesions, yielding a sensitivity of 59%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 50%. The overall complication rate was 9% and included pancreatitis,
Microscopic colitis may be difficult to diagnose as the disease can occur in a patchy manner throughout the large bowel. Various small studies and case reports have highlighted the usefulness of in vivo confocal imaging for diagnosis of lymphocytic and collagenous colitis [41–44]. Endomicroscopy is able to look below the colonic surface and is able to identify increased collagenous bands or increase amount of lymphocytes within the lamina propria.

Patients with chronic inflammatory bowel diseases (IBDs) are known to have an increased risk of developing colorectal cancer. Kiesslich et al. assessed the value of dye-based chromoendoscopy and endomicroscopy for diagnosis of intraepithelial neoplasias in a randomized controlled trial [45]. A population of 161 patients with long-term ulcerative colitis in clinical remission was randomized in a 1:1 ratio to undergo conventional colonoscopy or chromoendoscopy with endomicroscopy (Figure 153.2). Confocal imaging yielded a 4.75-fold increase in detection of neoplasias, which required 50% fewer biopsy specimens. The presence of neoplastic changes could be predicted by endomicroscopy with a sensitivity, specificity, and accuracy of 95%, 98%, and 98%, respectively. More recently, Günther et al. compared the efficacy of random quadrant biopsies, dye-based chromoendoscopy, and endomicroscopy for detection of neoplasia in patients with IBD [46]. Targeted biopsy protocols...
guided by either chromoendoscopy or confocal imaging led to higher detection rates of neoplasia. On the basis of their findings, the authors suggested that random biopsy protocols should be replaced by chromoendoscopy-guided protocols.

Beyond detection of colorectal lesions, various studies have also evaluated the potential of endomicroscopy to assess mucosal inflammation in IBD. Li et al. [47] assessed 73 patients with ulcerative colitis by the colonoscopy Baron score followed by endomicroscopy and mucosal biopsy samples. Confocal imaging appeared to be more accurate than conventional white-light endoscopy for evaluating macroscopic normal mucosa. Of note, more than half of the patients with seemingly normal mucosa on conventional white-light endoscopy showed acute inflammation on histology, whereas no patients with normal mucosa or with chronic inflammation seen during in vivo imaging were found to have acute inflammation on histology. Another study of 54 patients aimed to determine whether disease activity in patients with Crohn’s disease could be graded using endomicroscopy [48]. Increased colonic crypt tortuosity, enlarged crypt lumen, microerosions, augmented vascularization, and increased cellular infiltrates within the lamina propria were observed in patients with active Crohn’s disease. In quiescent Crohn’s disease, a significant increase in crypt and goblet cell number was detected compared to controls. Based on these findings the authors proposed the Crohn’s Disease Endomicroscopic Activity Score (CDEAS) for assessing Crohn’s disease activity in vivo. These studies suggest that endomicroscopy may be useful to diagnose mucosal inflammation in patients with either ulcerative colitis or Crohn’s disease.

Data has also indicated that endomicroscopy might be useful to predict relapse in IBD patients. Kiesslich et al. detected shedding epithelial cells and local barrier defects by confocal imaging in patients with IBD, a finding confirmed by Liu and coworkers [49,50]. In IBD patients in clinical remission, increased cell shedding was associated with subsequent relapse within 12 months following endomicroscopic examination. The sensitivity, specificity, and accuracy for the grading system to predict a flare were 63%, 91%, and 79%, respectively. More recently, Buda et al. assessed crypt and microvascular architecture and function in ulcerative colitis by endomicroscopy and evaluated whether these features have the potential to predict disease relapse [51]. Pericrypt fluorescence, crypt diameter, but not intercrypt distance were significantly increased in ulcerative colitis patients compared to controls. Patients with inactive disease showed a significant increase in fluorescence leakage, crypt diameter, and intercrypt distance compared to those with quiescent disease. A specially designed scoring system, combining fluorescence leakage and crypt diameter, was able to predict a disease flare during a 12-month follow-up period.

**Molecular imaging**

In molecular imaging, individual cell components are highlighted by their molecular signature. Early data in mice models and resection specimens demonstrated that molecular imaging can enable imaging of gastrointestinal cancers by targeting epidermal growth factor receptor or vascular endothelial growth factor [52,53]. Studies have suggested that the potential to achieve in vivo molecular imaging may be extended to patients. Hsiung and coworkers developed a probe for detection of colon cancer by screening a phage library against fresh human colonic adenomas for high-affinity ligands with preferential binding to premalignant tissue [54]. The specific probe identified was conjugated with fluorescein and tested in patients undergoing colonoscopy. The fluorescein-conjugated peptide bound more strongly to dysplastic colonocytes than to adjacent normal cells with a sensitivity and specificity of 81% and 82%, respectively. Another study investigated uptake of nano- and microparticles by the rectal mucosa of IBD patients. Significantly enhanced accumulation of microparticles was observed in ulcerous lesions compared to control patients. Only traces of nanoparticles were visible on mucosal surfaces of IBD patients [55]. The authors concluded that drug-containing particles may have a great potential to specifically target intestinal lesions to maximize therapeutic efficacy and minimize potential side-effects. Sturm et al. developed a peptide that binds specifically to high-grade dysplasia and adenocarcinoma. Confocal imaging was performed in 25 patients after topical application of the fluorescein-labeled peptide [56]. The authors described a 3.8-fold greater fluorescence intensity for esophageal neoplasia compared with Barrett esophagus and squamous epithelium yielding a sensitivity and specificity of 97% and 75%, respectively. Our group has evaluated in vivo imaging using fluorescent antibodies to tumor necrosis factor to predict therapeutic response in patients with Crohn's disease [57]. Topical administration of labeled antibody in patients with Crohn's disease enabled detection of intestinal membrane-bound TNF during confocal imaging. Patients with high numbers of cells positive for membrane-bound TNF showed significantly greater short-term response rates at week 12 upon subsequent anti-TNF therapy compared to patients with low numbers of cells positive for membrane-bound TNF cells. The clinical response in the former group of patients was sustained over a follow-up period of 1 year and associated with mucosal healing at follow-up endoscopy. These findings demonstrated the potential for molecular imaging to predict therapeutic responses to biological treatment allowing “personalized medicine” in Crohn's disease and autoimmune or inflammatory disorders.

**Summary**

Since the introduction of confocal laser endomicroscopy in 2003, various studies have shown the potential of the technique for in vivo diagnosis of a variety of disorders. These include esophageal squamous cell cancer, Barrett esophagus and associated neoplasia, gastritis and gastric cancer, celiac disease, diagnosis of colorectal polyps, microscopic colitis, and IBDs. In addition, endomicroscopy has the potential to improve
diagnosis of neoplastic lesions in patients with IBD. More recent work also demonstrates the potential of confocal imaging to predict clinical outcome and to guide endoscopic therapies. In addition, molecular endoscopic imaging has been shown to be safe and feasible in human trials and the first results suggest that confocal imaging may enable individualized patient management.

References are available at www.yamadagastro.com/textbook

Further reading


**C Pathology**

**CHAPTER 154**

Liver biopsy and histopathological diagnosis

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**Introduction**

This chapter deals with the indications, techniques, and complications of liver biopsy. It describes the morphological changes associated with various disease processes. Emphasis is placed on the changes that are most important in analyzing a liver biopsy to arrive at a diagnosis or differential diagnoses. Other chapters in this textbook deal with the clinical presentations and management of these disease processes.

When considering a liver biopsy, the first step is to establish the indication: the intent is to assess the structure of the liver, as well as evaluate cellular integrity. Histological examination also can assess any intracellular and extracellular deposition or infiltration. A targeted liver biopsy (or aspiration) can be used to characterize liver masses.

The second step is to obtain a satisfactory sample: typically a length of 15 mm is the minimum required for interpretation [1]. A sufficient number of portal tracts after fixation (at least six) is also important since many disease processes target ductular structures [1].

At microscopy, the pathologist assesses the lobular architecture differentiating normal from fibrosis, cirrhosis, and noncirrhotic nodular regeneration. Systematic analysis of the hepatic lobule starts with the examination of the portal tract, followed by terminal hepatic veins, and the assessment of the parenchyma and the sinusoidal spaces. Based on this analysis, the following differentiations are made:

- acute versus chronic inflammation
- parenchymal versus biliary disease
- possible etiological factors
- if neoplastic, benign versus malignant, and primary versus metastatic, and
- intracellular (fat, iron, pigment) versus extracellular infiltrates (amyloid).

Recently, several noninvasive alternatives have been used to assess the stage of fibrosis, particularly for viral hepatitis [2] (see section further on “alternatives to liver biopsy”). With the rapid improvements in therapy for hepatitis C and the high probability of sustained virological cures, the need for a liver biopsy assessment will likely decline [3].

**Technique of liver biopsy**

Histological examination of liver tissue has been useful for diagnostic and prognostic purposes since the 19th century [1]. Several approaches can be taken to obtaining liver tissue using a number of available biopsy needles, each with specific advantages and limitations.

The most common approach is transcutaneous (transabdominal or subcostal) with or without ultrasound or computed tomography (CT) guidance [4,5]. Occasionally, clinical circumstances prevent the transcutaneous route and alternative methods [6] must be considered as summarized in Table 154.1. Alternatively,
patients with coagulopathy can be biopsied transcutaneously after infusion of appropriate coagulation factors, platelets and fresh frozen plasma, and are followed by experienced hematologists [5–7]. However, the authors prefer to refer those patients to interventional radiology for transjugular (TJ) liver biopsy. The latter route appears superior in yield and safer than percutaneous biopsy in patients with renal disease undergoing hemodialysis [8]. In one study, the yield of TJ biopsy was appropriate for diagnosis in 98% of attempts but in one patient (0.27%) death was reported [6]. In another study, less pain was reported with the TJ route, while biopsy length was similar to the percutaneous route [9].

**Needle types**

Needles used for liver sampling rely either on suction (Menghini, Klatskin, and Jamshidi) or cutting technique (TruCut and Vim Silverman) [5]. The latter technique is applied with a spring-load mechanism (Quick-core, Cook Medical, Bloomington, IN; BioPince, Angiotech Medical, Denmark; or Inrad, SE Kentwood, MI) that allows a specific length of tissue, usually 15–30 mm, to be retrieved with a minimum of needle manipulation in the liver parenchyma [10]. In cirrhotic livers, cutting techniques result in less fragmented specimens than the suction technique (Table 154.2). Most percutaneous liver biopsies result in the retrieval of sufficient liver tissue for diagnosis (see further on) after a single pass, but more than one pass is required in 4%–12% of patients [4,11]. Although in the authors institution, the intercostal approach has been preferred, the subcostal approach with an 18-gauge needle has been shown to result in adequate samples with similar low frequency of adverse events [12].

**Imaging for liver biopsy**

The use of real-time imaging (ultrasound being more cost-effective than CT) or ultrasound X-marking of the entry site prior to biopsy has significantly decreased the percentage of patients who experience pain requiring analgesia [4,5,11], as well as the need for hospitalization [4]. A decrease in mortality has not been shown [4,11], but the sample size required to show a statistical difference would be exceedingly large.

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>N</th>
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<tr>
<td>Ascites ALONE</td>
<td>36</td>
<td>9</td>
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<tr>
<td>Abnormal coagulation</td>
<td>205</td>
<td>50</td>
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<td>Ascites and coagulopathy</td>
<td>81</td>
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<td>End-stage kidney disease</td>
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<td>Obesity</td>
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<tr>
<td>Combination of reasons/other reasons</td>
<td>50</td>
<td>12</td>
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From Smith et al. [6].

<table>
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<th>Disadvantages</th>
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<td>Jamshidi</td>
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<td>Long cores with minimal needle insertion</td>
<td>Fragmented tissue with increased fibrosis</td>
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<tr>
<td>Tru-Cut</td>
<td>16</td>
<td>Rare fragmentation, large core</td>
<td>17–20 mm maximum length in one pass, less tissue than other needles</td>
</tr>
<tr>
<td>Inrad, BioPince</td>
<td>16 or 18</td>
<td>Rare fragmentation, large core, adjustable throw up to 34 mm length with one pass</td>
<td>Long throw, more procedural pain</td>
</tr>
</tbody>
</table>

Adapted from deMan et al. [13].

**Surgical approaches**

Laparoscopic liver biopsy may be indicated in patients with ascites as hemostasis is carried out after liver sampling by the surgeon. The technique has the advantage of allowing visual inspection of the liver surface and biopsy of focal lesions [14]. One study suggested that the diagnosis of cirrhosis was increased with mini-laparoscopic biopsy, owing to the visual diagnosis of a nodular liver surface [14].

**Percutaneous approach**

The American Association for the Study of Liver Disease (AASLD) has published guidelines on patient selection and pre-procedure precautions to minimize complications [15]. Guidelines for the management of patients who take antiplatelet agents and anticoagulants have also been published [15]. Many patients use Gingko biloba or fish oil which can alter coagulation and use of other supplements should be solicited and discouraged. Risk, benefits and alternatives should be discussed with the patient prior to scheduling the biopsy.

In the authors Center, they routinely obtain a CBC and INR and proceed with the percutaneous approach as long as the platelet count is >100 000 and INR <1.4 [15]. Liver biopsy is usually performed without sedation, using a local anesthetic at the site of needle entry [16]. However, 1–2 mg of oral or sublingual temazepam can be safely given at the patient’s request. Some physicians administer intravenous midazolam prior to biopsy [17]. The preferred biopsy site is marked by ultrasound, ideally performed either at the bedside by the operator or in the imaging department, in the supine position and in deep expiration, where the entry site is marked with a permanent marker. When the mark is placed in the imaging department, sometimes, we have found that the mark overlays a rib, likely because
of changes in patient position. The angle of entry should avoid
large vessels and gallbladder. After the procedure approximately
half of patients have some epigastric or right shoulder pain [16].
Oral or intravenous analgesia is then administered. A history of
intravenous drug abuse (IVDA) has been associated with post-
procedure pain medication use [16].

The optimal position of the patient after liver biopsy has not
been studied. We have the patients lie supine in the most com-
fortable position for approximately 1 hour but mobilize them
early to assess for subjective orthostasis. Pulse and blood pres-
sure should be assessed 4 times in the first hour, then every 30
mins for 2 hours.

Typically 98%–99% of patients can be discharged after a
3-hour observation. Some radiology departments reimage the
patient 1 hour after the biopsy and if no hematoma is noted then
the patient can be discharged if he has no or minimal symptoms
[18]. However, delayed adverse events can occur. Death due to
bleeding has been described as late as several days after liver
biopsy [19].

Adequacy of specimen
Failure to obtain sufficient tissue occurs in 1%–3% of biopsies
[16]. Moreover, a biopsy length of less than 10 mm and with less
than six portal tracts is considered inadequate, although this
depends on the indication [1]. For example, it may be possible
to diagnose acute cellular rejection with a small biopsy but not
to stage parenchymal fibrosis accurately. A length equal or
greater than 25 mm and including ≥11 portal areas is usually
considered adequate [3]. Whether a specimen >40–50 mm in
length increases diagnostic yield is unsettled [2,3]. A 14-gauge
needle is likely to retrieve a thicker specimen and may provide
a better assessment of fibrosis stage [1]. However, a larger needle
also may be associated with more complications.

Complications
Following biopsy, approximately 1%–2% of patients need
admission [20]. About 50% of severe adverse events are due to
bleeding (hemoperitoneum or subcapsular hematoma) although
severe abdominal or right shoulder pain also can be prominent
[20–22]. Hemobilia (0.01%), arterial pseudoaneurysm and
sepsis (0.01%) are much less common [19,21,22]. Perforations
of other organs including gallbladder, lung, colon, kidney, or
adrenal gland have all been described [4,11,21]. Pancreatic
tissue has been observed together with liver tissue. Complica-
tions usually occur during the first 3 hours post biopsy although,
as noted, delayed complications have been well described [19].

Biopsy of malignant liver masses is associated with a small
but significant probability of seeding the track with neoplastic
cells: the percentage varies from 1% in hepatocellular cancer
(HCC) to 19% with colorectal metastases [23,24].

The vast majority of complications occur within the first 3
hours post biopsy, so a monitoring period of 3–6 hours is ap-
propriate; a family member or friend should be available after
discharge to assist the patient for up to 24 hours [22]. One study
of 629 high-risk patients, including those with HIV infection
[25], reported an atypically high (0.5%) mortality rate as well as
delayed bleeding after liver biopsy and thus patients in these
groups may deserve an increased level of surveillance. In the
general population who undergo liver biopsy, death has been
reported in 1 per 1000–10,000 cases, and almost always due to
massive hemoperitoneum in the setting of cirrhosis, or malign-
nancy [21,26,27]. The risk of bleeding appears to increase with
the number of biopsy passes, associated severe systemic disease
including infections, and the use of heparin or corticosteroids
[25]. Usually only two passes should be performed [19,26]. Of
interest, there is little difference in the complication rates that
occur with trainees versus attending physicians [16, 22, 26].
However, the former tend to retrieve less satisfactory specimens
compared with the latter [26]. Although not statistically signifi-
cant, arithmetically fewer complications occur when pediatric
liver biopsies are performed by more experienced operators
[28]. A retrospective review of the complications of liver biopsy
in transplant patients indicated a much higher frequency of
bacterial infections (approximately 1.5%) [29].

In the radiological literature, experience with ultrasound-
guided percutaneous liver biopsy does not correlate with speci-
men adequacy or complications [30]. There are some differences
in specimen adequacy and complications with suction, cutting,
or spring-load techniques (see Table 154.2) [4,11].

Alternatives to liver biopsy
Two noninvasive approaches have been employed to evaluate
hepatic fibrosis (and inflammation). The first is modeling of
blood tests to estimate the risk of fibrosis; some are easily
obtained (AST/platelets ratio [APRI], Forns Index, Fib-4, cir-
rhosis discriminant score [CDS]) [31]. Others, such as the
Fibrosure test, are proprietary and in the US cost about $200.
In general, these tests have a better positive predictive value
(PPV) for lower fibrosis levels and, depending on the cutoff
used, may eliminate the need for liver biopsy in 20%–25%
patients with hepatitis C [32]. Further validation is required for
other types of liver disease.

A second approach is to estimate the risk of fibrosis by assessing
hepatic stiffness (elastography). Several techniques are now
available, including shear wave, or ultrasound wave.

A negative predictive value of 99% for cirrhosis was noted
when the liver stiffness was less than 9.2 to 11 kPa [33,34]. Thus,
if the measured stiffness is less than the cutoff, the patient is not
likely to have cirrhosis. In patients with HCV, another study
found a cirrhosis PPV of 87% for >13.2 kPa; and levels ≤7.4
correctly predicted stages F0 and F1 in 90% [35]. In nonalco-
holic fatty liver disease (NAFLD), liver stiffness measurements
were not reliable in 14% of patients due to body habitus. The
new Fibroscan® (KNS Canada Inc.) probe showed improved
accuracy. There is little data on the usefulness of these nonin-
vasive tests in pediatric or chronic kidney disease patients.
Overall, it appears that blood tests are relatively accurate (acceptable PPV) in assessing lower levels of liver fibrosis. Elastography appears better for diagnosing possible cirrhosis when liver stiffness is increased (high kPa).

A recent review states that "VCTE (vibration-controlled transient elastography) remains the noninvasive standard to be beaten" for the estimate of liver fibrosis for a number of liver diseases [36]. However, liver biopsy remains the most accurate way to assess necrosis, inflammation of the liver and fibrosis when noninvasive tests fail or give discrepant results.

**Processing of liver biopsy tissues**

Fixation and processing techniques vary among laboratories; however, the most commonly used fixative is 10% buffered formalin. B5 solution containing 6 g of mercuric chloride and 2.074 g of hydrated sodium acetate dissolved in distilled water and mixed with 10 mL of 40% formaldehyde (pH 5.8) at time of use providing crisp nuclear details and rapid fixation. Embedding in plastic resins such as Araldite, compared with paraffin embedding, improves the ability to obtain thin (2–3 μm) sections with greater cytological details, such as cellular mitochondria, or microvesicular fat [37]. Beyond hematoxylin and eosin (H & E) stains, the most useful routine stains are Masson trichrome for collagen (Figure 154.1), periodic acid–Schiff (PAS) for glucose, diastase-digested PAS for glycoprotein (i.e., α1-antitrypsin) (Figure 154.2), iron stain (Figure 154.3), Shikata orcein stain for hepatitis B surface antigen (HBsAg) (Figure 154.4), copper-binding proteins (Figure 154.5), and reticulin stain for identification of cord sinusoidal structures. Other special stains helpful in diagnosis include those for acid-fast and fungal organisms in cases of granulomas; phosphotungstic acid–hematoxylin for fibrin in disseminated intravascular coagulation or necrosis in cases of Q fever: rubeanic acid for copper; and immunoperoxidase stains for viral proteins, α1-antitrypsin, α-fetoprotein, factor VIII, and others.

**Special requirements**

Frozen sections of fresh or fixed tissue are needed to demonstrate fat with oil red "O" stain in cases of Reye syndrome, fatty liver of pregnancy, and fat-soluble vitamin A in Ito cells in hypervitaminosis A. For quantitative analysis of hepatic copper or iron, either fixed or fresh frozen tissue needs to be saved prior to processing for paraffin embedding.
Figure 154.4 Shikata stain demonstrating the presence of HBsAg in the hepatocytes in chronic hepatitis B virus. (Original magnification × 200.)

Figure 154.5 Shikata stain demonstrating dark-black granules of copper-binding protein in periseptal hepatocytes in Wilson disease. (Original magnification × 200.)

Figure 154.6 Nodular regenerative hyperplasia demonstrating regeneration of parenchyma compressing the surrounding parenchyma without fibrous septa formation. (H & E stain; original magnification × 40.)

Figure 154.7 Submassive hepatic necrosis with collapsed perivenular reticulum network. (H & E stain; original magnification × 40.)

**Systematic approach to the review of liver biopsies**

Biopsy sections should be initially reviewed at low-power to screen all fragments present in the section and for assessment of overall architecture. Normal architecture indicates regularly placed portal tracts and hepatic venules in their proper relationship. Portal areas can be expanded from fibrosis. When there are fibrous septa from portal to portal or to perivenular areas with formation of regenerative nodules, a diagnosis of cirrhosis is made (Figure 154.1). In nodular regenerative hyperplasia, the parenchyma exhibits regenerative nodules compressing the adjacent hepatic cords without fibrous tissue around them (Figure 154.6). Collapsed reticulin fibers can be differentiated from true fibrosis by reticulin and trichrome stains. When there is confluent or submassive liver necrosis, loss of hepatocytes from hepatic cords results in a collapsed or compressed reticulum network. If this occurs in the perivenular region, it can mimic fibrosis (Figure 154.7). Following overall assessment of the hepatic architecture, attention should be directed to each of the components of the hepatic lobule.

**Portal areas**

Portal tracts can be enlarged due to either cellular infiltration or fibrosis. The cellular infiltrate can be inflammatory as in a variety of viral, drug-induced, or autoimmune types of hepatitis, or neoplastic as in lymphomas. Inflammatory infiltrates are further categorized as acute in which neutrophils are present,
crystals are often found in biopsies from intravenous drug abusers (Figure 154.12). The pattern of portal fibrosis varies with the type of disease. For example, in chronic biliary tract diseases the fibrosis is often periductal, concentric, and lamellar (Figure 154.13) in nature, whereas in chronic alcoholic liver disease it extends into the parenchyma in an irregular pattern reminiscent of a spider web (Figure 154.14). Bile ducts are involved in acute as well as chronic disease processes. In acute cholangitis, which is usually due to mechanical obstruction, there is dilation of the duct with periductal edema and polymorphonuclear leukocytes infiltrating the duct epithelium and within the duct lumina (Figure 154.8). In chronic biliary obstruction there is bile duct proliferation and biliary fibrosis with periductal orientation (Figure 154.15). Periductal
Polyarteritis nodosa and giant cell arteritis can produce a typical inflammatory reaction involving the arterial wall (Figure 154.21). Arterial hypoplasia is found in patients with congenital hepatic fibrosis. In Osler–Weber–Rendu syndrome there is an increase in abnormal vascular channels suggestive of arteriovenous shunting (Figure 154.22). Deposition of amyloid is typically present in the arterial wall in patients with systemic amyloidosis.

**Figure 154.12** A portal area under polarizing light to demonstrate polarizable crystals in an intravenous drug user. (H & E stain; original magnification × 200.)

**Figure 154.13** Lamellar periductal fibrosis in chronic bile duct obstruction. (H & E stain; original magnification × 100.)

**Figure 154.14** Arachnoid portal fibrosis with periportal extension of collagen in chronic alcoholic liver disease. (Masson trichrome stain; original magnification × 100.)

**Figure 154.15** Portal area with marked cholangiolar proliferation in mechanical duct obstruction. (H & E stain; original magnification × 100.)

Concentric fibrosis is also seen in sclerosing cholangitis (Figure 154.16). There is a chronic inflammatory reaction involving the duct epithelium in the early stages of primary biliary cirrhosis (PBC) (Figure 154.17); in the late stage, ducts are absent. Similar changes are observed in chronic rejection of a liver transplant. Anomalous duct changes include Meyenburg complexes (Figure 154.18) and cystic disorders such as Caroli disease. Paucity of bile ducts is seen in intrahepatic biliary atresia, whereas biliary fibrosis and bile duct proliferation are found in extrahepatic biliary atresia (Figure 154.19). Portal veins are thin-walled vascular structures, and are increased in number and dilated in patients with portal hypertension (Figure 154.20). There is inflammation and thrombosis of portal veins in pyelophlebitis. Primary or metastatic tumors can be seen in the portal venous structures. The hepatic artery often manifests hyalinization in diabetics. Polyarteritis nodosa and giant cell arteritis can produce a typical inflammatory reaction involving the arterial wall (Figure 154.21). Arterial hypoplasia is found in patients with congenital hepatic fibrosis. In Osler–Weber–Rendu syndrome there is an increase in abnormal vascular channels suggestive of arteriovenous shunting (Figure 154.22). Deposition of amyloid is typically present in the arterial wall in patients with systemic amyloidosis.

**Terminal hepatic venules**

Terminal hepatic venules are thin, endothelial-lined vascular spaces without associated underlying collagen. Perivenular fibrosis is present in most forms of alcoholic liver disease (ALD) (Figure 154.23). Endophlebitis with inflammatory reaction of terminal hepatic venules is found in association with acute
Figure 154.16 Primary sclerosing cholangitis with evidence of periductal fibrosis and chronic inflammatory infiltrate. (H & E stain; original magnification × 100.)

Figure 154.17 Primary biliary cirrhosis with granuloma. (Original magnification × 200.)

Figure 154.18 A few dilated duct structures with abnormal epithelium surrounded by loose collagen representing Meyenburg complex. (H & E stain; original magnification × 100.)

Figure 154.19 Biliary fibrosis and ductular proliferation in a 3-month-old infant with extrahepatic biliary atresia. (H & E stain; original magnification × 100.)

Figure 154.20 Increased number of thin-walled vascular structures representing portal venous radicles reflective of portal hypertension. (H & E stain; original magnification × 100.)

Figure 154.21 Severe necrotizing inflammatory reaction around hepatic arteriole in polyarteritis nodosa. (H & E stain; original magnification × 100.)
when there are small scattered foci of hepatocytolysis replaced by small groups of hyperplastic Kupffer cells. Confluent necrosis occurs when a larger number of liver cells, such as an entire zone, is necrotic (Figure 154.26). Submassive and massive necrosis are more severe forms. In submassive necrosis, entire lobules are involved with sparing of a few perportal hepatocytes, whereas in massive necrosis no viable hepatocytes are present (Figure 154.27). The term granulomatous necrosis is used when the area of necrosis is well circumscribed and comprises a compact arrangement of macrophages, lymphocytes, and plasma cells (Figure 154.28). This differs from true granulomas because they lack epithelioid cells and multinucleated giant cells. Coagulative necrosis denotes eosinophilic change of hepatocytes with loss of nuclei and maintenance of reticulin without inflammatory infiltration. This is observed in patients

**Hepatic parenchyma**

Evaluation of the hepatic parenchyma should be undertaken in relation to the three zones of Rappaport. Zone 3, or the perivenular zone, is most susceptible to anoxic changes and most drug-induced liver necrosis occurs here. Acute alcoholic injury, as well as acute viral hepatitis, reveals a predominance of zone 3 involvement. Periportal cell necrosis can be seen in some patients with acute type A viral hepatitis, ferrous sulfate toxicity, and toxemia of pregnancy. The term “spotty necrosis” is used when there are small scattered foci of hepatocytolysis replaced by small groups of hyperplastic Kupffer cells. Confluent necrosis occurs when a larger number of liver cells, such as an entire zone, is necrotic (Figure 154.26). Submassive and massive necrosis are more severe forms. In submassive necrosis, entire lobules are involved with sparing of a few perportal hepatocytes, whereas in massive necrosis no viable hepatocytes are present (Figure 154.27). The term granulomatous necrosis is used when the area of necrosis is well circumscribed and comprises a compact arrangement of macrophages, lymphocytes, and plasma cells (Figure 154.28). This differs from true granulomas because they lack epithelioid cells and multinucleated giant cells. Coagulative necrosis denotes eosinophilic change of hepatocytes with loss of nuclei and maintenance of reticulin without inflammatory infiltration. This is observed in patients
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who have sustained anoxia (Figure 154.26), or toxic necrosis due to either halothane, or acetaminophen (Figures 154.29 and 154.30).

Parenchymal inclusions

The most common pigment found in liver cells is lipochrome or lipofuscin ("wear-and-tear" pigment) prominent in zone 3. Hemosiderin pigment is usually observed in periportal hepatocytes (Figure 154.3). Bile can be present in the hepatocytes and Kupffer cells but often it is associated with canalicular bile plugs. Mallory hyalin appears as eosinophilic clumps in hepatocytes that are hydropic, representing aggregates of intermediate filaments. In acute ALD, hyaline necrosis is associated with neutrophilic infiltrates which are usually found in perivenular areas (Figure 154.31). Though usually associated with ALD, Mallory bodies can also be seen in periportal hepatocytes in chronic biliary diseases such as primary biliary cirrhosis or chronic obstruction (Figure 154.32). Eosinophilic inclusion bodies, often spherical but of variable size, are present in periportal hepatocytes of patients with heterozygous or homozygous deficiency of α₁-antitrypsin. These globules are PAS-positive and resistant to diastase digestion (Figure 154.2). In some cases of ALD, giant mitochondria that are spherical or needle-shaped can be found in hepatocytes (Figure 154.33). Important viral inclusions include ground-glass hepatocytes with excessive HBsAg in chronic hepatitis B virus (HBV) infection, nuclear and cytoplasmic inclusions of cytomegalovirus (CMV), and nuclear inclusion of herpes simplex.
Cord pattern
Hepatocytes are arranged in a radial fashion alternating with the sinusoidal blood spaces. In cases of diffuse cell swelling, this pattern is altered. When there is uniform cell enlargement with crisp nuclei and the cells are arranged in a cobblestone formation, it indicates focal regenerative activity (Figure 154.34). A diffuse cobblestone pattern is seen in persistent viral hepatitis.

Nuclear changes
Nuclear changes of hepatocytes include dysplasia, defined as enlargement of a group of cells with a high nuclear to cytoplasmic ratio (Figure 154.35). Nuclear polyplodidy means irregularity and enlargement of individual cell nuclei. Nuclear membrane invagination and glycogen vacuolization are other frequent changes (Figure 154.36). Syncytial change represents multinucleated liver cells; it is often found in patients with neonatal hepatitis (Figure 154.37).

Sinusoidal spaces and lining cells
In chronic passive congestion and outflow obstruction, the sinusoids in zone 3 are dilated in conjunction with atrophy of hepatocytes (Figure 154.38). In left-sided heart failure, red cells traverse the space of Disse and enter the hepatic trabecula (Figure 154.39). Focal sinusoidal dilation can be seen in space-occupying lesions in the adjacent parenchyma. Collagen deposition in the space of Disse eventually leads to narrowing and occlusion of sinusoidal spaces (Figure 154.40). This is commonly observed in ALD, hypervitaminosis A, chronic outflow obstruction including constrictive pericarditis, and inferior vena cava web lesions, as well as methotrexate toxicity. In
Figure 154.34 Focal regeneration with cobblestone arrangement of hepatocytes in chronic hepatitis. (H & E stain; original magnification × 200.)

Figure 154.35 Focal dysplastic change consisting of enlarged cells with large nuclei in chronic hepatitis B. (H & E stain; original magnification × 200.)

Figure 154.36 Hepatocytes with glycogen vacuolated nuclei. (H & E stain; original magnification × 200.)

Figure 154.37 Syncytial hepatocytes in neonatal hepatitis. (H & E stain; original magnification × 200.)

Figure 154.38 Chronic passive congestion causing perivenular sinusoidal dilation and atrophic hepatic cords. (Masson trichrome stain; original magnification × 400.)

Figure 154.39 Perivenular hepatic parenchyma with dilated sinusoids and the presence of red blood cells within the hepatic cords in left-sided heart failure. (H & E stain; original magnification × 100.)
amyloidosis, deposition of amyloid occurs in a reticular pattern or as globular amyloid in the space of Disse (Figures 154.41 and 154.42). Hypertrophy of Kupffer cells occurs in many inflammatory diseases of the liver, but is most striking in salmonellosis (Figure 154.43). Stellate cells or Ito cells located in the space of Disse are the site of storage of retinoids (vitamin A metabolites). Through a process of activation, these cells can transdifferentiate into myofibroblasts and produce sinusoidal fibrosis (Figure 154.44). Peripheral circulating cells are visualized in sinusoidal blood spaces. Atypical cells of mononucleosis, leukemic cells, and cells of hairy cell leukemia can also be seen (Figure 154.45). Fibrin thrombi packed within the sinusoids occur in patients with either disseminated intravascular coagulation or toxemia of pregnancy (Figure 154.46). Sickled red blood cells are often seen in small clumps within the sinusoidal in sickle-cell anemia patients (Figure 154.47).
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Cell. Macrovesicular fatty change involving zone 3 is often present in ALD (Figure 154.49) as well as diabetes mellitus and obesity. Steroid-induced fatty change involves all zones. Microvesicular fat, composed of small droplets of fat, sometimes appears as foamy change of the cytoplasm, without displacement of the hepatic nucleus. This is found in alcoholic foamy degeneration, fatty liver of pregnancy, tetracycline toxicity, Reye syndrome, and in valproic acid toxicity (Figure 154.50).

Terminal hepatic venules and venous outflow

The most common pathological change of terminal hepatic venules is perivenular and obliterator sclerosis seen in alcohol-induced liver injury (Figure 154.23). Similar fibrosis also can be observed in Budd-Chiari syndrome and other causes of outflow obstruction, such as constrictive pericarditis, inferior vena caval

Figure 154.45 Leukemic cells in the sinusoidal blood space in a case of lymphocytic leukemia. (H & E stain; original magnification × 200.)

Figure 154.46 Periportal sinusoidal space filled with fibrin thrombi in toxemia of pregnancy. (H & E stain; original magnification × 100.)

Figure 154.47 Clumps of sickled red blood cells packed in the sinusoidal spaces. (H & E stain; original magnification × 200.)

Figure 154.48 Cholestasis in dilated canaliculi in zone 3 in chlorpromazine-induced liver disease. (H & E stain; original magnification × 200.)

Cholestasis

Cholestasis in zone 3 is often associated with biliary obstruction or drug-induced injury (Figure 154.48), whereas periportal (zone 1) bile stasis is observed in late stages of primary biliary cirrhosis. Simple cholestasis with no associated morphological changes of bile ducts is seen in benign recurrent intrahepatic cholestasis, benign postoperative cholestasis, pregnancy, and in association with some drugs such as estrogen or anabolic steroids, as well as in bacterial sepsis.

Fat

Two major types of fatty changes can occur in hepatocytes; including macrovesicular and microvesicular types. Macrovesicular fat droplets appear as a large vacuole dislocating the nucleus and the cytoplasmic material to the periphery of the cell. Macrovesicular fatty change involving zone 3 is often present in ALD (Figure 154.49) as well as diabetes mellitus and obesity. Steroid-induced fatty change involves all zones. Microvesicular fat, composed of small droplets of fat, sometimes appears as foamy change of the cytoplasm, without displacement of the hepatic nucleus. This is found in alcoholic foamy degeneration, fatty liver of pregnancy, tetracycline toxicity, Reye syndrome, and in valproic acid toxicity (Figure 154.50).
The tumor cells are benign with normal nuclear-to-cytoplasmic ratios, and portal tracts and terminal veins are not present in the lesions. There are prominent, thick-walled arteries along the edge of the tumor (Figure 154.52). Focal nodular hyperplasia has a typical central stellate scar with loose vascularized fibrous tissue containing atypical ductal elements along the periphery (Figure 154.53). This lesion also lacks normal portal areas and terminal hepatic veins (Figure 154.54). Hepatocellular carcinoma (HCC) is the most common form of primary malignant neoplasms of the liver [40]. Other forms include cholangiocarcinoma and angiosarcoma. The tumor cells of the majority of typical HCCs have a trabecular pattern with increased numbers of cells forming finger-like projections into vascular spaces. These trabeculae are lined by endothelial cells and surrounded by vascular spaces (Figure 154.55). The tumor can have focal acinar changes with secretory material in the lumina. Sclerosing obstructive, or web lesions. Endotheliolitis or inflammatory cell infiltration of terminal hepatic venules is a feature of acute rejection of liver transplants (Figure 154.24).

**Space-occupying lesions of the liver**

A CT- or ultrasound-guided liver biopsy of a solid mass can result in a sample that is diagnostic. Cysts and abscesses are usually aspirated.

**Primary tumors: benign and malignant**

Among the benign solid mass lesions, focal nodular hyperplasia is one of the most common and must be differentiated from liver cell adenoma [38,39]. Liver cell adenoma does not have a capsule but compresses adjacent parenchyma (Figure 154.51).
hepatic carcinoma is a variant with a dense collagenized stroma (Figure 154.56). The fibrolamellar variant has lamellar strands of collagen separating thin cords of large eosinophilic neoplastic hepatocytes [41] (Figure 154.57). Cholangiocarcinomas are composed of neoplastic ductal elements surrounded by dense fibrous stroma [40] (Figure 154.58). The tumor is clearly demarcated from the surrounding liver. Immunohistochemical markers can be helpful in differentiating HCC from other primary and metastatic tumors of the liver [42].

**Nodular regenerative hyperplasia**

Nodular regenerative hyperplasia (NRH) is a rare form of hyperplasia of liver cells with formation of nodules without fibrous septa [43]. Microscopically, the hyperplastic nodules are better identified on low power exhibiting compression by the surrounding parenchyma (Figure 154.6). A reticulum stain outlines these nodules, which can vary from small and microscopic to very large (>20 cm). Patients with nodular regenerative hyperplasia may have evidence of portal hypertension.

**Metastatic tumors**

Metastatic tumors in the liver can be easily diagnosed on the basis of an ultrasound-guided needle biopsy. Tumor cells usually grow into the adjacent sinusoids, compressing and separating the hepatic trabeculae (Figure 154.59). Examination of the junction between the tumor and nontumorous tissue is useful in differentiating HCC from metastatic tumors. In HCC, the tumor cells merge into the hepatic cords where there is a transition from normal to neoplastic cells (Figure 154.60). In metastatic tumors, the tumor grows into the sinusoidal spaces.
Without epithelioid cell formation. These lesions are seen in viral infections (e.g., CMV, Epstein–Barr virus [EBV]), rickettsial infections (e.g., Q fever), and in liver injury caused by drugs such as phenytoin, allopurinol, phenylbutazone, and sulfonamides. Some of these drugs can also elicit an epithelioid reaction with true granuloma formation (Figure 154.65). Hepatic granulomas can also be associated with Hodgkin disease, postjunoileal bypass, and PBC (Figure 154.17). Some distinctive features useful in the differential diagnosis of hepatic granulomas include:

1. a central vacuolated space with a fibrin ring in granulomas [32] of Q fever representing the so-called “donut” lesions (Figure 154.64);
2. demonstrations of acid-fast and fungal organisms using special stains;

Granulomas

Granulomas are identified in up to 25% of all liver biopsies [44]. Sarcoidosis is the most common cause of epithelioid granulomas in the liver (Figure 154.61). Among infectious agents causing granulomas, the most common are *Mycobacterium tuberculosis, Mycobacterium avium intracellulare*, Q fever, and brucellosis (Figures 154.62, 154.63, and 154.64). Fungal infections such as blastomycosis and coccidioidomycosis are the next most common causes. Parasitic infections such as schistosomiasis with hepatic granulomas are common in some endemic areas of the world. Epithelioid granulomas are well circumscribed and comprise multinucleated giant cells, epithelioid cells, and lymphocytes along the periphery. Granulomatous lesions, which are not true granulomas, are small punched-out areas of hepatic necrosis with aggregates of macrophages and lymphocytes.

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**Figure 154.57** Eosinophilic neoplastic hepatocytes with lamellar fibrous stroma in fibrolamellar hepatocellular carcinoma. (H & E stain; original magnification × 100.)

**Figure 154.58** Neoplastic ductal structures with fibrous stroma in cholangiocarcinoma. (H & E stain; original magnification × 100.)

**Figure 154.59** Metastatic, poorly differentiated adenocarcinoma infiltrating into the sinusoids. (H & E stain; original magnification × 200.)

**Figure 154.60** Junction of tumor and nontumor liver in hepatocellular carcinoma. The tumor cells grow into the hepatic cords (arrows). (H & E stain; original magnification × 100.)
3. the presence of eosinophils in granulomas associated with drug reactions, parasitic diseases, and Hodgkin disease;
4. the presence of remnants of ova in schistosomiasis (Figure 154.66); and
5. caseation necrosis, occurring rarely in tuberculous granulomas (Figure 154.62).

**Differential diagnosis of cirrhosis**

Cirrhosis of the liver can be classified as alcoholic, nonalcoholic, biliary, and cardiac cirrhosis based on morphological features. A broad distinction is made between micronodular (<3 mm nodules), and macronodular (>3 mm nodules) cirrhosis based on the size of the regenerative nodules. Typical alcoholic cirrhosis is of micronodular type and is diagnosed by the presence of dense, broad, fibrous scars with small parenchymal nodules exhibiting sinusoidal collagenosis (Figure 154.1). Fat, alcoholic hyaline, and other acute changes due to alcohol can be superimposed. Mild chronic inflammatory reaction of a nonspecific nature can be present in the fibrous septa without perisepetal or parenchymal activity. Cirrhosis due to hemochromatosis, also a micronodular cirrhosis, is characterized by the presence of hemosiderin deposition in the parenchymal cells as well as in the fibrous septa and in bile duct epithelia. There is a striking lack of inflammatory process in this type of cirrhosis.

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**Figure 154.61** Partially segmented, exuberant epithelioid granuloma of sarcoidosis. (H & E stain; original magnification × 100.)

**Figure 154.62** Epithelioid granuloma with Langhans giant cells in *Mycobacterium tuberculosis* infection of liver. (H & E stain; original magnification × 100.)

**Figure 154.63** Well-circumscribed clusters of large foamy histiocytes in *Mycobacterium avium intracellulare* infection of the liver. These cells contain abundant acid-fast organisms on special stain (not shown). (H & E stain; original magnification × 100.)

**Figure 154.64** Granulomatous lesion with central vacuolization surrounded by a fibrin ring in Q fever. (H & E stain; original magnification × 200.)
Nonalcoholic cirrhosis, usually of macronodular type, is a broad category of cirrhosis which is the end result of chronic hepatitis of various etiologies. Fibrous septa are relatively thin and vascularized and reveal prominent chronic inflammatory infiltration. The inflammation extends into the perisepal parenchyma, which exhibits a varying degree of necroinflammatory activity. In biliary cirrhosis, fibrous septa exhibit a characteristic lamellar pattern and extend from portal to portal areas leaving islands of parenchyma. This is best described as a jigsaw puzzle-like appearance (Figure 154.67). In contrast, cardiac cirrhosis has a reverse lobular pattern, as the perivenular fibrous areas form septa leaving the portal areas relatively uninvolved. Following morphological identification of the type of cirrhosis, efforts to determine etiology can be undertaken. The morphology of alcoholic cirrhosis can also be seen in postjejunointestinal bypass liver disease. Among the etiologies of nonalcoholic cirrhosis, chronic HBV infection can be confirmed by the presence of ground-glass cells (Figure 154.68) and significant dysplastic changes of the hepatocytes (Figure 154.35). Autoimmune hepatitis can be suspected as the etiology if there is a predominance of plasma cells among the portal and parenchymal infiltrates (Figure 154.11). In addition, areas of collapse may exist even in the cirrhotic stage in these cases. Wilson disease is suggested by increased hepatic copper and copper-binding protein (Figure 154.5). In biliary cirrhosis, absence of bile duct elements with the presence of lymphoid infiltrates in the septa is suggestive of primary biliary cirrhosis, whereas evidence of bile duct proliferation with or without acute cholangitis is suggestive of biliary obstruction leading to cirrhosis. Cirrhosis in infants and children due to \( \alpha_1 \)-antitrypsin deficiency, intra- or extrahepatic biliary atresia, and in cystic fibrosis involving the liver also appears biliary in nature. Clinical, laboratory, and radiological
data are needed to establish an accurate etiological diagnosis in most patients.

**Specific liver diseases**

**Necroinflammatory diseases**

**Acute viral hepatitis**

Regardless of the etiological agent, typical perivenular hepatocytolysis, extreme hydropic swelling of the hepatocytes, marked Kupffer cell hyperplasia, and mononuclear exudative reaction in the parenchyma as well as the portal tracts are found in patients with acute viral hepatitis [45] (Figures 154.69 and 154.70). Numerous acidophilic bodies also are present. The acidophilic bodies represent individual hepatocytes undergoing necrosis with cytoplasmic condensation and nuclear pyknosis. Cholestasis may or may not be present. The hepatocytes in zone 1 usually reveal uniform hydropic change suggestive of regeneration. Portal tracts are expanded with inflammation without fibrosis (Figure 154.70). Some distinctive changes are associated with specific viral agents. Acute type A hepatitis can exhibit a periportal accentuation of the necrosis [46]. Enteric (hepatitis E virus, HEV) acute hepatitis tends to have prominent acinar changes with hepatocytes arranged around dilated biliary canaliculi resembling rosettes throughout the lobules [47] (Figure 154.71). In acute hepatitis due to delta (hepatitis D virus, HDV) agent, the presence of hepatitis D antigen (HDAg) can be demonstrated by immunoperoxidase. When the necrosis in acute viral hepatitis (AVH) is severe, it involves the entire zone 3 and is called confluent necrosis. When the necrosis involves zones 2 and 3 and part of zone 1 with hepatocytes remaining viable in the periportal zones, it is classified as submassive necrosis. Massive necrosis is the term used when necrosis involves all zones without any viable hepatocytes.

**Chronic viral hepatitis**

**Terminology**

Chronic hepatitis encompasses patients whose virological markers persist for more than 6 months in the presence of abnormal liver enzymes. Terms used in the past to characterize the histopathology of chronic hepatitis such as persistent hepatitis, chronic active hepatitis, and chronic lobular hepatitis are no longer considered useful by pathologists. The diagnosis of “chronic hepatitis” is further elaborated by the causative virus (i.e., type B, type C, or type D) and by the assessment of necroinflammation and fibrosis using a semiquantitative method, that distinguishes grades (0–4) and stages (1–4) as proposed by Ludwig [48]. Quantitative schemes have included many scoring

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**Figure 154.69** Perivenular zone in acute viral hepatitis demonstrating hydropic hepatocytes, hepatocytolysis, inflammatory exudate, and rare acidophilic bodies. (H & E stain; original magnification × 200.)

**Figure 154.70** Portal area in acute viral hepatitis with mononuclear infiltration extending to the periportal regions. (H & E stain; original magnification × 200.)

**Figure 154.71** Prominent acinar transformation of hepatocytes in enterically transmitted acute hepatitis, type E. (H & E stain; original magnification × 200.)
The target hepatocytes (Figure 154.74). The degree of necrosis depends on the disease activity – more severe in exacerbations or reactivation, and less so in quiescent stages. Fibrosis progresses to cirrhosis with associated ongoing perisepal inflammatory activity. The term piecemeal necrosis is used to describe the periporal extension of mononuclear inflammation in association with hepatocytolysis involving the limiting plate. In chronic hepatitis B there is significant nuclear dysplasia (Figure 154.73). The most common morphological features of chronic viral hepatitis are portal fibrosis, portal and periporal mononuclear inflammation, and parenchymal necroinflammatory changes with an irregular distribution among lobules. Regenerative activity is also irregular in distribution (Figures 154.72 and 154.73). Lymphocytes and Kupffer cells are seen cuffing around the target hepatocytes (Figure 154.74). The degree of necrosis depends on the disease activity – more severe in exacerbations or reactivation, and less so in quiescent stages. Fibrosis progresses to cirrhosis with associated ongoing perisepal inflammatory activity. The term piecemeal necrosis is used to describe the periporal extension of mononuclear inflammation in association with hepatocytolysis involving the limiting plate. In chronic hepatitis B there is significant nuclear dysplasia (Figure 154.35). In cases of chronic hepatitis C the following distinctive features are seen in most patients: macrovesicular fatty change, mild sinusoidal collagenosis in the periporal areas, prominent lymphoid reaction of portal areas, and moderate to marked atypia of the bile duct epithelium [52] (Figures 154.75 and 154.76). In chronic hepatitis B, immunoperoxidase

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<td>B. Confluent necrosis</td>
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Modified staging: fibrosis and cirrhosis

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<tbody>
<tr>
<td>No fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>Fibrous expansion of some portal areas</td>
<td>1</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas</td>
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</tr>
<tr>
<td>Fibrous expansion with occasional portal to portal (P-P) bridging</td>
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</tr>
<tr>
<td>Fibrous expansion with marked bridging</td>
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</tr>
<tr>
<td>Marked bridging with occasional nodules, incomplete cirrhosis</td>
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<tr>
<td>Cirrhosis, probable or definite</td>
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minimal necroinflammatory changes in patients on steroid therapy with good response.

Other viral infections
A mononucleosis pattern of hepatitis can be associated with hepatitis due to EBV, CMV, and some instances of hepatitis C virus (HCV) infection [56]. In this form, hepatocytes are not swollen and the cord pattern is maintained. There is striking sinusoidal lymphocytosis, and many of these cells are atypical (Figure 154.78). There is portal infiltration by the same type of cells. In addition, multifocal punched-out hepatocytolysis (Figure 154.28) without confluent or zonal necrosis present. Rarely, epithelioid granuloma can be seen. In immunocompromised individuals, CMV infection results in an abundance of virally infected cells with typical nuclear inclusion bodies in the bile duct epithelium or reticuloendothelial cells. Following an
Alcoholic liver disease

Changes in liver histology due to alcohol can be divided into acute cellular damage, and chronic, slowly progressive changes with evidence of chronic liver disease.

Acute changes

The most common acute damage is fatty change of a macrovesicular type with or without cholestasis. Large vacuoles of macrovesicular fat involve the perivenular hepatocytes (Figure 154.49). Occasionally, the entire lobule is involved. Cholestasis and sinusoidal fibrosis may be seen. Acute foamy fatty change (FFC) represents a variant of acute alcoholic hepatitis [60], in which perivenular hepatocytes are enlarged with foamy or microvesicular fat (Figure 154.50). The nucleus is central in location and the cells may exhibit abnormal giant mitochondria visible as eosinophilic round bodies (cherry bodies) (Figure 154.33). Sinusoidal collagen deposition can be prominent in the perivenular zones. FFC can also be seen in association with the acute sclerosing hyaline necrosis (ASHN) in patients with alcoholic hepatitis [61]. The morphological hallmarks of ASHN are:

1. hydropic hepatocytes with cytoplasmic Mallory hyaline bodies, appearing as cytoplasmic eosinophilic ropy material;
2. neutrophil reaction around these cells with hyaline necrosis (Figure 154.31); and
3. sclerosis of the terminal hepatic venules with sinusoidal collagenosis.

Orthotopic liver transplantation, CMV infection causes microabscess formation with the polymorphonuclear leukocytes surrounding the cells with viral inclusion bodies [57,58] (Figure 154.79). Viral antigen in CMV hepatitis is demonstrable using immunochemical methods. Herpes simplex infection of the liver is rarely encountered because liver biopsies are typically not performed due to prolonged prothrombin time in these patients. However, typical changes consist of large, discrete, irregular zones of coagulative necrosis of parenchymal cells with the presence of eosinophilic intranuclear inclusions in the viable hepatocytes at the margins of necrosis [59] (Figure 154.80).
within the portal tract without any orientation to the bile ducts. These portal tracts often have classic arachnoid fibrosis.

**Chronic alcohol-induced liver damage**

The primary manifestation of chronic alcohol-induced liver damage is fibrosis. Three forms of progressive fibrosis are seen [62]; including:

1. portal and perivenular fibrosis leading to fibrous septa formation, resulting in cirrhosis with small regenerative nodules (Figure 154.1);
2. diffuse interstitial fibrosis in which collagen extends throughout the lobule encircling individual hepatocytes and without parenchymal regeneration or septal formation (Figure 154.81); and
3. progressive perivenular fibrosis with dense scar-like collagen involving zone 3 with relatively minimal portal fibrosis (Figure 154.82).

In the early stages, the fibrous septa appear thin, with larger pseudo lobules or parenchymal nodules. There is evidence of prominent intra nodular sinusoidal fibrosis. As the disease progresses, the septa become denser and wider, and the nodules become subdivided into smaller nodules, with continued sinusoidal fibrosis in the perisepal regions. In advanced stages, there is extensive scarring leaving islands of parenchymal nodules scattered within. Masson trichrome and PAS stains clearly define the ratio of fibrous tissue to the parenchyma. In an established state of cirrhosis, if there is prolonged abstinence from alcohol, regenerative parenchymal nodules enlarge, pushing the fibrous septa centrifugally with reduction in the amount of collagen both within the parenchyma and the septa. At this inactive stage, it may be difficult to distinguish alcohol from other etiologic causes of cirrhosis. All of the acute cellular changes described previously can occur superimposed on a cirrhotic or fibrotic liver. The distribution of Mallory hyaline, neutrophilic infiltrate or fatty change may be irregular and focal, rather than uniform. When there are additional complications, such as anoxia due to variceal bleeding or general anesthesia, coagulative necrosis can be seen within the central zone of the cirrhotic nodules.

**Differential diagnosis**

Nonalcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD) (see further on) are often present as progressive liver disease with histological features resembling alcoholic liver disease [63,64]. Morphological changes identical to those in ASHN can be seen in patients with Indian childhood cirrhosis, and drug-induced reactions in patients receiving amiodarone [65]. These findings were also found in patients with morbid obesity who underwent jejunooileal bypass, although this procedure is no longer performed. Mallory bodies without accompanying neutrophilic reaction occur in a number of conditions such as Wilson disease, primary biliary cirrhosis, chronic biliary obstruction, and in livers bearing HCC (in either the tumor or nontumor cells). Sinusoidal collagen deposition resembling typical ALD can be found in association with chronic HCV hepatitis, hypervitaminosis A, and methotrexate toxicity. A much more localized perivenular fibrosis can be observed in venous outflow obstruction such as Budd–Chiari syndrome. In many patients, the liver biopsy reveals features of both ALD and chronic hepatitis of HCV type consistent with a high prevalence of serologic markers of HCV in patients with ALD [66]. There is an increased degree of chronic inflammatory infiltrate in the portal tracts or fibrous septa with spillover to the perisepal parenchyma.

**NAFLD**

NAFLD spans the spectrum from fatty liver to NASH to end-stage cirrhosis. Although these are not necessarily sequential,
type 2 manifest by steatosis along with portal inflammation and portal fibrosis without ballooning or perivenular fibrosis. Several scoring systems have been devised to rate the severity and stage of NAFLD. Factors used in these scoring systems include microvesicular and macrovesicular steatosis, perivenular and periportal sinusoidal fibrosis with or without necroinflammation, and Mallory bodies. Degree of necroinflammation and ballooning changes (score of 1–3) as well as fibrosis (1–4) have been graded by a system developed by Brunt and colleagues [64]. Subsequently, a NASH clinical research network group proposed a scoring system called the NAFLD activity score, or NAS [68]. This scores the sum of steatosis (scale of 0–3), lobular inflammation (0–2), and ballooning of hepatocytes (0–2). A score greater than five is diagnostic of NASH, whereas a score less than three excludes NASH. The fibrosis stage ranges from 0–4, with 1 = perisinusoidal or periportal; 2 = perisinusoidal and periportal; 3 = bridging fibrosis; and 4 = cirrhosis. Although other features such as Mallory hyaline and megamitochondria are often seen in NASH, these features are associated with hepatocyte ballooning change, which is a component of the NAS system and therefore these features are not independent.

**Biliary diseases**

**Mechanical duct obstruction**

Mechanical obstruction of the bile duct is usually diagnosed without the need for liver biopsy. However, when other diagnostic modalities, such as ultrasound, endoscopic retrograde cholangiopancreatography (ERCP) are inconclusive, a liver biopsy may be necessary. The changes associated with biliary obstruction can be parenchymal and portal. Parenchymal cholestasis in the perivenular hepatocytes, is one of the earliest changes found in these patients, followed by canalicular dilation with bile plug formation. The hepatocytes become hydropic with a reticular rarefaction of the cytoplasm termed “feathery degeneration.” The portal tracts reveal edema with loose fibrous tissue around dilated bile ducts. Portal inflammatory reaction includes polymorphonuclear leukocytes (PMNs) and mononuclear cells. PMN infiltration around the bile duct, and within the duct lumen, strongly suggests mechanical duct obstruction (Figure 154.8). Prolonged biliary obstruction results in cholangiolar proliferation as well as periductal fibrosis (Figures 154.13 and 154.15). Long-standing obstruction can lead to disappearance of the ducts resulting in an appearance resembling PBC. During the acute stage, drug-induced cholangitic and cholestatic reaction, acute viral hepatitis of cholestatic type, impaired regeneration syndrome, changes due to parenteral hyperalimentation, and septic shock should be considered in the differential diagnosis. Biliary fibrosis and cirrhosis follow if there is continued duct obstruction (Figure 154.67).

**PBC and primary sclerosing cholangitis**

The accurate diagnosis of PBC based on a needle liver biopsy requires that an adequate number of portal tracts be visualized.
In addition to the classic destructive duct lesions with marked lymphoplasmacytic infiltrates, the presence of granulomas, absence of ducts in small portal tracts, hydropic changes of perportal hepatocytes containing Mallory hyaline and copper-binding protein (Shikata-positive granules), as well as perportal cholestasis are all helpful morphological features in diagnosing PBC [69]. A staging system of 1–4 has been used by some; briefly, the histological hallmarks of each of these stages are as follows:

- **Stage 1:** destructive changes of interlobular bile ducts with or without granulomas
- **Stage 2:** proliferation of atypical ductules mostly along the periportal areas
- **Stage 3:** absence of interlobular bile ducts in most of the portal tracts and portal-to-portal bridging fibrosis
- **Stage 4:** cirrhosis.

In many patients, the biopsies demonstrate changes overlapping between different stages [70].

Diagnosis of primary sclerosing cholangitis (PSC) is much more difficult in needle biopsies of liver. A wide range of pathological changes from minimal portal fibrosis and inflammatory reaction, to changes of biliary obstruction secondary, to extrahepatic sclerosing cholangitis, and to typical marked concentric periductal fibrosis with chronic inflammation can be seen [71] (Figure 154.16). Radiological studies are necessary for definitive diagnosis.

**Drug-induced liver injury**

Liver biopsy interpretation should always consider the possibility of drug-induced changes in the differential diagnosis [72]. A thorough history of drug intake should be obtained prior to final morphological diagnosis [73]. Systematic evaluation of the liver biopsies from patients included in the drug induced liver injury (DILI) network [72] resulted in 18 predefined histologic patterns out of which five were most common: acute hepatitis, chronic hepatitis, acute cholestasis, chronic cholestasis and cholestatic hepatitis. This study also found limited correlation between the biochemical categorization and the pathological pattern of injury.

**Parenchymal changes**

Parenchymal changes resembling acute viral hepatitis are seen in both isoniazid- and methyldopa-induced hepatic damage (Figure 154.85). Changes resembling mononucleosis pattern are seen in liver disease induced by diphenylhydantoin, paraaminosalicylic acid, and, occasionally, sulfonamides (Figure 154.86). Higher degrees of necrosis are associated with more severe clinical outcomes [73]. Coagulative necrosis without much inflammatory reaction is seen in acetaminophen- and halothane-induced damage (Figures 154.29 and 154.30). The necrosis is typically in perivenular and mid-zonal locations. Periportal coagulative necrosis is seen in ferrous sulfate poisoning. Fatty change of a microvesicular type is caused by tetracycline and valproic acid. This is accentuated in zone 3, resembling alcoholic FFC. Macrovesicular fatty change is most commonly seen with corticosteroid and methotrexate use. Carbon tetrachloride and tritetrachlorethylene toxicity results in fatty change as well as liver cell necrosis without inflammatory changes. Hepatocyte necrosis with Mallory body formation can be seen with amiodarone, perhexilene maleate, and with synthetic estrogen preparations used for prostatic carcinoma. Parenchymal cholestasis in zone 3 without inflammation or necrosis can be seen with the use of anabolic steroids and with oral contraceptives. Cholestasis with mild hepatocellular necrosis is associated with total parenteral hyperalimentation, antibiotics such as erythromycin, penicillin, sulfonamides, nitrofurantoin, oral hypoglycemic agents, some tranquilizers such as chlorpromazine (Figure 154.48), antihypertensive agents, captopril, gold therapy, and some antineoplastic agents. Drugs, such as sulfonamides, cause granulomatous necrosis in

![Figure 154.85](Image)

Hepatitis-like activity resembling acute viral hepatitis in Aldomet-induced hepatotoxicity. (H & E stain; original magnification \( \times 200 \).)

![Figure 154.86](Image)

Dilantin-induced hepatic changes resembling mononucleosis. (H & E stain; original magnification \( \times 100 \).)
addition to cholestasis. Rare cases of allopurinol-induced submassive hepatic necrosis have been reported. Morphological patterns of CAH can result from hepatotoxicity from nitrofurantoin, oxyphenisatin, dantrolene, papaverine, and, occasionally, isoniazid. A number of drugs can elicit granulomatous reactions in the liver. Sulfonamides cause granulomas resembling sarcoidosis, either portal or parenchymal. Allopurinol, Dilantin, quinidine, nitrofurantoin, and, rarely, isoniazid can cause a granulomatous reaction, consisting of punched-out areas of hepatocytolysis replaced by hyperplastic Kupffer cells, lymphocytes, and other inflammatory cells in a circumscribed fashion resembling a granuloma. Among the drugs causing hepatocyte inclusions, a ground-glass appearance can be caused by cyanamide, and proliferation of smooth endoplasmic reticulin (SER), resulting in a similar appearance, by phenobarbital, chlorpromazine, and Dilantin [74].

**Portal tract changes**
Oral hypoglycemic agents and tranquilizers mentioned previously, as well as allopurinol, can cause variable degrees of portal inflammation and bile duct epithelial abnormalities, resembling mechanical duct obstruction or PBC. Dilantin toxicity results in a mononucleosis pattern along with a portal inflammatory reaction with a predominance of eosinophils (Figure 154.9). Allopurinol causes portal eosinophilia with a cholangitic reaction.

**Vascular changes**
Vascular changes include sinusoidal dilation following administration of oral contraceptive agents or anabolic steroids, and azathioprine therapy, and peliosis hepatitis seen in anabolic steroid and methyl testosterone treatment (Figure 154.87). Venous outflow occlusion with its hepatic morphological changes can be seen as follows: perivenular sclerosis with sinusoidal collagenosis resembling alcohol is associated with hypervitaminosis A, methotrexate (Figure 154.88), azathioprine, and some antineoplastic drugs, such as mitomycin C. Venoocclusive disease with coagulative necrosis and severe congestion in zone 3 is seen in toxicity due to bush tea containing pyrrolizidine alkaloids, as well as toxicity resulting from 6-thioguanine and azathioprine. Hepatic vein thrombosis leading to Budd–Chiari syndrome has been associated with prolonged use of oral contraceptives (Figure 154.25).

**Liver biopsy changes in systemic diseases**

**Hematopoietic system**
Lymphomas with hepatic involvement reveal monomorphic portal infiltrates of neoplastic lymphocytes (Figure 154.89). Bile ducts and parenchymal cells are not involved. However, in Hodgkin disease, the portal infiltrate, including atypical or typical Reed–Sternberg cells, seems to produce destructive lesions of bile ducts (Figure 154.90). In addition, epithelioid granulomas of a nonneoplastic nature are seen in both portal and lobular zones. Cholestasis can also be a prominent feature.
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Patients typically results in numerous clusters of bloated Kupffer cells, appearing foamy and containing numerous acid-fast stainable organisms (Figure 154.63). No true granulomas are seen. Similarly, fungal infections such as cryptococcosis reveal a lack of granuloma formation in the presence of organisms identified by special stains and cultures. Viral inclusion bodies of CMV and herpes simplex involving either the reticuloendothelial cells or duct epithelium cells, or parenchymal cells can be seen. Cryptosporidiosis involving the biliary system can be identified by examining the luminal surface of the duct epithelial cells using special stain such as Giemsa (Figure 154.92). Sclerosing cholangitis identified in patients with AIDS has been described as a sequela of CMV and cryptosporidiosis of the biliary system [76]. In patients with Kaposi sarcoma elsewhere in the body, liver biopsy can also exhibit the presence of the tumor [77] (Figure 154.93). Because these patients are on a number of

**Figure 154.90** Portal infiltrate in Hodgkin lymphoma with an atypical Reed–Sternberg cell. (H & E stain; original magnification × 200.)

**Figure 154.91** Portal area with lymphopenia in a patient with AIDS. (H & E stain; original magnification × 200.)

**Figure 154.92** Bile duct epithelium along the luminal surface demonstrates the presence of cryptosporidiosis, which are 3–4 μm size. (H & E stain; original magnification × 400.)

**Figure 154.93** Kaposi sarcoma involving the liver. (H & E stain; original magnification × 100.)
drugs on a long-term basis, hepatotoxic changes due to the drugs should also be considered in the differential diagnosis.

Pathology of transplantation

Allograft rejection
Following transplantation, acute rejection is seen in up to 70% of allografts. The histological characteristics and grading of acute liver allograft rejection have been defined by the International group [78]. The histological features include portal inflammatory infiltration, inflammation and destructive changes of interlobular bile ducts, and endothelialitis involving hepatic and portal venous structures (Figure 154.94). Portal inflammation consists of activated lymphocytes or “immunoblasts,” neutrophils, and eosinophils. These cells infiltrate the epithelial cells of interlobular bile ducts. In addition, the duct epithelium exhibits pyknosis of the nuclei, hydropic changes, and disruption of basement membrane. Endothelialitis is manifest as lymphocytes attached to the venous endothelium and infiltrating through the subendothelium. The hallmark of chronic rejection consists of progressive destruction and eventual loss of bile ducts [79] (Figure 154.95). In addition, there is perivenular cholestasis and multifocal hepatocytolysis. There is also evidence of obliterative vascular lesions involving hepatic arteries and arterioles. Chronic rejection is much less common than acute rejection and occurs in about 4% of graft recipients.

Harvest or preservation injury
In the majority (54%) of orthotopic hepatic grafts, marked ballooning of hepatocytes is present in acinar zone 3 (Figure 154.96). This usually occurs in the first 2 weeks and in some patients as early as 48 hours. This feature is often associated with cholestasis and high serum alanine aminotransferase (ALT) levels. Ischemia is considered one pathogenetic factor. Ballooning without associated necrosis has a better prognosis and is not a sign of graft rejection. Microvesicular fatty change and mild acidophilic degeneration of the hepatocytes are manifestations of preservation injury.

Cytomegalovirus hepatitis
Cytomegalovirus hepatitis in allografts is often associated with parenchymal microabscesses, seen as small aggregates of neutrophils in the hepatic lobule. Infected cells have large eosinophilic intranuclear inclusions. Immunoperoxidase stains demonstrate these inclusions clearly.
Recurrent hepatitis B in allograft
Liver allograft recipients who had chronic hepatitis B with cirrhosis invariably develop recurrence of hepatitis B infection of the graft. Recurrence usually develops more than 3 months posttransplant but can occur earlier in association with an accelerated course. Recurrent HBV infection is similar to that seen in nonliver-graft patients. The acute process consists of lobular disarray and ballooning hepatocytes with necroinflammatory changes (Figure 154.97). Portal areas reveal inflammatory hyperplasia without any evidence of bile duct epithelial changes or vascular endothelial damage. At this early stage, HBcAg in the hepatocytes is demonstrable by immunoperoxidase stains. Although the acute events can be self-limited, viral infection is never cleared and invariably leads to chronic infection, with progressive increase in the expression of viral antigens in the liver. A unique variant of recurrent hepatitis in the allograft is termed “fibrosing cholestatic hepatitis” [80]. The characteristic pathological changes include peripoal fibrosis with thin strands of pericellular collagen, cholestasis, and ballooning of hepatocytes with apoptotic necrosis. Abundant HBsAg and HBCAg is demonstrable in hepatocytes. Lymphocytic infiltrates are minimal. This morphology has been associated with a poor outcome. Chronic hepatitis and cirrhosis are the eventual outcomes.

Recurrent hepatitis C
Reinfection of allografts is universal but the disease progression varies widely. Acute changes can be seen as early as 80–90 days posttransplant. They include sinusoidal lymphocytosis, acidophilic bodies, and lobular disarray. Portal lymphoid aggregates, progressive fibrosis, and changes similar to chronic HCV in the nontransplant setting are seen in later stages. A small percentage (2%–10%) of patients with recurrent HCV develops severe fibrosing cholestatic hepatitis similar to that seen in recurrent HBV [81].

Recurrent AIH, PBC and PSC
Recurrent AIH with perivenular inflammation and necrosis with plasma cell infiltrate can be indistinguishable from acute rejection. Recently, Fiel et al. [82] have described de novo AIH as a variant of rejection seen in patients with hepatitis C infection with poor outcome. Recurrence of PBC and PSC has been reported with histological features similar to those seen in native livers.

References are available at www.yamadagastro.com/textbook

Further reading
CHAPTER 155

Endoscopic mucosal biopsy – histopathological interpretation

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General principles of gastrointestinal biopsy interpretation

The key principle of gastrointestinal (GI) biopsy interpretation is that the GI tract has a limited repertoire of responses to a host of injuries, and diagnosing the type of injury in any given biopsy often requires correlation with clinical details. When dealing with mucosal biopsies of the GI tract, it should also be noted that they only display the mucosa (and possibly a small amount of submucosa), a feature that is obvious but sometimes forgotten by endoscopists and pathologists alike. Of course, mucosal biopsies should not include muscularis propria. When they do, it is a good practice for the pathologist to contact the endoscopist and discuss the possibility of endoscopic perforation. A discussion of every entity that can be encountered on mucosal biopsies is beyond the scope of this chapter, but those most commonly encountered and certain classical entities are described. (For discussion of the clinical features of the disorders and lesions described below, the reader should refer to the relevant chapter in this textbook.)

Overview comments on the GI tract

The innermost layer of the GI tract is the mucosa, consisting of three components:
1. Epithelium (protective, secretory, or absorptive properties).
2. Lamina propria. This is a loose connective tissue zone supporting the avascular epithelium. In the esophagus, stomach, and small bowel, it is rich in lymphatics whereas it is less so in the lower tract. This is of clinical significance in evaluating carcinomas as they can attain lymphatic access with minimal invasion in the upper tract but not in the colon. In the stomach and esophagus, there are few immune cells (lymphoid and plasma cells) in the lamina propria whereas in the small bowel and colon, lamina propria lymphocytes and plasma cells are more abundant. Neutrophils are abnormal in either the lamina propria or the epithelium. Eosinophils are a normal lamina propria constituent but mucosal biopsies from all sites must be assessed for prominence in the normal inflammatory components.
Muscularis mucosae. This is a slender double layer of smooth muscle separating the mucosa from the submucosa. It has an inner circular and outer longitudinal arrangement and in this respect can be regarded as a miniaturized muscularis propria.

The submucosa is composed of connective tissue and houses Meissner’s nerve plexus as well as large caliber vessels. The muscularis propria is the main wall of the GI tract and is composed of an inner circular and outer longitudinal layer of smooth muscle. Between these layers is Auerbach’s nerve plexus. The outermost component is either adventitia or serosa. The former lacks a mesothelial membrane lining.

Parasympathetic ganglion cells are found in the nerve plexi (both Meissner’s and Auerbach’s) but the submucosal Meissner’s plexi contain neuronal cell bodies of the intrinsic sympathetic nerve system that function on the local area of the gut. These are the neurons that have chemoreceptors and mechanoreceptors. They synapse on both other ganglion cells and muscle or secretory cells.

In assessing any biopsy from the GI tract, the pathologist should note the gender, age, and race/ethnicity (if known) of the patient and the site of the biopsy. These pieces of information are all useful in directing interpretation and the endoscopist should provide them as well as a brief synopsis of the indications for the biopsies and the clinical concerns. Examples of the utility of mentioning simple demographics include celiac disease, found in about 1% of all Americans, and infrequently detected in Southeast Asians. Collagenous colitis is typically a disease of older women as is autoimmune gastritis. Assessments of all biopsies from infants should include a systematic review of each compartment of the tissue. For example, the epithelial surface is reviewed with an eye towards malabsorptive diseases (such as microvillus inclusion disease in the small intestine), the lamina propria is scanned for the presence of plasma cells (their absence suggests common variable immunodeficiency) and the muscularis mucosae is assessed for eosinophils (which should be absent).

The type of mucosa in the biopsy is compared to the recorded biopsy site to address metaplasias (or “switched” specimens) and the normal architectural structures are noted, such as villous contours of the small intestine. Before making a diagnosis, the features are compared to the history to assure that the interpretation “makes sense” in light of the clinical information. If the information is scant but required or inconsistent with the microscopic findings, this too must be addressed.

With a consistent approach, the pathologist interpreting gastrointestinal biopsies can provide important information that can occasionally be life-saving (in certain instances of ischemic disease) and can often be reassuring to the ever-increasing group of patients undergoing GI tract mucosal biopsies. The gastroenterologist who remembers that diseases have many overlapping histologic features will be better served by supplying clinical details to increase the possibility of the most accurate interpretation.

**Sampling**

The most important sampling issues concern sampling error and knowing where to biopsy. Whenever feasible, jumbo forceps provide better information than smaller ones. There are certain general principles that apply to many settings. For example, when sampling an ulcer with a clinical concern of cytomegalovirus (CMV) infection, it is prudent to sample areas expected to harbor granulation tissue since the CMV viral cytopathic effect is usually found in endothelial cells. In contrast, if herpes simplex viral cytopathic effect is sought, intact epithelium must be present on the slides for review. Consequently both types of tissue should be sampled when assessing for viral lesions in erosions or ulcers in immunosuppressed patients. Similarly, in attempting to establish a cancer diagnosis in an ulcerated zone, always take more rather than fewer biopsies, as sampling error is often a factor. When obtaining biopsies to address the possibility of microscopic colitis, remember that it is best seen in the right and transverse colon; a negative rectal biopsy does not exclude “microscopic” colitis. Lastly, remember that gastric polyps (other than fundic gland polyps) seldom occur in isolation, but rather in the context of gastric pathology in the surrounding flat mucosa, so it is a good idea to sample this when one samples a polyp in the stomach, especially if the polyp is in the antrum [1,2]. Of course, this contrasts with the colon, where polyps are usually isolated findings; sampling the background flat mucosa is only necessary in the setting of inflammatory bowel disease.

**Esophagus**

**Nonneoplastic and benign polyps**

**Inlet patch (cervical gastric heterotopia)**

Inlet patches are believed to be embryologic vestiges from early gestation when the esophagus is lined by columnar epithelium. They are found in about 1% of patients undergoing upper endoscopy assessed retrospectively through biopsy records, but incidences of up to 10% are recorded [3,4]. They are found in the cervical esophagus and are usually asymptomatic. However, there are occasional complications – local injury (webs, strictures, ulcers, fistulas) can result in symptoms (pain and dysphagia). Rarely, carcinomas complicate inlet patches.

Inlet patches may be small 0.2–0.3 cm up to about 4 cm. They typically consist of oxyntic gastric-type mucosa (containing parietal cells) but a transitional or cardiac pattern (lacking oxyntic glands and negative for gastrin on immunohistochemistry) may also be found. Lesions are often inflamed and may occasionally harbor *Helicobacter pylori*. Intestinal metaplasia in inlet patches is occasionally found. Some studies have explored a link between inlet patches and Barrett esophagus and indeed these conditions are found together more than coincidence would suggest. Of course some studies are difficult to interpret since criteria for Barrett esophagus have changed with...
the recent requirement for intestinal metaplasia to diagnose lesions as Barrett esophagus (see section further on Barrett esophagus). Pancreatic tissue may also be a component of “inlet patch”.

**Glycogenic acanthosis**

Glycogenic acanthosis of the esophagus is a common benign entity [5–19], found in up to 15% of esophagi (but probably overall in closer to 3% of cases [19], characterized by single or multiple plaques of hyperplastic squamous epithelium with abundant intracellular glycogen deposits. Lesions appear as slightly raised grey-white plaques which are usually 2–10 mm in diameter and may be confluent. They cause a finely nodular or cobblestone mucosal pattern demonstrable on double-contrast views of the well-distended esophagus. The findings are not associated with mucosal ulcerations, luminal narrowing, or mobility disturbance, although some patients may have coexistent hiatal hernia and gastroesophageal reflux. There is also an association of glycogenic acanthosis with Cowden’s disease. It does not appear to be linked with diabetes and it does not regress with acid suppression when associated with reflux disease. In one Japanese study, it was commonly found in adjacent nonneoplastic mucosa in patients with squamous cell carcinoma of the esophagus [12].

In general, it is essentially an incidental finding. The endoscopist notes a white plaque and a biopsy displays prominent intraepithelial glycogen extending to within one cell layer of the basement membrane with just a single row (or two) of basal cells between the glycogenized squamous cells and the basement membrane. For the endoscopist, the differential diagnosis is with *Candida esophagitis* whereas pathologists often do not notice glycogenic acanthosis. However, probably the most important reason for the pathologist to diagnose patients with glycogenic acanthosis is to provide the endoscopist with an explanation for the abnormal gross appearance of the biopsied lesion.

**Findings in mechanical/anatomic disorders**

Typically, biopsies from webs, rings, and from the squamous mucosa in patients with achalasia display normal squamous mucosa unless the condition has resulted in long-term reflux. There may be parakeratosis, a response to the process of food passing over the protuberant ring or the constricted segment, or erosions may appear where retained food pressures on the static segment proximal to the attenuated lumen.

**Reflux disease**

Gastroesophageal reflux disease (GERD) is among the most common of gastrointestinal track disorders and many patients undergo endoscopic biopsies in the course of evaluation for reflux symptoms. Findings in these can range anywhere from “classic” reflux changes (basal cell hyperplasia, elongation of vascular papillae, and intraepithelial eosinophils), to ulcers, intraepithelial lymphocytosis (which correlates poorly with pH studies), or “balloon” cells, which appear distended and have pale abundant pink cytoplasm.

Reflux esophagitis is an example of an “-itis” that often lacks a prominent component of inflammation. The pathology reflects injury to the squamous epithelium, followed by attempts of the epithelium to regenerate (Figure 155.1). Mild features of cellular injury include balloon cells (squamous cells with ballooned cytoplasm from accumulation of plasma proteins) and vascular lakes (dilated small blood vessels in the mucosa, not areas of hemorrhage, which often are seen endoscopically as erythema, or redness). Severe injury can result in mucosal sloughing with erosions or ulcers. Regenerative changes include hyperplasia of the basal zone to >15% to 20% of the epithelial thickness. The upper limit of the basal cell layer can be defined as the level above which the nuclei are separated by a distance greater than the nuclear diameter [20]. There is elongation of the vascular papillae to greater than two thirds of the epithelial thickness. Inflammation is typically mild and includes scattered eosinophils. Less commonly, scattered neutrophils are present and can be more prominent in cases with more severe injury, including erosions and ulcers. Parakeratosis can be a component as well (but foci of parakeratosis should still be screened for fungal organisms). Fairly reproducible criteria that have been established by Fiocca and colleagues [20] as abnormal and associated with clinical reflux include:

- thickened basal layer (>15% or 5–6 layers)
- increased papillary length (>50% of the squamous thickness)
- intraepithelial eosinophils, neutrophils (>1–2 cells/40 × field)
- intraepithelial mononuclear cells (>10/40 × field)
- dilated/widened intercellular spaces (which may appear as “bubbles” or “ladders”).

It is important to keep in mind that the severity and extent of the histologic changes seen on a biopsy does not necessarily correlate well with the severity of the patient’s symptoms (heartburn or pyrosis).
Severe complications of GERD are unusual. Complications include development of an ulcer, bleeding from an ulcer, and a stricture formation resulting from scarring, due to deep injury. The complication of Barrett esophagus occurs in approximately 10% of patients with symptomatic reflux.

**Injury due to chemical or physical agents**

There are a few agents resulting in injury that leave a “footprint” that can be recognized on biopsies although often there is no microscopic clue.

**Iron**

In our patient population, in which inpatients are well-represented, mucosal iron (ferrous sulfate) is found in about 1% of patients undergoing upper tract endoscopic biopsies. Iron is well-recognized for its capacity to cause corrosive injury in the esophagus. While it can be argued that such a phenomenon is a result of a prior injury in which an iron tablet becomes embedded, the corrosive and toxic nature of iron itself suggests that the iron pill has caused the injury. Abraham and colleagues [21] studied the clinical and histologic features of 36 upper GI tract biopsies from 33 patients (24 gastric, 9 esophageal, 1 gastro-esophageal junction, and 2 duodenal) containing characteristic brown crystalline iron material, and evaluated the amount and tissue distribution of the iron. The biopsies typically displayed luminal crystalline iron adjacent to the surface epithelium or admixed with luminal fibrinoinflammatory exudates (Figure 155.2). Most biopsies (83%) showed crystalline iron deposition in the lamina propria, either covered by an intact epithelium, subjacent to small superficial erosions, or admixed with granulation tissue. Three biopsies (8%) demonstrated iron-containing thrombi in mucosal blood vessels. Erosive or ulcerative mucosal injury was present in the majority of biopsies (83%). The amount of iron accumulation in cases with mucosal injury was greater than in cases without mucosal injury. Iron medication (usually ferrous sulfate) was confirmed in 25 of 33 patients (76%). However, as an argument for iron causing injury as a secondary event, half of the patients (17 of 33, 51%) also had underlying infectious, mechanical, toxic, or systemic medical conditions that could have initiated or exacerbated tissue injury.

**Kayexalate**

The use of Kayexalate (sodium polystyrene sulfonate) for the management of hyperkalemia was approved for use in the United States in 1975. It is a cation-exchange resin that can be instilled into the lower GI tract as an enema preparation, or into the upper GI tract either orally or by nasogastric tube. When administered orally, or by nasogastric tube, sodium cations are first released from the resin and exchanged for hydrogen ions in the acidic milieu of the stomach. As the resin passes through the intestines, hydrogen is exchanged for potassium, which is then eliminated in the feces along with the remainder of the altered resin, thereby lowering the serum potassium concentration.

In the early use of Kayexalate, the resin was administered as a suspension in water. Although generally well tolerated, some patients were reported to develop gastric and bowel opacifications as a result of concretions of resin. It therefore became increasingly popular to administer Kayexalate in a suspension with hypertonic sorbitol, which reduces the frequency of bezoar formation and colonic impaction by promoting an osmotic diarrhea. Subsequently Lillemoe and colleagues reported five uremic patients who developed colonic necrosis temporally associated with the use of Kayexalate in sorbitol that contributed to death in four of the five patients [22]. That study also provided experimental (murine) evidence implicating sorbitol as the agent responsible for colonic necrosis.

It has become apparent that Kayexalate can be associated with severe mucosal injury in the upper GI tract as well [23]. In most instances, the medication is easy to recognize in endoscopic biopsies (Figure 155.3). Kayexalate crystals are lightly basophilic on hematoxylin and eosin (H & E) stain, red on PAS/Alcian blue and acid-fast stains, and blue on Diff-Quik staining. Crystals display a characteristic crystalline mosaic pattern resembling fish scales. It is this mosaic pattern that allows the distinction from between Kayexalate crystals and histologically similar cholestyramine crystals. Kayexalate crystals are refractile but not polarizable.

**Taxol/colchicine**

Taxol, an antineoplastic agent with a novel mechanism of action, can cause striking mitotic arrest (Figure 155.4) associated with epithelial necrosis and ulceration of the esophagus [24]. The mitotic arrest is associated with bundling of intermediate filaments secondary to accumulation of polymerized microtubules. Thus the histologic correlate is the presence of arrested mitoses with ring forms. With taxol, the findings tend to be striking in the esophagus, whereas, in colchicine toxicity, which has similar

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**Figure 155.2** Iron pill esophagitis. The brown material in the image is iron pigment. The associated squamous epithelium shows reparative features.
PART 5 Diagnostic and therapeutic modalities in gastroenterology

Abraham and colleagues reported 10 patients who experienced erosive/ulcerative esophagitis while ingesting alendronate [29]. Biopsies from all patients showed inflammatory exudates and inflamed granulation tissue as characteristic of any ulcer site. Polarizable crystalline foreign material was present in 6 of 10 biopsies (60%). Multinucleated giant cells, within the inflammatory exudates, were near the crystalline foreign material in 3 of 10 biopsies (30%). Adjacent squamous epithelium typically showed active inflammation and a reactive appearance with enlarged, hyperchromatic nuclei. Multinucleated squamous epithelial giant cells were present in 2 of 10 cases (20%). Micro-organisms were unusual; scattered fungi and/or viral inclusions were present in only 2 of 10 biopsies (20%). Although there is no specific histologic finding, it is worthwhile to be aware of this complication with such medicines and relay that concern appropriately to the clinician. There have been reports of esophageal mucosal injury in patients taking all of the bisphosphonates, but it is likely that many of the patients had additional risk factors. In a study that adjusted for the risk of esophagitis, esophageal ulcers, and esophageal perforations before and after initiation of the bisphosphonates, only alendronate, and etidronate were associated with an increased risk of esophageal damage [30].

The Food and Drug Administration (FDA) has also received reports of esophageal cancers developing in patients taking alendronate [31]. However, when this issue is studied with proper controls, there seems to be no causal association between bisphosphonate use and esophageal carcinomas [32–37]. Although biphosphonates are classically associated with esophageal injury, other medications can lodge in this area and induce similar damage. As with biphosphonates, pill fragments may be evident microscopically.

**Corrosive ingestion (e.g. lye, bleach)**

Like the esophageal injury associated with Fosamax, corrosive injury does not result in a specific pattern of injury (although saponification may accompany lye ingestion) and cannot be identified directly (like iron or Kayexalate). However, it can usually be correlated with an ingestion history in a pediatric or psychiatric patient. Endoscopically, severe ulceration is seen and endoscopists have described a strong bleach-like odor even when the patient has ingested lye. Microscopically, extensive necrosis is found. Those who survive are likely to have severe stricturing disease with all its complications. Such patients require lifetime follow-up based on their proclivity to develop squamous cell carcinoma [38].

**Graft versus host disease**

Biopsies from patients with graft versus host disease (GVHD) in the esophagus show intraepithelial lymphocytosis, basilar vacuolization, epithelial apoptosis (Figure 155.5), and necrosis in severe disease. Many patients manifest a characteristic endoscopic appearance [39–47], and a bullous presentation akin to
that of bullous pemphigoid is one of the possible presentations. Probably the most important goal in patients in whom GVHD is a clinical consideration is to exclude infectious etiologies since generally such patients are empirically treated with steroids.

**Dermatologic disease affecting the esophagus**

Dermatologic conditions that are well known to involve the esophagus include pemphigus vulgaris, mucous membrane bullous pemphigoid, epidermolysis bullosa, lichen sclerosis, lichen planus, and toxic epidermal necrolysis. Esophageal involvement by cutaneous diseases is not well recognized by pathologists or clinicians, resulting in delayed diagnosis and continued esophageal inflammation. In the case of lichen planus, for example, dysphagia and esophageal strictures are frequently initially attributed to reflux disease.

Lichen planus [48] is a subacute to chronic mucocutaneous disorder of unknown etiology. It can involve the skin, nails, and mucosal surfaces. Lichen planus of the skin affects both genders with equal frequency at any age, but most patients are middle-aged adults. Cutaneous lichen planus is characterized by eruptions of violaceous, scaling papules, and plaques. These plaques typically are intensely pruritic and most commonly localized to the extensor surfaces of the forearms and legs. Mucosal lichen planus may affect the perineum, oral mucosa, and pharynx. Unlike cutaneous disease, mucosal lichen planus predominantly affects middle-aged women. Oral involvement, in particular, coexists with skin lesions in approximately 30% to 50% of patients, but can be the only manifestation.

Esophageal lichen planus is a rarely described manifestation. It is an important diagnosis because of its tendency to cause persistent dysphagia resulting from esophagitis and stricture formation. Further trauma resulting from therapeutic dilation can lead to exacerbation of oral lichen planus in a Koebner-like phenomenon.

The pathologic features of esophageal lichen planus differ from those in skin. The epidermal reaction in cutaneous lichen planus typically includes hypergranulosis, hyperorthokeratosis, acanthosis, and “saw-tooth” elongation of the rete pegs. In contrast, the esophageal epithelium, which does not normally contain orthokeratin or a granular layer, frequently shows parakeratosis rather than orthohyperkeratosis and frequently lacks hypergranulosis. In addition, the epithelium may be atrophic. The histologic features, therefore, more closely resemble those of oral rather than cutaneous lichen planus. All sites of involvement reveal the typical band-like inflammatory infiltrate with a predominance of mature T cells and basal layer degeneration, including characteristic Civatte bodies (Figure 155.6).

Lymphocytic infiltration alone is not diagnostic of esophageal lichen planus. Medications (gold, thiazides, and antimalarials) can induce lichen planus-like lesions and must be excluded by clinical history and a lymphocytic esophagitis pattern is often a feature of esophageal Crohn’s disease. Patients with HIV or viral hepatitis can manifest a lichenoid esophagitis [49]. Although infectious agents are usually easily excluded on biopsy material, exclusion of esophagitis resulting from pill ingestion or caustic substances requires clinical correlation. In addition, lymphocytic infiltrates are occasionally prominent, although often focal, in patients with gastroesophageal reflux. Reflux can usually be excluded on the basis of other criteria such as the lack of clinical symptoms, the results of pH probe studies, and the failure of the inflammatory condition to respond to intensive antireflux therapy. Other histologic criteria for gastroesophageal reflux, including intraepithelial eosinophils, are also usually absent. Furthermore, the typically upper or mid-esophageal locations of the pathologic findings and stricture sites would be unusual in gastroesophageal reflux disease. However, it is difficult to positively diagnose lichen planus on histology; it can only be suggested and correlated with other features. Systemic treatment is usually required to
forestall stricturing disease whereas topical treatment is often sufficient for oral lesions.

**Bullous diseases**
The bullous diseases are similarly challenging to diagnose specifically in the esophagus and must also be correlated with clinical findings. When esophageal biopsies show bullae, in the absence of an infectious explanation, additional biopsies can be submitted fresh for immunofluorescence studies to arrive at a more specific diagnosis.

**Pemphigus vulgaris (PV),** the most common form of pemphigus, affects the sexes equally, most commonly during the fourth and fifth decades. Skin and the mucous membrane involvement are typical. Although any mucosal surface can be involved, oral lesions are the hallmark; these occur in almost every case and are the presenting sign in half of affected patients.

There are a few reports of esophageal involvement in PV, which was believed to be rare in early literature, but it is found in most patients if sought [50]. Because patients with esophageal involvement may be asymptomatic, such involvement has been under-recognized. Although esophageal involvement may be frequent in active mucocutaneous PV, its occurrence in the absence of other manifestations of the disease is rare [51].

Odynophagia and dysphagia are the usual symptoms of esophageal PV, as with other mucosal blistering diseases, including herpetic or esophageal candidiasis. Endoscopy is required for diagnosis; it allows evaluation of the appearance of the lesions and tissue sampling. Essentially normal esophageal mucosa may be seen on initial passage of the endoscope, followed by the appearance of erosions and sheets of sloughed mucosa on withdrawal of the instrument. Histopathologic findings of suprabasal clefting, cells with a “tombstone” appearance, and acantholysis are features of PV; immunofluorescence shows intercellular deposition of IgG and C3. Indirect immunofluorescence detects pemphigus antibodies in about 75% of cases; a negative result can occur if the disease is in remission, or in an early localized stage.

**Bullous pemphigoid (BP)** affects the esophagus more rarely than other skin diseases [52,53]. It is a chronic, autoimmune, subepidermal, blistering skin disease that rarely involves mucous membranes. It primarily affects elderly individuals in the fifth through seventh decades of life (average age at onset – 65 years). In France and Germany, the reported incidence is 6.6 cases per million people per year. In Europe, BP was identified as the most common subepidermal autoimmune blistering disease. The mucosa is affected in 10%–25% of patients.

Bullous pemphigoid is characterized by immunoglobulin G (IgG) autoantibodies specific for the hemidesmosomal BP antigens BP230 (BPAg1) and BP180 (BPAg2). IgG autoantibodies bind to the epithelial basement membrane and activate complement and inflammatory mediators. Eosinophils are characteristically found in bullae, although their presence is not an absolute diagnostic criterion. Serum levels of autoantibodies against BPAg2 correlate with disease activity in some studies.

**Esophagitis caused by infectious agents**
When an infectious etiology is suspected in erosive esophagitis, the endoscopist should biopsy the base of the erosion/ulcer to detect cytomegalovirus (CMV) (Figure 155.7) whereas the epithelium is more likely to demonstrate herpes simplex virus (HSV) (Figure 155.8). Greenson has demonstrated that a prominent mononuclear infiltrate adjacent to the infected epithelium often accompanies HSV esophagitis and is a clue to search for the organism [54], whereas macrophages tend to be present in a perivascular distribution in granulation tissue as a clue to search for CMV esophagitis [55]. In the case of HSV, the background infiltrate may suggest the need to perform immunohistochemistry for HSV as the organisms may not be apparent on routine H & E stains. Zones of parakeratosis, however small, are
worth study at high magnification to exclude Candida (Figure 155.9). Pseudohyphal forms must be sought since budding yeast alone might be a reflection of oral contamination, or colonization. Bacterial esophagitis is poorly understood. Walsh and colleagues [56] proposed a definition of “histopathologically demonstrable bacterial invasion of esophageal mucosa or deeper layers with no concomitant fungal, viral, or neoplastic involvement or previous surgery of the esophagus.” Bacterial esophagitis should be considered in immunocompromised patients presenting with odynophagia and may not be accompanied by an inflammatory response, but simply by numerous bacterial forms seen “embedded” in the squamous mucosa. Apparently bacterial esophagitis can be a source of occult sepsis [57].

**Allergic/eosinophilic esophagitis**

Overall, eosinophilic esophagogastritis is an uncommon benign inflammatory condition characterized by eosinophilic infiltration of GI tract. The diagnostic criteria include gastrointestinal symptoms; eosinophilic infiltration of the GI tract usually with intraepithelial eosinophils; and no evidence of parasitic infestation. Many patients (in addition to their GI involvement) also have a history of allergy, asthma, drug sensitivities, peripheral eosinophilia and increased IgE levels. Although food intolerance has been postulated as an etiologic factor, most cases lack a specific allergen and are attributed to multiple allergens. Eosinophilic esophagogastritis predominantly affects patients in the third to sixth decades. However, 15%–20% of cases are seen in the pediatric age group and, in some cases, milk allergy may be demonstrated.

Any part of GI tract from the esophagus (Figure 155.10) to the rectum can be involved—the stomach and small bowel are commonly involved. Eosinophilic esophagogastritis can show preferential involvement of the mucosa, muscularis propria, or serosa. Symptoms depend on the site and extent of eosinophilic infiltration. Mucosal disease can present as diarrhea, malabsorption, and protein losing enteropathy. Submucosal disease presents as obstruction and abdominal pain, and patients can develop eosinophilic ascites with serosal involvement. Rarely patients can present with an acute abdominal emergency necessitating emergency laparotomy.

Patients with eosinophilic esophagitis (limited to esophagus) present with dysphagia and strictures. The differential diagnosis is with reflux esophagitis. However, unlike in reflux esophagitis, the upper and mid esophagus are commonly affected with relative distal sparing. In striking cases, the esophagus can display “rings” on endoscopy, an appearance termed “feline esophagus” since this appearance resembles that seen in cats [58–60].

On histologic examination, superficial epithelial clusters of eosinophils that slough into the lumen are more common in eosinophilic esophagitis and there may be infiltration present deep in the esophageal wall and not just limited to mucosa in eosinophilic esophagitis. The eosinophilic infiltrate can be patchy and multiple, localized or diffuse. In 10% of cases, mucosal biopsies can be nondiagnostic due to the patchy nature of the disease or mucosal sparing. In daily practice, there are cases in which a distinction between allergic/eosinophilic esophagitis and reflux esophagitis cannot be made on histologic grounds and the diagnosis requires correlation with pH monitoring studies, or with other stigmata of allergic disease. A threshold of 15 eosinophils per high-power field (HPF) is suggested for diagnosis [61]. The distinction between reflux and eosinophilic esophagitis can have significant management implications as patients with eosinophilic esophagogastritis may respond to steroids while use of these agents in patients with GERD would be inappropriate.

**Crohn’s disease affecting the esophagus**

Reports on the prevalence of esophageal Crohn’s disease vary widely in both adults and children. Decker and colleagues [62]
reported that only 20 of 9900 (0.2%) adults with Crohn's disease seen over a period of 22 years had esophageal involvement. A higher prevalence was reported by D’Haens (11%) [63]. Both studies were retrospective and used only macroscopic endoscopic evidence that likely resulted in an underestimation of the prevalence. In contrast, a prospective study of esophageal Crohn's disease in adults yielded a prevalence of 5.1% [64]. There have been few pediatric studies. In one prospective study, endoscopy identified in esophageal Crohn's disease 2 of 40 (5%) children with Crohn's disease, and a total of 17 of 40 (42.5%) had histologic evidence of esophageal Crohn's disease [65]. In a large cohort of 210 children with Crohn's disease the lowest estimate of prevalence for endoscopic esophageal Crohn's disease was 7.6% and the highest estimate was 17.6% when including histology findings as diagnostic criteria [66]. These findings suggest that the prevalence of esophageal Crohn's disease in adults and children may be similar and is at least 5%. There is wide variability in the clinical manifestations of esophageal Crohn's disease and many patients do not have specific esophageal symptoms. Isolated esophageal Crohn's disease is uncommon.

Esophageal Crohn's disease is usually associated with advanced ileocolonic disease but upper GI tract symptoms do not always correlate well with endoscopic and biopsy findings. Cameron [66] reported upper GI symptoms were present in only 15% of children with Crohn's disease but found that 42% had endoscopic lesions. Alcantara found that 17% of 41 adults had upper GI symptoms but only 5% had endoscopic esophageal Crohn's disease [64]. In the pediatric age group, there is often an overlap of symptoms (such as nausea, anorexia, and abdominal pain) between esophageal and small bowel Crohn's disease. It is therefore difficult to identify an upper gastrointestinal site of disease based on clinical evaluation alone. Thus upper endoscopy and biopsies are important in the evaluation of pediatric inflammatory bowel disease, even in the asymptomatic child.

The presence of histologic abnormalities in radiologically and endoscopically normal mucosa is not unusual. Hence, endoscopy with biopsy is generally considered the gold standard for diagnosis of early asymptomatic lesions. The spectrum of esophageal injury in Crohn's disease varies from mild esophagitis with small erosions to transmural involvement with perforation and fistulization to adjacent organs. In addition to aphthous ulcers, other findings in esophageal Crohn's disease are erythema, ulceration, erythematous nodules, and polypoid lesions. Pseudomembrane formations, progressive esophageal narrowing resulting in strictures and formations of multiple mucosal bridges, have been described in advanced stages.

Epithelioid granulomatas in the correct clinical setting are considered diagnostic for Crohn's disease (Figure 155.11). Focal infiltration with mononuclear cells and histiocytes into the lamina propria that extends to the muscular layer is in keeping with Crohn's esophagitis. Unfortunately, nonspecific upper tract lesions can also be found in pediatric patients with classic ulcerative colitis [67].

**Polyps**

**Fibrovascular polyp of the esophagus**

Giant fibrovascular polyps (GFVP) are rare, benign pedunculated intraluminal masses that originate in the esophageal submucosa, usually in the area of the cervical esophagus. These lesions are characterized by their tendency to attain enormous sizes (up to 25 cm) and their ability to cause peculiar clinical symptoms. Although the main presenting complaint is dysphagia (87%), some patients report odynophagia, substernal chest pain, epigastric pain, intermittent regurgitation of undigested food, and weight loss. Respiratory complaints may also occur including cough, choking, wheezing, or inspiratory stridor. A giveaway piece of information to those familiar with the entity is when patients report a history of regurgitation of a fleshy mass into the pharynx or mouth and subsequently swallowing it [68]. Endoscopic biopsies do not play a major role in diagnosis and, in fact, may lead to misdiagnosis when the pathologist is unaware of the radiologic and clinical findings [69]. Imaging is key in the diagnostic work-up of these patients with barium studies revealing a sausage-shaped intraluminal mass with smooth or lobulated contours and bulbous distal tips. Barium is seen surrounding the lesions, indicative of intraluminal location. On CT, the appearance is heterogeneous with varying proportions of soft tissue and fat density [68]. Histologic exam reveals polypoid masses covered by unremarkable squamous epithelium composed of varying amount of fibrovascular and adipose tissue. A rare case of rhabdomyomatous well-differentiated liposarcoma has been described in association with this entity [70]. An atypical lipomatous tumor/well differentiated liposarcoma supported by positive immunohistochemical staining with MDM2 (amplified gene on chromosome
12q15 in cases of liposarcomas and atypical lipomatous tumors) and p53 has also been reported [71]. Such tumors have been variably regarded as liposarcomas in the past and most have behaved indolently, presumably because they came to medical attention when relatively small. As such, we are unaware of reports of dedifferentiation in such neoplasms. Removal is necessary due to potentially life-threatening complications related to airway obstruction as a result of polyp regurgitation [72,73]. Esophagotomy is typically required for excision although a few cases have been removed endoscopically [74,75]. Recurrences have been reported [76].

Squamous papillomas
These are uncommon lesions usually found incidentally at endoscopy [77,78].

Squamous papillomas are seen as tiny polyps at endoscopy. On histologic evaluation, they consist of bland polypoid squamous mucosa with fibrovascular cores (Figure 155.12). Exceptional cases display viral cytopathic effects. Several studies have evaluated the presence of HPV in these lesions by both immunohistochemistry and in situ hybridization [77–80]. They are negative in most cases and the possibility of PCR contamination would seem likely in one of the studies [80]. However, a subset of patients with HPV-associated laryngeal papillomatosis has HPV-related squamous papillomas of the esophagus and occasional esophageal examples have been reported unassociated with laryngeal lesions.

Squamous papillomas of the esophagus do not appear to “degenerate” into esophageal malignancies, and no dysplasia is seen histologically. Evidence of recurrence is unusual, but synchronous or metachronous carcinomas of the ororespiratory tract have been described. Many reports suggest a role for mucosal injury and regeneration in the pathogenesis of these lesions. The association with other malignancies may be significant but, in our material, these have been “incidental” lesions.

Barrett esophagus
Barrett esophagus (BE) is a change of the esophageal mucosa of any length that is visible at endoscopy, and contains intestinal metaplasia on biopsy [81]. While in the USA intestinal metaplasia is still (as of 2011) required for a diagnosis of BE, the American Gastroenterological Association (AGA) has defined BE as follows: “the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal esophagus” [82]. This acknowledges the view of British (and Japanese) colleagues that either cardia or intestinal-type epithelium supports the diagnosis of BE [83], but the AGA has opted to retain the requirement for intestinal metaplasia in the USA as of 2011 [82]. Because of their increased risk of malignancy, patients are subjected to periodic surveillance esophagogastroduodenoscopies with biopsies to identify patients with dysplasia, who are at an even higher risk of developing carcinoma.

Histologic requirement for intestinal metaplasia ensures that patients with hiatal hernias are not placed in the same risk category as those more likely to progress to adenocarcinoma. However, it is well known that intestinal metaplasia can often be found at the gastroesophageal (GE) junction when no endoscopic lesion is apparent. This was first systematically studied by Spechler and colleagues, who found that among 142 patients without endoscopically apparent Barrett esophagus, 26 (18%) had intestinal metaplasia [84]. All these patients were white, and the male-to-female ratio was 1.9. In contrast, non-whites accounted for 14% of the 114 patients without intestinal metaplasia and the male-to-female ratio was 0.8. The groups did not differ significantly in the frequency of symptoms or endoscopic signs of GE reflux. From these data, Spechler and colleagues concluded that adults frequently had unrecognized segments of specialized columnar mucosa (displaying intestinal metaplasia) at the GE junction, and raised the possibility that this might underlie the rising frequency of cancer of the GE junction in the USA and Europe [85–90]. In all likelihood, the soil in which intestinal metaplasia in the esophagus develops, at least in a subset of patients, is acquired cardiac-type metaplasia, as a consequence of reflux [91,92]. The gastric cardia, itself, seems to be a very small zone in utero and in babies, which expands proximally as a consequence of injury (reflux). As such, pathologists currently evaluating esophageal biopsies or GE junction biopsies should probably report precisely what is seen, and apply the term “Barrett esophagus” to biopsies that are from the tubular esophagus and show intestinal metaplasia.

Dysplasia in Barrett esophagus
Dysplasia refers to neoplastic change in epithelium that remains confined to the neoplastic gland in which it arose. In other organ systems, usually the term “intraepithelial neoplasia” is applied, but “old fashioned” terminology remains in place for the hollow viscus organs. Criteria in the esophagus were established at a consensus meeting [93].
Grading dysplasia in Barrett esophagus

Algorithm The algorithm outlined is based on four mucosal features in Barrett esophagus. The algorithm presupposes that the biopsy in question is taken from the esophagus containing compatible endoscopic features of Barrett esophagus, and that intestinal metaplasia is found.

- surface maturation compared to the underlying glands
- architecture of the glands
- cytological features
- inflammation and erosions/ulcers.

Applying the algorithm, the classification of dysplasia is as follows.

Barrett esophagus, negative for dysplasia In Barrett esophagus without dysplasia (Figure 155.13), the surface appears more mature than the underlying glands in that the nuclear-to-cyttoplasmic ratio of surface cells is lower than that of the deeper glands. The architecture is normal, with abundant lamina propria between glands. The cytological features are normal, noting that mitoses may be present in deeper glands as well as nuclear stratification. The individual nuclei should have smooth nuclear membranes, and nucleoli, if present, should be small with smooth outlines. Nuclear polarity should be maintained in deep and superficial aspects of the biopsy. If inflammation is a component, reparative features may be present. In this setting, nuclear membranes should remain smooth, although the cells may display nuclear-to-cyttoplasmic enlargement and nucleoli may become more prominent but retain smooth contours. The surface should show maturation compared to the deeper glands but there may be some loss of surface mucin.

Barrett esophagus, indefinite for dysplasia Using the algorithm, included cases which had deeper cytologic changes suggestive of dysplasia but which showed surface maturation in the indefinite category whereas other observers have used the indefinite category as a “wastecan” [94]. Cases in the indefinite category could have normal architecture or some degree of glandular crowding. On cytologic evaluation, lesions could have hyperchromasia, nuclear membrane irregularities, and increased mitoses in the deeper aspects and these matured to the surface. Loss of nuclear polarity was not a feature of indefinite. In the presence of inflammation, more striking architectural abnormalities were to be included in the indefinite category. This interpretation can also be applied when tangential embedding does not allow assessment between the glands and the surface. Some cases display peculiar morphology and it is unclear whether they are neoplastic or reparative. We often offer an explanation for resorting to this category as a note when it is assigned.

Barrett esophagus, low-grade dysplasia In Barrett esophagus with low-grade dysplasia (LGD) (Figure 155.14), the surface appears similar to the underlying glands at low magnification or displays only slight maturation. The architecture may be mildly to markedly distorted with glandular crowding although lamina propria should be identifiable between glands. The cytologic features are important and the changes should extend at least focally to the surface. These include nuclear hyperchromasia with some chromatin clumping. The nuclei show nuclear membrane irregularities but not pronounced nuclear enlargement, although there may be focal marked enlargement if the other features support an interpretation of LGD. Nucleoli are not typically prominent in LG. Loss of nuclear polarity is not a feature of low-grade dysplasia, though nuclear stratification similar to that seen in colonic adenomas is within the spectrum of LGD and may be present at the surface. Inflammation is
Barrett esophagus, high-grade dysplasia (HGD) As in LGD, in HGD, surface maturation is lacking (Figure 155.16). The architecture may show crowding of cytologically abnormal glands or be markedly distorted with prominent glandular crowding and little intervening lamina propria. If the cytologic features are sufficiently dysplastic, lesser architectural distortion is acceptable. Nuclei are hyperchromatic and nuclear membranes irregular. Most examples are similar to dysplasia in the uterine cervix in not displaying prominent nucleoli which, like in the cervix, tend to be present in either marked repair or when invasion has begun, both are situations that are associated with ulcers. Cells may have either delicately clumped dark heterochromatin and inconspicuous nucleoli or prominent irregular nuclei with irregularly clumped chromatin and irregular nucleoli. Markedly enlarged hyperchromatic cells are a feature of HGD and these may extend to the surface. Loss of nuclear polarity is seen in HGD. Mitoses are readily identifiable. Inflammation is typically minimal. There is some evidence to suggest that HGD accompanied by an ulcer is a worrisome feature for an associated unsampled invasive carcinoma and we suggest additional biopsies and/or endoscopic ultrasound when we see this pattern [96].

Intramucosal carcinoma The distinction between HGD and the earliest intramucosal carcinoma (defined as invasion through the basement membrane into the lamina propria or muscularis mucosae but not beyond) remains difficult and observer variation between HGD and intramucosal carcinoma is not good. In general, these cases begin to demonstrate an effacement of lamina propria architecture and a syncytial growth pattern, extensive back-to-back microglands, and an intermingling of single cells and small clusters within the lamina propria. Typically, desmoplasia is absent to incompletely developed at this stage, hence its recognition is difficult and subjective. In
endoscopic mucosal resection (EMR) specimens After collection, the EMR specimen should be placed in a marked container filled with a generous amount of 4% neutral buffered formalin. Before they are placed in formalin, specimens can be pinned to an appropriate surface (e.g., a cork-board); this is not mandatory. The tissue is prone to shrinking upon fixation and if pinning is chosen tissue should not be under tension. Once placed into formalin, the specimen must remain in the formalin for a minimum of 6 hours to ensure adequate fixation. There is no scientific evidence for this but HER2 testing is sometimes later required and such testing has been standardized [97]. An alternative to formalin is to place the EMR specimen on a saline-soaked gauze, put it in a container and deliver it directly to the pathologist. The pathologist must be immediately available since any delay in processing may impair the sample quality.

The evaluation of an EMR specimen requires an understanding of how the specimen was obtained. EMR allows for superb characterization of dysplasia and neoplasia, but has a few pitfalls. First, since the plastic cup is applied to the surface of the mucosa, the surface epithelial layer of the EMR sample may be damaged such that dysplasia must be evaluated in the absence of an intact surface; this sometimes can require retrieving prior diagnostic samples and comparing the changes. Second, pathologists have observed duplicated muscularis mucosae in esophagi damaged by many cycles of reflux injury. In the majority of patients with BE, the original muscularis mucosae is present but a second delicate smooth muscle layer is found closer to the luminal surface; this feature has been identified in over 90% of resection samples [98], and nearly 70% of EMR samples [99]. This duplicated muscularis mucosae creates a pitfall when examining superficial biopsies as some observers may interpret lamina propria underneath the more superficial duplicated layer of muscularis mucosae as submucosa. The density of blood and lymphatic vessels in the superficial and deep lamina propria in Barrett esophagus is similar to that of non-Barrett esophagus [100]. Awareness of this phenomenon should prevent diagnosis of submucosal invasion (T1b) in patients whose invasive carcinoma is restricted to the lamina propria (T1a). This distinction is important because T1a lesions can often be treated endoscopically whereas submucosal invasive lesions (T1b) require more aggressive treatment. A third pitfall is diathermy induced contraction of the muscularis mucosae pulls the lateral edges of the sample together such that the sample becomes convex (Figure 155.17). This can result in the false impression that lateral margins are instead deep margins. One should make an attempt to characterize the depth of invasion in EMR samples in addition to assessing the margins. This is difficult in EMRs because the total thickness of the submucosa is not known. Essentially, the mucosa can be divided by any of several methods to assign a depth of invasion (Table 155.1). The submucosa can be similarly divided into sm1-sm3 [101,102]. The trouble is that since, in an EMR, it is not clear where the submucosa ends (as the EMR is obtained by transecting the submucosa) and thus must be estimated by the pathologist. Submucosal adenocarcinomas can be classified into those with invasion equal to or less
Adenocarcinomas invasive only into the mucosa have minimal potential for metastases. Consequently, endoscopic resection and ablation is considered an equivalent cancer therapy to esophagectomy for HGD or an intramucosal adenocarcinoma that is less than 2 cm in size without lymphovascular invasion. The presence of lymphovascular invasion in an otherwise intramucosal tumor is associated with an increased risk for lymph node metastases and is an indication for esophagectomy with lymph node dissection. An adenocarcinoma invasive into the submucosa to a measured depth greater than 500 μm is best treated by esophagectomy because of the significant risk of lymph node involvement. This is true irrespective of any other feature. However, tumors with signet cell histology may be exceptions and require esophagectomy.

### Tumors

#### Adenocarcinoma

Recognizing esophageal adenocarcinomas on biopsies is generally not a challenge as they exhibit the same features as other adenocarcinomas (i.e. malignant cells with glandular differentiation either in the form of ductal structures or mucin production) (Figure 155.18). However, finding an in situ/high-grade dysplasia component is useful in assuring that the esophagus is indeed the primary site (rather than the lung). It is often not possible to distinguish between a subset of poorly differentiated carcinomas and high-grade lymphomas without histochemistry. Poorly differentiated carcinomas may also assume spindle cell morphology (a more common scenario with squamous cell carcinomas) and, in the absence of an in situ component, immunohistochemistry is required.

Preoperative neoadjuvant chemotherapy and radiotherapy followed by esophagectomy is the preferred treatment; there is an especially poor prognosis when the patient presents with symptoms in the absence of surveillance for early detection.

### Squamous cell carcinoma

Squamous carcinomas are most common in middle third of esophagus. On imaging studies, the presence of an esophageal mass in the middle third of the esophagus is in keeping with squamous cell carcinoma but there are no specific radiologic features of this type of tumor.

On biopsies, squamous carcinoma of the esophagus appears similar to squamous carcinomas elsewhere (Figure 155.19). They are usually well differentiated squamous carcinoma with prominent keratinization. Background squamous epithelial dysplasia (intraepithelial neoplasia) including "carcinoma in situ" (HGD/intraepithelial neoplasia) is frequent at the periphery of invasive tumors. Dysplasia alone without invasion is uncommon. Some squamous carcinomas assume a prominent spindle cell appearance. This latter subtype tends to present as a polypoid mass. Short-term survival of such tumors is better than that for flat typical carcinomas owing to their exophytic growth but long-term follow-up erases an apparent survival advantage. Squamous cell carcinomas of the esophagus, like squamous carcinomas elsewhere, express CK5/6 and the host of epithelial markers. Most examples are not a diagnostic problem. When spindled, melanoma and sarcomas must be excluded. The best way to do this is by sampling as much of the overlying squamous mucosa as possible in order to detect an in situ component.

### Granular cell tumors of the esophagus

Granular cell tumors in general are rare. The most common sites are the tongue and skin [105]. A subset is multicentric and rare examples are malignant [106]. Granular cell tumors of the esophagus comprise about 1%–2% of all granular cell tumors and the esophagus is the most common gastrointestinal site

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**Figure 155.18** Esophageal adenocarcinoma. In this field, the adenocarcinoma undermines adjoining squamous mucosa.

**Figure 155.19** Esophageal squamous cell carcinoma. There is a squamous pearl towards the right of the field. In this biopsy, the lesion has invaded the muscularis mucosae, seen as slender pink strips.
Most esophageal granular cell tumors arise in the distal esophagus and about 5%–10% are multicentric. There is a female predominance and these tumors are relatively more common in African Americans than in Caucasians. Rare malignant esophageal granular cell tumors have been reported [108,109]. Esophageal granular cell tumors are most likely to be identified incidentally at endoscopy but some patients are symptomatic. Most appear as well-margined masses on imaging studies. Associated concentric narrowing can also be found.

On microscopic examination, tumors are centered in the submucosa with minor extensions into mucosa and muscularis propria and are well-margined but not encapsulated (Figures 155.20, 155.21). They are composed of plump neoplastic cells with abundant lightly amphophilic granular cytoplasm which displays retention of PAS (periodic acid Schiff) staining on diastase digestion. The cells are typically closely packed. Nuclei are small to pyknotic with occasional nucleoli. About half display squamous (pseudoepitheliomatous) hyperplasia in the overlying mucosa, which can raise the possibility of squamous cell carcinoma on superficial biopsies. Based on this hyperplastic squamous pattern, often mucosal biopsies contain predominantly the proliferated squamous epithelium and only a handful of lesional cells in the superficial lamina propria.

The vast majority of granular cell tumors behave in a benign fashion. Those rare examples that have metastasized typically displayed prominent cytological alterations and/or mitotic activity.

Leiomyoma
This is the most common spindle cell tumor of the esophagus. It displays smooth muscle differentiation. Esophageal leiomyomas occur in a relatively young population (median age, 35 years [110] and there is a male predominance. Leiomyomas of the esophagus are, of course, benign. They show eosinophilic cytoplasm, and are positive for desmin and smooth muscle actin (SMA), and negative for CD117/c-kit and CD34. Rarely, leiomyosarcomas arise in the esophagus and are typically large high-grade tumors that show muscle cell markers but no CD117. These tumors are seldom encountered on biopsy as they tend to be intramural in location.

Gastrointestinal stromal tumors
Leiomyomas are the most common esophageal mesenchymal neoplasms even though they are distinctly uncommon in the remainder of the GI tract, despite the abundance of mural smooth muscle. In contrast, gastrointestinal stromal tumors (GISTs) predominate in the stomach and intestines but are truly rare in the esophagus. Using the files of the Armed Forces Institute of Pathology and the Haartman Institute of University of Helsinki, Miettinen and colleagues were only able to accumulate 17 examples of esophageal gastrointestinal stromal tumors [110]. The esophageal GISTs occurred in 12 men and five women with a median age of 63 years (range, 49–75 years). All tumors were from the lowest third of the esophagus, and the most common complaint was dysphagia, whereas two tumors were detected incidentally. Histologically the tumors had the usual appearances of gastrointestinal stromal tumors, displaying an overall basophilic appearance and combinations of solid, myxoid, and perivascular collar like patterns with a spindle cell histology in 13 patients and epithelioid histology in four patients. All tumors were positive for CD117 and for CD34, whereas two patients were also positive for alpha-smooth muscle actin (α-SMA) and three patients were positive for desmin. Nine patients died of disease, including all who had a tumor larger than 10 cm, and also one patient whose tumor showed five mitoses per 50 HPFs.

Melanoma
Primary melanoma of the esophagus is quite rare with fewer than 300 cases reported. The affected patients are adults, with a mean age of about 60 years [111–115]. They are more common in men than women but there is no racial predominance.
Lesions predominate in the distal esophagus. At endoscopy, they are polypoid and pigmented in about 85% of cases. Imaging studies show bulky polypoid masses that bulge intraluminally without resultant obstruction. When biopsied, the findings in esophageal melanomas are similar to those elsewhere. Examples regarded as primary may display an in situ component. Obviously, finding this is extremely useful in establishing the esophagus as the primary site. Otherwise, cells are spindled to epithelioid with variable pigment, prominent nucleoli, and prominent intranuclear pseudo-inclusions.

Primary esophageal melanomas have a dismal prognosis. Only rare patients whose tumors present early can be cured.

**Stomach**

The stomach has four main zones with divergent types of mucosa. The simplest way to consider the different parts of the stomach is that the ends (cardia and antrum) protect the esophagus and duodenum from acid and enzymes whereas the middle of the stomach (body and fundus) produces the acid and enzymes.

The empty stomach is thrown into rugae (folds). Tiny surface invaginations are termed gastric pits and are the conduits of secretions. Histologically the entire stomach has a surface of foveolar cells which secrete neutral mucus that appears magenta to pink on the PAS stain. In the isthmus region of the body and fundus, parietal cells (oxyntic cells) dominate but mucous neck cells are also present. Mucous neck cells are seen in the neck, and chief cells dominate in the base. Endocrine cells are in the deep isthmus towards the base. In the cardia and antrum, things are simpler since the layers all predominantly produce mucus although the antrum has G cells that produce gastrin. Gastrin is secreted by the antrum but not the body and fundus. The lamina propria of the stomach should contain only a small population of lymphocytes, plasma cells, mast cells, and eosinophils, in contrast to the intestines, where these constituents are more abundant. Bacteria are usually not seen in the normal gastric mucus (in contrast to the colon, where they are normally present).

When pathologists consider biopsies from the stomach, features that help in diagnosis often involve correlation with clinical information. The endoscopist will be better served by providing information since the histologic features of gastric diseases display considerable overlap. Even the gender and ethnicity can be of some value. For example, autoimmune metaplastic atrophic gastritis typically affects older females [116]. Any specific clinical concerns, especially the possibility of focal cancer should be clearly conveyed to the pathologist.

**Inflammatory disorders**

**Acute hemorrhagic gastritis**

Acute hemorrhagic gastritis is prototypically associated with alcohol abuse [117,118] but other agents that are injurious to the gastric mucosa can also be responsible [119,120]. In early literature was was difficult to separate effects of *Helicobacter* gastritis from pure alcohol injury but we presently believe that the acute injury from alcohol is similar to a corrosive one with little inflammation but with abundant edema, hemorrhage, and reactive epithelial changes.

**Chemical gastritis/chemical gastropathy/reactive gastropathy**

This type of injury which is seen mostly in the antrum is common, as it is attributed to bile reflux, and thus is usually seen in patients being evaluated for gastroesophageal reflux disease (which, in reality, is duodenogastroesophageal reflux disease) [121,122]. Bile reflux is injurious to the gastric antrum as well as to the esophagus. In patients in whom the antrum has been removed, bile reflux injures the gastric body and contributes to the development of so-called “stump” cancers found in the postantrectomy setting. The other typical scenario for reactive gastropathy/chemical gastritis is in patients taking nonsteroidal antiinflammatory medications, a significant percentage of individuals. The general features of reactive gastropathy are foveolar hyperplasia, lamina propria edema, muscular stranding, and vascular ectasia (Figure 155.22). Active and chronic inflammation are minimal, hence some observers prefer the term “reactive gastropathy” rather than “chemical gastritis”.

**Mucosal calcinosis**

Mucosal calcinosis is seen in some renal failure patients and has been attributed to antacid use in these patients [123] but probably mostly reflects disorders of calcium metabolism that are typical in such patients [124]. Regardless, mucosal calcinosis seems to be of no significance in and of itself but an incidental finding in patients with renal failure.

![Figure 155.22](image-url)
**Protein pump inhibitor effects**

Protein pump inhibitors (PPIs) are commonly taken by patients having gastric biopsies. Examples of these medications are Prilosec (omeprazole), Prevacid (lansoprazole), and Nexium (esomeprazole). These medications reduce acid secretion by gastric parietal cells and have a morphologic correlate of an appearance of apocrine-like cytoplasmic swelling of parietal cells. PPIs are associated with an increased risk (fourfold) of fundic gland polyps but the risk of dysplasia is insignificant. Gastric carcinoids have been reported with long-term use of PPIs in rats but not in humans [125].

**Injury due to chemical agents**

**Iron** Iron pill gastritis appears similar to iron pill esophagitis [21], as discussed previously but is of particular note since striking epithelial changes in the setting of iron pill gastritis sometimes mimic gastric carcinoma.

**Kayexalate** Kayexalate can be found associated with gastric mucosa and gastric erosions/ulcerations just as in the case of the esophagus. In the stomach, kayexalate bezoars may formed [23].

**Colchicine** Colchicine is an alkaloid with antimitotic ability used to treat a variety of medical conditions, especially gout. Colchicine toxicity can result in multiorgan failure and death. If patients are taking colchicines at therapeutic doses, there are no abnormal biopsies. However, in patients who are colchicines toxic (this typically occurs in the setting of renal insufficiency), distinct morphologic changes, seen as metaphase mitoses, epithelial pseudostratification, and loss of polarity, and abundant crypt apoptotic bodies are seen in biopsy material [126]. These morphologic features are best seen in the biopsies from duodenum and gastric antrum, with relative sparing of the gastric body in the upper GI tract. Ki67 staining demonstrates an expansion of the proliferating region. Recognition of these features is important because colchicine toxicity can be fatal if undiagnosed clinically.

**Helicobacter gastritis**

Helicobacter gastritis has been a source of gastritis for years but was not recognized until Marshall and Warren identified the organism [127]. Marshall ultimately fulfilled Koch’s postulates by swallowing a pure culture of the organism and acquiring gastritis [128]. There have been over 20,000 publications devoted to this organism in the ensuing 20 years and Marshall and Warren have been awarded a Nobel Prize for their observations. *H. pylori* is now recognized as a curved flagellated gram negative rod that has variant forms (especially a coccoid form seen in treated patients) that is now known to be associated with both gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Another variant, called *Helicobacter helmanii*, is more tightly coiled and rare (<1% of *Helicobacter* isolates) but it cross reacts with the immunohistochemical stain for *H. pylori* and is fully capable of producing gastritis and associating with MALT lymphoma and gastric adenocarcinoma. Like *H. pylori*, it produces antral-predominant gastritis but this gastritis is less severe than *H. pylori* gastritis [129]. *Helicobacter* gastritis was formerly known as diffuse antral gastritis, type B gastritis (Figures 155.23, 155.24) (whereas autoimmune gastritis was type A), and superficial gastritis. In modern practice of pathology, all gastric biopsy reports should include an assessment for *Helicobacter* status. While the organisms may be observed on routine H & E stain, this can be complemented by other stains (Figure 155.25) [130]. Immunochemistry is rarely necessary or warranted but can identify small coccoid forms found in partially treated patients.

The endoscopic findings in *H. pylori* gastritis (and in assessing gastritis in general), correlate imperfectly with pathologic
findings although some observers have learned to recognize a “mamillated” endoscopic corpus appearance and an abnormal antral appearance [131].

Histologically, *Helicobacter pylori* organisms are seen in gastric mucus and overlying surface and foveolar epithelium. They do not colonize nonsurface or foci of intestinal metaplasia. There is typically abundant lymphoplasmacytic chronic inflammation of the lamina propria with lymphoid follicles (MALT). There is often abundant active inflammation (neutrophils). The inflammation is concentrated in the upper mucosa, hence the old term “superficial gastritis”. Following treatment, the active inflammatory component resolves but the chronic inflammatory component persists for months to years.

**Inactive chronic gastritis** There is extensive literature on grading chronic gastritis, complete with published pictograms [132,133]. However, the pictograms for chronic gastritis are seldom valued in daily practice but they are a useful construct for standardization in research studies. Chronic gastritis is generally attributable to prior *Helicobacter* infection based on serologic studies and is a common finding in biopsy material. However, the threshold for diagnosing it is not entirely clear. In a fashion that is more practical than evidence-based, we diagnose inactive chronic gastritis at 4× and confirm at higher magnification. At low magnification, the lamina propria of the stomach should have only a few inflammatory cells, which appear as small dots. We essentially use a slight prominence in dot density as the criterion for a low magnification diagnosis of inactive chronic gastritis.

**Metaplastic atrophic gastritis** Metaplastic atrophic gastritis occurs in two distinct types and, because of this, it is best if biopsies are obtained from both the gastric antrum and the body. These two types are termed “environmental” and autoimmune. Some authors have published studies with cartoons to use as templates for grading the degree of inflammation and atrophy in gastritis but these are of little value in daily practice [132,133].

**Autoimmune metaplastic atrophic gastritis** Autoimmune metaplastic atrophic gastritis (AMAG) was called “type A” gastritis in the past (before the role of *Helicobacter* was elucidated). This is a disease in which antibodies attack parietal cell. It is a disease typically affecting older women [116]. Patients have antibodies to parietal cells and to intrinsic factor (and thus are prone to severe vitamin B12 deficiency/pernicious anemia). They are at threefold risk of developing gastric cancer but not ask risk for ulcers since their parietal cells are reduced in number to absent and thus little to no acid is produced. Since parietal cells are the type affected, the changes are only in zones where parietal cells are found. Thus there is metaplasia and atrophy only in the body and fundus. An affected patient with biopsies from the antrum and the fundus has no significant inflammatory disease in the antrum (hence the importance of taking biopsies from both sites). Fundus biopsies show extensive loss of parietal cells and metaplasia. In some cases there are residual nests of parietal cells with chronic inflammatory cells (T cells) in the process of destroying them. In fact, the residual more normal mucosa sometimes appears as polyps to the endoscopist in a sea of severe atrophy [134]. Metaplasia may be of the intestinal type or the “pseudopyloric” type. In pseudopyloric metaplasia, the oxyntic mucosa resembles antral mucosa in that it lacks parietal and chief cells (oxyntic glands) but differs from it by not secreting gastrin. Only the true antrum secretes gastrin. Thus, immunohistochemistry for gastrin in biopsies from the body lacks reactive cells, a finding that can be exploited to both establish a diagnosis or to exclude inaccurate sampling (i.e., the endoscopist has biopsied the antrum and labeled it as “body”). In AMAG, there is no metaplasia in the antrum, which often shows hyperplastic features, possibly secondary to bile reflux (Figures 155.26, 155.27). Since the patients are hypo-acidic due to loss of parietal cell mass, a feedback loop causes the antral G cells to produce abundant gastrin to stimulate acid secretion. As there are few to no parietal cells (Figure 155.28), gastrin levels become progressively elevated in these patients and this gastrin stimulates proliferation of endocrine cells in the gastric body as a side-effect. Thus chromogranin stains show linear and nodular endocrine cell hyperplasia (Figure 155.29) in the body, none of which is attributable to G cells. If this condition persists, small indolent carcinoid (well-differentiated neuroendocrine) tumors can result.

**Environmental metaplastic atrophic gastritis** *Helicobacter* gastritis is probably the most important cause of environmental gastritis that we know but it is probably not the cause of all cases. Other associations include various dietary factors such as excessive salt, smoked foods (nitrites), paucity of green vegetables and fruits (lack of Vitamins C, E, β-carotene,
selenium), and nitrosamines. Nitrosamines can be produced from nitrites in the setting of colonization by anaerobic bacteria in a hypo-acidic stomach. This type of gastritis has been called type B gastritis and multifocal atrophic gastritis.

The key feature is that environmental atrophic gastritis is most marked in the antrum. Multiple foci first appear in the transition zone between antrum and body at the area of the lesser curvature. Over time the entire antrum is affected but the body relatively spared. There is less disease in the body, first in the distal body, and over many years affecting more of the body. The body can display pseudopyloric and intestinal metaplasia just as in autoimmune gastritis, but of course the antrum is affected as well. These patients retain enough parietal cell mass that they seldom develop pernicious anemia. They can become hypochlorhydric but achlorhydria is rare. Their serum gastrin is usually normal and they can have both ulcers and develop cancers. In the United States, it is usually seen in patients older than 50 years but in certain parts of the world, atrophy appears in patients in their third or fourth decades (e.g., Japan, Andean South American).

**Gastric antral vascular ectasia (GAVE/watermelon stomach)**

“Watermelon stomach” was first described by Jabbari in 1984 and refers to an endoscopic appearance [135]. In this condition, longitudinal antral folds have visible reddened vessels radiating from the pylorus in a distribution resembling a watermelon rind. Patients present with iron deficiency secondary to chronic...
gastrointestinal bleeding. The typical patient is an elderly woman with achlorhydria, chronic liver disease, CREST syndrome, or lymphoma. Some cases are associated with scleroderma [136]. In some patients the endoscopic appearance is atypical and consists of diffuse gastric erythema. The etiology is not well-known, but it is probably an acquired lesion. Some patients have antral prolapse [135].

Histologic examination discloses features that reflect a mucosal prolapse component: there is foveolar hyperplasia with dilated mucosal capillaries, focal thrombi, and fibromuscular hypertrophy [137] (Figures 155.30, 155.31). Similar features may be seen in patients who have portal hypertension but the dilated capillaries in portal hypertension lack fibrin thrombi but patients with watermelon stomach may also have portal hypertension [138]. Treatment of watermelon stomach often entails mucosal ablation since the patients have uncontrolled blood loss. Endoscopic therapy, including contact and noncontact thermal ablations of the ectatic vascular lesions, is the mainstay of conservative therapy. However, many patients fail endoscopic therapy and develop recurrent acute and chronic GI bleeding episodes. Surgical resection may be the only reliable method for achieving a cure and eliminating transfusion dependency. Traditionally, surgery was used only as a last resort after patients failed prolonged medical and/or endoscopic therapy. However, based on the experience garnered from the literature some authors have recommend a more aggressive surgical approach in patients who fail a short trial of endoluminal therapy [139].

**Lymphocytic gastritis**

The term lymphocytic gastritis simply describes a pattern of inflammation rather than a specific etiology. Lymphocytic gastritis is an uncommon form of chronic gastritis characterized by lymphocytosis of foveolar and surface epithelium. Lymphocytic gastritis is associated with celiac disease, *H. pylori* gastritis, and a varioliform gastritis pattern (an endoscopic form of gastropathy comprising enlarged folds, nodules and erosions, also called “octopus sucker” appearance [140]. Wu and colleagues [141] studied 103 patients with lymphocytic gastritis classified according to the associated entities, including the distribution and severity of the gastritis in the 70 patients from whom biopsy specimens of both antrum and body were available. In 84 patients (82%), a distinct associated entity was identified, including 39 with celiac disease, 30 with *H. pylori* infection, four with varioliform gastritis, two each with inflammatory polyp, Crohn’s disease, human immunodeficiency virus (HIV) infection, lymphoma, and esophageal carcinoma, and one with lymphocytic gastroenterocolitis. Lymphocytic gastritis was found in 33% of patients with celiac disease and 4.1% of histopathologically defined *H. pylori* gastritis. Lymphocytic colitis was common (38%, 5 of 13) in patients with celiac disease and lymphocytic gastritis. The authors concluded that lymphocytic gastritis most commonly occurs in celiac disease and *H. pylori* infection, but rarely with other entities. There is no need to count lymphocytes to arrive at a diagnosis of lymphocytic gastritis; they should simply be “prominent” and the diagnosis is made by pattern.

**Collagenous gastritis**

This term describes a rare pattern of injury in which prominent subepithelial collagen, intraepithelial lymphocytosis, and surface damage is present in the stomach. It has been associated with lymphocytic and collagenous colitis, and also with celiac disease, and patients can have watery diarrhea. There is a female predominance and the changes may be found throughout the stomach [142–150].

**Gastric Crohn’s disease**

In the absence of granulomas, it is difficult to know in gastric biopsies whether inflammatory changes reflect unspecified...
gastritis or are a manifestation of the patient's systemic disease. However, some observers have used the term “focally enhanced gastritis” to refer to a pattern of gastritis seen in Crohn's disease [151]. This refers to a pattern in which most of the biopsy has little to no gastritis and only a single area displays a more striking inflammatory infiltrate. We have also found that identification of this pattern of focally enhanced gastritis is helpful in identifying upper tract Crohn's disease but it is not wholly specific, especially in children [152].

Granulomatous gastritis
Granulomatous gastritis is attributable to Crohn's disease in about half of cases seen in Western populations and has also been associated with Helicobacter in populations with prevalent infection [153], but its etiology often remains unexplained, and it seems to be of little clinical significance. In daily practice, when confronted with isolated granulomas in a gastric biopsy, we make an attempt to correlate with a history of Crohn's disease or sarcoidosis and exclude infectious etiologies, including Helicobacter gastritis. Rare cases of granulomatous gastritis have been associated with adenocarcinoma, so this is always sought [154]. If a necrotizing appearance is present rather than isolated small granulomas, vasculitis is considered but we are reluctant to diagnose vasculitis definitively on any mucosal biopsy.

Other inflammatory conditions
A discussion of every cause of gastrointestinal inflammation is beyond the scope of this chapter, but some such conditions merit brief mention. Like the esophagus, the stomach can also be the principal focus of GI tract allergic disease (eosinophilic gastritis) and prominent eosinophilia involving epithelium and muscularis is sought (since scattered eosinophils are a normal lamina propria constituent). These are generally not quantified but rather, prominent presence should be noted to suggest correlation with other stigmata of allergic disease. Genta and colleagues have suggested a threshold to designate abnormal eosinophil counts (≥30 eosinophils/high power field), but the clinical significance requires validation [155].

Cytomegalovirus is relatively common in inpatient material, where it can be found in both epithelial and endothelial cells and is accompanied by gastritis. A pitfall in diagnosis can be the monocytic reaction it can invoke, which can be mistaken for lymphoma. This is also a potential pitfall with the more rare Epstein Barr virus (EBV) gastritis, which appears similar to large-cell lymphoma in the manner that infectious mononucleosis simulates leukemia.

Gastric GVHD
Gastric GVHD shows the same features as GVHD elsewhere in the GI tract, with epithelial apoptosis and ulcers/erosions to a varying degree [39]. We make an attempt to grade these changes as mild, moderate and severe in which severe changes include ulcers/erosions, and to compare current biopsies with prior ones when possible to assess improvements (or lack thereof). Such biopsies are carefully studied for cytomegalovirus inclusions as well.

Hyperplastic gastropathy
A simple but useful approach to hyperplastic gastritis or “giant folds” is to consider whether the cell type resulting in the thickened folds is foveolar hyperplasia or hyperplasia of oxyntic glands.

Foveolar hyperplasia
The syndrome of hypertrophic gastric folds, oxyntic gland loss (and thus achlorhydria), and protein loss is also termed “Ménétrier's disease” [156–161]. However, this term often describes a phenotype rather than an etiology when used to encompass the host of lesions that can display hyperplastic mucosa [156–174]. When used this way, it is another example of the limited repertoire of mucosal response to a variety of insults and, in fact, probably the original cases reported by Ménétrier were not a single entity. However, some observers suggest isolating those cases that display massive diffuse foveolar hyperplasia in the absence of inflammation as the "true" disease (massive foveolar hyperplasia) [157]. The mucin in this condition has a profile that differs from the mucin extracted from normal stomachs [171].

Ménétrier's disease is a rare disorder that has been described in adults as well as children, average fourth to sixth decades. It is more common in men (ratio 3:1). The disease course is usually chronic with an unfavorable prognosis. Patients present with hypoproteinemia and peripheral edema with loss of immunoglobulins, albumin and transferrin. Symptoms appear insidiously and become progressive consisting of epigastric pain, dyspepsia, anorexia, peripheral edema, hematemesis, and vomiting. The risk of developing carcinoma with Ménétrier's disease is subject to debate. Approximately 15% of Ménétrier's disease cases in the literature have been associated with carcinoma. In contrast to adults, children have a self-limited course for hyperplastic gastropathy, and cytomegalovirus infection has been frequently implicated. Overexpression of transforming growth factor-α (TGF-α) has a possible role in the pathogenesis of Ménétrier's disease. Transgenic mice that overproduce TGF-α in the stomach have many features of Ménétrier's disease such as foveolar hyperplasia, increased mucin content, decreased parietal cell mass and reduced acid production. In fact this phenomenon has been exploited to treat affected patients with targeted therapy to related ligands in the epidermal growth factor receptor (EGFR) pathway [175–177].

On a mucosal biopsy, this condition appears indistinguishable from a gastric hyperplastic polypl, consisting of hyperplastic foveolar epithelium arranged in a disorderly fashion with loss of oxyntic mucosa in biopsies from the body or fundus (Figure 155.32). Making a diagnosis requires correlation with the endoscopic and imaging findings.
Endoscopic mucosal biopsy – histopathological interpretation CHAPTER 155

hypertrophic gastropathy is referred to as a component of Zollinger–Ellison syndrome. Since the gastrin in Zollinger–Ellison syndrome also stimulates endocrine cells, endocrine cell hyperplasia is also a component of this condition. On a mucosal biopsy, the oxyntic component is markedly expanded and thick but the key feature is that parietal cells are seen insinuated in the epithelium nearly at, or even at, the surface between residual foveolar cells instead of nested down deeper in the mucosa.

Polyps and neoplasms
Nonneoplastic polyps
Endoscopically and pathologically, gastric polyps are defined simply as projections above the adjacent mucosal surface. The polyp itself may be reactive/inflammatory, hamartomatous, or neoplastic. Gastric polyps can arise from or be present in tissue anywhere in the layers of the stomach wall; however, polyps that are endoscopically biopsied are most commonly one of a wide variety of epithelial lesions.

Hyperplastic polyps
Hyperplastic polyps are the second most common gastric epithelial polyps [178]. These polyps can range from a few millimeters to many centimeters, and as such may be mistaken endoscopically for carcinoma. They are composed of characteristic hyperplastic, elongated, and dilated foveolae within an edematous, inflamed stroma (Figures 155.34, 155.35). The lining of the hyperplastic foveolae is generally that of mature gastric mucin cells, but foci of intestinal metaplasia are found in about 15%. The lining cells can be markedly reactive in appearance (especially when surface erosions are present), but true dysplasia arising in hyperplastic polyps is uncommon [179,180]; in a review of 160 patients with gastric hyperplastic polyps biopsied at the authors hospital, dysplasia was found in only 4% [1]. Similarly, adenocarcinomas are occasionally reported to occur in these polyps but this is unusual; Abraham and colleagues found adenocarcinoma within a hyperplastic in only one (0.6%) of 160 patients [1].

Hyperplastic polyps may arise anywhere in the stomach with a slight preference for the antrum and are multiple in approximately 20% of patients. One of the major reasons to diagnose hyperplastic polyps histologically is their significant association with a wide range of background gastric mucosal abnormalities.

Hyperplasia of oxyntic glands
Giant folds may be imparted by marked hyperplasia of the oxyntic component of the mucosa as well as by the surface component (Figure 155.33). This happens in the setting of hypergastrinemia. Of course hypergastrinemia can result from an interrupted feedback loop when there is “loss” of oxyntic mucosa in autoimmune gastritis but of course there cannot be hyperplasia of oxyntic mucosa if it has been destroyed by an autoimmune process! However, if there is intact gastric oxyntic mucosa, hypergastrinemia can be the result of a gastrin-producing neoplasm (a “gastrinoma”) and the resultant
Hyperplastic polyps in the stomach

Hamartomas are polypoid lesions formed from disorganized tissue elements that are native to that site. Hamartomatous syndromes that may involve the stomach include Peutz–Jeghers syndrome and juvenile polyposis, and less commonly Cowden's disease. Peutz–Jeghers is an autosomal dominant condition caused by germline mutations in the **LKB1/STK11** gene on chromosome 19p13.3 and is characterized by polyposis and distinctive melanin pigmentation around the lips, buccal mucosa, and sometimes hands and eyelids. The pigment may fade after puberty and thus the syndrome is not excluded if it is absent in an adult presentation. The polyps of Peutz-Jeghers syndrome primarily occur in the small bowel (65%) and are slightly less common in the colon and stomach [181–185]. Importantly, unlike the small bowel polyps which show prominent arborization of the muscularis mucosae, gastric Peutz-Jeghers polyps are composed mostly of dilated or branching mucus filled pits and may have relatively inconspicuous smooth muscle. Occasional examples of gastric Peutz-Jeghers' polyps have the classic arborizing architecture with strands of smooth muscle, but most have less specific features (but some degree of smooth muscle proliferation). Essentially they are best distinguished from hyperplastic polyps by correlation with the history. Dysplasia is rare in these polyps; however, patients with Peutz-Jeghers syndrome are at significant risk for gastric and other adenocarcinomas developing outside of the hamartomas [181].

Juvenile polyposis is a genetically heterogeneous condition in which some families have autosomal dominant germline mutations in the **DPC4** gene on chromosome 18q21. The polyps in juvenile polyposis can be limited to the colon or can be generalized, involving the colon, small bowel, and stomach. In addition, patients who appear to have juvenile polyposis predominantly confined to the stomach have been described. Juvenile polyps in the stomach frequently show a rounded surface contour with superficial mucosal erosions and an abundant, edematous, and inflamed lamina propria. The foveolae are frequently hyperplastic and dilated. Superimposed epithelial dysplasia or even mixed adenomatous/juvenile polyps occurs in up to one-third of juvenile polyps. Cowden's disease is an autosomal dominant condition that is relatively poorly characterized, but some families have germline mutations in the **PTEN** gene on chromosome 10q22–23. The gastrointestinal polyps in Cowden's disease are

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*Figure 155.34* Gastric hyperplastic polyp. There is prominence of mucin-producing epithelium and cystically dilated glands. This lesion has overlap with hypertrophic gastropathy and diagnosis of either condition requires correlation with the endoscopic appearance.

*Figure 155.35* Gastric hyperplastic polyp. It is not uncommon for large hyperplastic polyps to display surface erosions/ulcers and reparative epithelial changes.
usually a minor component of the syndrome (affected individuals typically show more prominent facial trichilemmomas and oral papillomas, as well as being at increased risk for breast and thyroid carcinomas). Detailed reports of the gastric polyps in Cowden's disease have not been made, but they are reported to be histologically indistinguishable from small hyperplastic polyps [186]. Dysplasia is not reported in these polyps [184].

There are some clinical and pathologic clues that can help to distinguish between gastric hyperplastic polyps and hamartomatous polyps: (1) The patient may have a previously characterized polyposis syndrome; (2) there may be biopsies of the nonpolypoid gastric mucosa showing an atrophic or inflammatory gastropathy of the type associated with the development of hyperplastic polyps; (3) hyperplastic polyps frequently show a more lobulated or villiform surface as compared to the often rounded surface of juvenile polyps; and (4) hyperplastic polyps often contain a more prominent edematous, inflamed lamina propria as compared with Peutz–Jeghers polyps, which can sometimes but not always show smooth muscle arborization. However, it is not generally possible to distinguish between a hyperplastic or hamartomatous polyp based solely on the histologic features of a polyp that is resected, or biopsied. Unfortunately all these syndromic polyposids are difficult to diagnose in the stomach, whereas they are quite easy to diagnose in the small bowel and colorectum [187].

**Fundic gland polyps**

Fundic gland polyps (FGPs) occur in two forms: sporadic and familial adenomatous polyposis (FAP) associated. FGPs were originally described in patients with FAP, believed to be a manifestation of that syndrome, but they are now recognized as the most common type of gastric polyyp in individuals without FAP. Sporadic FGPs are found in 1%–2% of routine upper endoscopic examinations and are most common in middle-aged females. They are typically small (a few millimeters and only rarely more than 1 cm), sessile, and dome-shaped. Sporadic FGPs may be single but are commonly multiple (usually a few polyps). Rarely patients without FAP have numerous FGPs proliferating in a manner that resembles a polyposis syndrome. Unlike hyperplastic polyps, FGPs are not particularly associated with any type of inflammatory or atrophic background mucosal pathology and are essentially an incidental finding.

FGPs associated with FAP syndrome differ from sporadic FGPs in their epidemiologic, clinicopathologic, and genetic features. For example, FAP-associated FGPs occur in a majority of patients with FAP and show a more equal gender distribution than sporadic FGPs. They are also more numerous than sporadic FGPs, and hence patients with FAP are more likely to have fundic gland “polyposis.” FAP-associated FGPs also occur at younger ages, including children, whereas FGPs are rare in the non-FAP pediatric population. In addition, approximately 25% of FAP-associated FGPs demonstrate low-grade epithelial dysplasia [188]. While dysplasia in sporadic FGPs can occur, it is distinctly unusual [189]. A retrospective histologic evaluation of several hundred sporadic FGPs at the authors hospital revealed <1% with low-grade dysplasia, and one of these cases was subsequently determined to be a member of an attenuated FAP family [188]. Syndromic and sporadic fundic gland polyps differ genetically in alterations in genes of the Wnt signaling pathway, specifically APC and CTNNBI (which encodes beta-catenin).

Despite the genetic differences, the natural history of sporadic and syndromic FGPs is surprisingly similar. Both sporadic and FAP-associated FGPs can increase, decrease, or remain constant in number, as seen when patients are followed with serial upper endoscopic examinations. Sporadic FGPs, even in fundic gland polyposis, have never been reported to progress to gastric adenocarcinoma [189–191]. The presence of dysplastic or nondysplastic FGPs is regarded as an incidental finding and virtually never requires surgical resection. Even surveillance of dysplastic FGPs remains controversial.

The morphology of fundic gland polyps overlaps considerably with that of PPI effects. An endoscopic nodule correlates with dilated oxyntic glands, some of which contain cells with apocrine-like snouts (Figure 155.36). Distinguishing between these two processes is principally done by correlation with the presence of an endoscopic lesion.

**Inflammatory fibroid polyp**

The first systematic description of these tumors was provided by J. Vaněk and appeared in the *American Journal of Pathology* in 1949 [192], although there were prior case reports. Helwig and Ranier coined the present term “inflammatory fibroid polyp” in the early 1950s [193] (which has been retained despite the fact that we now know these lesions are neoplasms), but these lesions have also been called “gastric submucosal granuloma with eosinophilic infiltration,” eosinophilic granuloma, granuloblastoma, neurofibroma, and hemangiopericytoma. The vast majority of these tumors occur in the stomach, where they...
PART 5 Diagnostic and therapeutic modalities in gastroenterology

Topic tissue may contain admixture of pancreatic acinar tissue, ducts, islet cells in varying proportion. Since the lesion is often submucosal, superficial biopsies containing only the overlying mucosa may be nondiagnostic.

Gastric xanthomas
Gastric xanthomas are pale yellow nodules or plaques, usually less than 3 mm in size, in the gastric mucosa. They are frequently found in groups, most often along the lesser curvature and pyloric regions. They consist of lipid-laden histiocytes in the lamina propria occasionally extending into the submucosa (Figure 155.39). There is no correlation between gastric
xanthomomas and hypercholesterolemia. The lesion is of little significance, except as it may be misdiagnosed as carcinoma [200]. However, in any concerning case, performing a keratin and CD68 stain can be reassuring. Some authors have associated gastric xanthomomas with atrophic gastritis and Helicobacter gastritis [201].

**Gastric adenomas and gastric dysplasia**

*Intestinal and gastric foveolar type gastric adenomas*

Much literature in this area has been difficult to interpret. Although there is massive experience with gastric cancer and its precursors in Japan, pathologists there have used different diagnostic criteria from Western pathologists, as pointed out by Lauwers and colleagues in 1999 [202]. The observation that Japanese pathologists did not require invasion to diagnose carcinoma (and “invasion” was not listed as a criterion in the 1990 World Health Organization [WHO] classification) presumably has informed their far better cure rates for early carcinomas, compared to results in Western countries. Based on these observations, an international panel convened in Vienna published consensus definitions of gastric epithelial neoplasia in 2000 [203], which distinguished between noninvasive lesions and invasive ones.

Currently, if such a lesion produces a polyp, it is referred to as an adenoma and the dysplasia is graded, whereas flat lesions are termed “dysplasia” and are graded using criteria similar to those in the esophagus. This is not particularly scientific, but is a convention that has worked. Both types of lesions confer risk, and both require evaluation of the entire stomach to exclude invasive carcinoma. As in the case of gastric hyperplastic polyps, the background pathology is important. To illustrate this, Abraham and colleagues studied 61 gastric adenomas from 51 patients between 1985 and 2001 [2]. The adenomas were classified as intestinal-type, containing at least focal goblet cells and/or Paneth cells (Figure 155.40); gastric foveolar type (Figure 155.41), lined entirely by gastric mucin cells, as shown on periodic acid Schiff/Alcian blue staining (PAS/AB) indeterminate. Intestinal-type adenomas were significantly more likely than gastric foveolar-type adenomas to show high-grade dysplasia \((P < 0.0001)\), adenocarcinoma within the polyp \((P = 0.016)\), intestinal metaplasia in the surrounding stomach \((P < 0.000001)\), and gastritis \((P = 0.002)\). Patients with intestinal-type adenomas were also more likely to have separate adenocarcinomas, as seen in five cases (100%), although this did not reach statistical significance. However, there is confusion in the literature regarding the natural history of these gastric polyps because essentially the same term (“foveolar-type gastric dysplasia”) has been used to describe a different type of polyp [204]. In a Korean study, intestinal metaplasia was identified in the background mucosa in all cases of so-called “foveolar”, “hybrid”, and “adenomatous” dysplasia, and these polyps were all gastritis-associated. Rather than using the previously discussed morphologic criteria, the authors of this study performed immunolabeling for mucins and found that their “hybrid” polyps with both intestinal and gastric foveolar differentiation were more aggressive than those with only intestinal type differentiation [204]. For pathologists practicing in the West, the Abraham criteria are most applicable and allow the pathologist to assign risk categories for gastric adenomas. Since the “gastric foveolar type adenoma” is rare, associated with APC alterations [205], unassociated with background pathology, and appears as an isolated sporadic lesion akin to a colonic sporadic adenoma, the patients are at low-risk for progression to a more advanced lesion [206]. Since gastric adenomas are rarely truly “sporadic” lesions (the vast majority in daily practice in the
United States are of the intestinal type and associated with background intestinal metaplasia. Thorough sampling of the surrounding gastric mucosa is essential to understand the clinicopathologic context of the adenoma. A Korean study also found increased risk of colorectal adenomas (48.3% vs. 33.3% in control group, \( P = 0.022 \)) in patients with gastric adenomas, arguing for screening colonoscopies in patients with this type of gastric polyp [207].

Flat dysplasia is typically encountered incidentally also in the setting of atrophy as a result of long-standing injury due to *Helicobacter* infection or autoimmune atrophic gastritis. There are no guidelines regarding patient management in this situation as the flat dysplasia is not detected endoscopically. Low-grade dysplasia has been reported to “regress”, persist, and progress to a higher grade dysplastic lesion/adenocarcinoma in 53.3%, 31.1%, and 6.6%/8.8% of cases, respectively. High-grade lesions, however, are unlikely to regress and are associated with a significant risk of progression to invasive carcinoma, reported at 69% (11/16 patients) by Rugge and colleagues (in this study however, it was unclear if the studied cases represented flat or polypoid lesions) [208]. “Regression” in the setting of flat low-grade dysplasia is a term that must be used with caution as these lesions are not grossly evident and are unlikely to be identified endoscopically. These patients are typically followed endoscopically and their stomachs mapped with multiple biopsies. High-grade dysplastic lesions are typically managed with endoscopic mucosal resection (EMR) or surgical resection.

**Pyloric gland adenoma**

These lesions have been mentioned briefly over the years and in the 1990 WHO classification of gastric neoplasms but were fully characterized in 2003 by Vieth and colleagues [209]. Pyloric gland adenoma (PGA) is a neoplastic polyp known to occur in the stomach, gallbladder, duodenum, and main pancreatic duct. These polyps show a preference for the gastric corpus, account for 2.7% of all gastric polyps, are typically seen in older patients (median age 73 years), and gastric examples show a remarkable female predominance [206,209]. More than 1/3 occur in patients with AMAG [206,209] and account for 10% of polyps found in patients with AMAG [116]. *H. pylori* or chemical gastritis may also be present in the background mucosa [209]. Histologically, these polyps are composed of closely packed pyloric-type glands with cuboidal to low columnar epithelium showing pale or eosinophilic, “ground glass” cytoplasm (Figure 155.42). Nuclei are round without prominent nucleoli. Foci of dysplasia/carcinoma are commonly encountered. Low-grade and high-grade dysplasia are seen in 12% and 39% of the cases, respectively [206] while invasive carcinoma is associated with 12%–47% of the lesions, depending on the authors’ criteria for carcinoma; using Western criteria, the figure is probably closer to 10%–15% [206,209]. PGAs show coexpression of MUC6 (marker of pyloric gland mucin) and MUC5AC (marker of foveolar mucin) and lack expression of MUC2 (marker of intestinal mucin) and CDX2. While foveolar-type gastric adenomas show MUC5AC expression, they lack expression of MUC6 and MUC2 [206]. Some cases, however, show areas of transition from gastric to intestinal differentiation and these foci may show immunolabeling with MUC2 and CD10 [210]. As with other types of adenomas, complete excision of PGA with biopsy of the background flat mucosa is appropriate. Interestingly, PGAs are over-represented in individuals with familial adenomatous polyposis [211].

**Oxyntic gland polyp/adenoma**

Encountered in the literature as “chief cell hyperplasia with structural and nuclear atypia” and “chief cell proliferation of the gastric mucosa”, this peculiar lesion was initially described in 2003 by Müller-Höcker and Rellecke and later in 2005 by Matsukawa and colleagues as an unusual variant of fundic gland polyp arising in the cardia/corpus [212,213]. Initial reports described anastomosing cords of irregularly branched tubules composed of monotonous epithelial cells with central, round nuclei and amphophilic cytoplasm associated with oxyntic and foveolar microcysts. The case described by Matsukawa and colleagues reports nuclear atypia in the form of nuclear stratification, suggestive of a tubular carcinoma. However, mitotic figures and Ki67 labeling index were low in both reports. Chief cell origin for these proliferations is supported by ultrastructural findings and positive immunohistochemical staining for pepsinogen-I. However, scattered parietal cells were observed within these proliferations. In both of these reports an adjacent fundic gland polyp could be identified [212,213]. More recently, Ueyama and colleagues described similar lesions with the term “gastric adenocarcinoma of fundic gland type”. In their report of 10 cases, the Ki67 labeling index was also low and none of the patients died or suffered recurrences during the 10–70 month follow-up period [214]. Similar polyps have been diagnosed at this authors institution as “oxyntic gland polyp/adenoma” [215] (Figure 155.43). Because of their rarity and lack
of long-term studies endoscopic follow-up to assure complete removal of the lesion seems sensible.

**MALT lymphoma**

Low-grade B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) are believed to arise in organized lymphoid tissue in the gastric mucosa that is usually acquired in response to *H. pylori* infection. They are also termed “extra-nodal marginal zone lymphomas”. The close association between *H. pylori* and the lymphoma is further reflected by the demonstration that the proliferation of the lymphoma cells can be driven by the presence of *H. pylori* organisms through a complex path of cellular interactions involving specific T cells [216–221]. From these observations it was suggested that removal of one of the proliferative drives to the neoplastic cells in the form of eradication of the organism might induce a remission in the tumor [220]. Long-term remissions can indeed be induced in low-grade MALT lymphomas in 70% to 80% of cases. The lymphomas that are most likely to respond to *H. pylori* eradication are those that are located superficially within the gastric mucosa. It has been suggested that certain genetic abnormalities, such as t(11;18) and the Bcl-10 mutation, may be associated with lack of response to this therapy. Recurrences of low-grade lymphoma are encountered in patients treated by *H. pylori* eradication, but these appear to be infrequent and may be self-limiting and spontaneously regress without further therapy.

In assessing such a case at low magnification, the lamina propria is expanded with small uniform cells, some of which have a “halo” around them. We always assess the muscularis mucosae at low magnification (with confirmation at high magnification) as physiological lymphoid collections typically do not infiltrate the muscular mucosae whereas MALT lymphomas do (Figure 155.44). The classic “lymphoepithelial lesion”, in which lymphocytes are seen peppered in residual gland epithelium (Figure 155.45), is not present in every case. At high magnification, before wasting resources on immunohistochemical stains, the cell composition is assessed: numerous plasma cells are more often an indicator of a reactive lesion (*Helicobacter gastritis*). We perform an abbreviated immunophenotyping panel consisting of CD20 (B-cell marker), CD3 (T-cell marker), and CD43 (normally found in T cells) and assess for CD20 reactive B cells that aberrantly express CD43. The CD3 stain is necessary since it is normal for T cells to express CD43 and the various stains must be compared. Unfortunately not every MALT lymphoma coexpresses CD43 (about half do) but the diagnosis can still be made on a B-cell rich infiltrate with typical
morphology. The pathologist should always make an attempt to document the presence (or absence) of Helicobacter. Probably it is most important for both the endoscopist and pathologist to remember that these lesions regress slowly over time upon initiation of therapy and can linger for up to 18 months.

**Adenocarcinoma**

Gastric carcinoma is often easy to recognize on biopsies but it can also be extremely subtle (Figures 155.46, 155.47). When there is a high index of suspicion, each fragment should be examined carefully, concentrating on any focus that appears distinct or fibrotic at low magnification. Biopsies from patients who are status post partial gastrectomies should be reviewed attentively as these are high-risk patients based on their continuous bile reflux. In doubtful cases, a keratin stain is helpful but should not be ordered in ulcerated cases as regenerative mucosa can give a false impression of a “single cell pattern”. Carcinomas of the intestinal type can be extremely subtle on superficial biopsies but there is the correlate of a mass. Diffuse carcinomas are very difficult to spot on biopsies but there is the correlate of a stomach that does not distend on insufflation. It always behooves the endoscopist to provide information concerning these features. Some carcinomas are so poorly differentiated that they require keratin stains for diagnosis. Occasional gastric carcinomas have a clear cell pattern. Rare gastric carcinomas have squamous differentiation and still rarer ones have hepatoid differentiation. Some observers have suggested that carcinomas having parietal cell differentiation have an improved prognosis over other gastric carcinomas but this seems doubtful based on our material. We do not make an exercise of typing gastric carcinomas in our practice.

**Mesenchymal tumors**

**Gastric stromal tumors**

The stomach is the most common site for GISTs and they are occasionally diagnosed on mucosal biopsies. Typically those diagnosed on biopsies are aggressive lesions that have invaded the mucosa. GISTs are mesenchymal tumors arising in the GI tract and occasionally within the abdomen with no GI connection. The earlier literature attempted to classify them as smooth muscle or nerve sheath tumors, but even in the benign tumors evidence for such differentiation was difficult to find. Mazur and Clark introduced the term stromal tumor in 1983 [222]. GISTs show differentiation towards (and supposedly arise from a precursor of) interstitial cells of Cajal which are normally concerned with motility of the gut [223,224]. The availability of specific antibodies and clarification of their immunohistochemical profile has facilitated diagnosis.

Most gastric GISTs display KIT mutations, but some are characteristically wild type and still have expression of KIT protein. These include GISTs associated with neurofibromatosis and those associated with succinate dehydrogenase deficiency. The tumors in patients with neurofibromatosis (NF)1 have retained succinate dehydrogenase activity [225–227].

Some epithelioid gastric stromal tumors are associated with paraganglioma and pulmonary chondroma in Carney’s triad. As above, a subset of GISTs, usually pediatric ones, displays loss of succinate dehydrogenase. Patients with Carney–Stratakis syndrome (GISTs and paragangliomas) have germline mutations of the gene encoding for succinate dehydrogenase [226].

About 20% of gastric GISTs are malignant. The consensus is that five mitoses per 50 HPF and >5 cm are adverse prognostic factors. The 5-year survival of malignant gastric GISTs is about 40%, with improvement in completely resected cases. There is no evidence that radical surgery improves survival, so that the least extensive surgical procedure compatible with complete excision is advisable. Gastric GISTs are more frequent in males, but young patients (especially females) have an improved outcome.
Most GISTs are spindle cell tumors with variable palisading, peculiar paranuclear vacuoles, and collagen fibrils (Figure 155.48). On a practical note, epithelioid GISTs (Figure 155.49) on mucosal biopsies are readily mistaken for a host of epithelioid and epithelial neoplasms. It is advisable to perform an immunohistochemical panel in assessing them to include CD117/c-kit, S100 protein (to address melanoma) and a cytokeratin stain to address signet cell carcinoma. The vast majority of GIST have kit mutations and are CD117/c-kit stain positive, but about 5% lack kit mutations and many in the c-kit negative subset have alternate mutations of platelet derived growth factor-α instead [228–230]. Since about 70% of GISTs express CD34, this can also be included in a diagnostic panel. Another helpful antibody is DOG1 (detected on GISTs1) [231], although gastric carcinomas can express this protein [232]. On mucosal biopsies, it is difficult to assess tumor size and mitotic counts to prognosticate but it is possible to make a diagnosis in many cases.

The Armed Forces Institute of Pathology (AFIP) group probably has the largest accumulated series of gastric stromal tumors with follow-up from the preimatinib era, and have reported a large series of 1765 GISTs confined to the stomach with good follow-up information [233]. Histologic variants recognized among the spindle cell tumors included sclerosing, palisaded-vacuolated, hypercellular, and sarcomatous and among the epithelioid tumors, sclerosing, dyscohesive, hypercellular, and sarcomatous. Outcome was strongly dependent on tumor size and mitotic activity. Only 2% to 3% of tumors <10 cm and <5 mitoses/50 HPFs metastasized, whereas 86% of tumors >10 cm and >5 mitoses/50 HPFs metastasized. However, tumors >10 cm with mitotic activity <5/50 HPFs and those <5 cm with mitoses >5/50 HPFs had a relatively low metastatic rate (11% and 15%). A small number of patients survived intraabdominal metastasis up to over 20 years. Tumor location in fundus or gastroesophageal junction, coagulative necrosis, ulceration, and mucosal invasion were all unfavorable factors (P < 0.001), whereas tumor location in antrum was favorable (P < 0.001). Probably the key feature of this very large series is that it allowed separating out a “benign” category of gastric GISTs based on large numbers of cases [233]. Another important feature of the AFIP study is that mucosal extension by gastric GISTs was evidence that the tumor was biologically aggressive. Based on the large AFIP series of gastric GISTs, CD117/c-kit is found in 91% of gastric GISTs, CD34 in 82%, SMA in 18%, and desmin in 5%; the latter two tend to be focal.

**Gastric Neural Tumors**

These are not typically encountered on gastric mucosal biopsies. Most gastric nerve sheath tumors have been classified as schwannomas [234], although there is no reason that a patient with syndromic nerve sheath tumors (neurofibromas, neuromas, and ganglioneuromas) cannot manifest gastric lesions. Most gastrointestinal schwannomas occur in the stomach involving submucosa and muscularis propria. They rarely arise in the esophagus or colon. They typically do not affect the mucosa but are surrounded by a lymphoid cuff, which is more likely to be biopsied than the underlying mesenchymal lesion.

GI tract schwannomas are not encapsulated, a feature that distinguishes them from schwannomas in the peripheral nervous system [235]. They can also be plexiform. They have a lymphoid cuff with germinal centers, and intralesional lymphocytes can be seen. They are composed of interlacing bundles of spindle cells that are only loosely palisaded (in contrast to GISTs which, ironically, often display striking palisading). They appear quite similar to GISTs but the lymphoid cuff is a tip-off that these are Schwannian. These benign tumors are strongly S100 protein positive and lack muscle markers and CD117. They may have CD34 as well. The differential diagnosis is with GIST. The inflammatory backdrop is the key morphologic
feature that should prompt the consideration of a nerve sheath tumor.

**Other gastric mesenchymal tumors** Other gastric mesenchymal tumors include lipomas, and glomus tumors. Glomus tumors are usually deep in the gastric muscularis propria and not encountered on mucosal biopsies. In the present era of better control of HIV disease, we seldom encounter Kaposi’s sarcoma in our gastrointestinal react material but when it is seen, there is a history of extreme immunosuppression and a proliferation of CD34 reactive spindle cells. Antibodies to HHV8 are also available to confirm this impression.

**Well-differentiated neuroendocrine (carcinoid) tumors**

Though historically known as carcinoid tumors, these are classified as well-differentiated neuroendocrine tumors (WDNET or NET G1, neuroendocrine tumor, grade 1) by the WHO [236]. Strictly speaking, a “carcinoid” tumor is serotonin-producing and is associated with with clinical evidence of carcinoid syndrome and hence the terminology well-differentiated neuroendocrine tumor is considered preferable. A tripartite classification system for gastric WDNET’s is now in common use: (a) tumors associated with chronic atrophic gastritis with hypergastrinemia; (b) tumors associated with Zollinger–Ellison syndrome, or multiple endocrine neoplasia (and thus with hypergastrinemia from a gastrinoma); and (c) sporadic lesions (without hypergastrinemia). These subsets of tumors have been classified as types I–III, respectively. Gastric WDNET’s associated with hypergastrinemia (types I and II) are relatively benign, whereas sporadic lesions require aggressive surgical management. Gastric WDNET’s can be managed initially by endoscopic excision of accessible tumors, evaluation of the setting in which they have arisen, and follow-up by regular endoscopic surveillance. Some studies have shown regression of type I and II gastric WDNT’s following treatment with somatostatin analogues [237,238]. A striking increase in gastric WDNET’s has been reported in the past 50 years, including an 800% increase in gastric carcinoids in white women although these trends may reflect ascertainment biases [116].

In the two settings in which trophic effects of hypergastrinemia on gastric endocrine cells produce a tumor, the tumors have essentially little to no metastatic risk. The cutoff for classifying a lesion as endocrine cell hyperplasia versus a neoplasia is often set at 5 mm (but sometimes at 0.5 mm), but the distinction has little clinical significance. It is more important to determine the source of the excess gastrin by attention to background gastric changes – atrophy versus hyperplasia of the acid-producing cells. Hyperplasia of intact parietal cells is the hallmark of Zollinger–Ellison syndrome, in which there is a gastrin-secreting neoplasm (often in the duodenum). In such a case the type 1 WDNET is gastrin negative on immunolabeling since it is composed of enterochromaffin-like cells whereas the gastrinoma of the pancreas or duodenum express gastrin on immunolabeling. The morphology of gastric WDNT’s is similar to those found elsewhere, characterized by small round proliferating cells (Figures 155.50, 155.51, and 155.52). The diagnosis can be confirmed by performing endocrine stains. Some of these tumors do display cytologic atypia but this does not imply a worse prognosis. Mitotic activity or Ki-67 immunolabeling are the parameters used for grading foregut WDNT’s and a three-tiered system is used [236,239]:

- **Grade 1:** $<2$ mitoses/10 high power fields or $<2\%$ Ki-67 index
- **Grade 2:** mitotic count 2-20 per 10 high power fields or 3–20% Ki-67 index
- **Grade 3:** tumors are high-grade neuroendocrine carcinomas (large-cell or small-cell types) and are characterized by $>20$ mitoses/10 HPFs or $>20\%$ Ki-67 index.

![Figure 155.50](image1.png)

*Figure 155.50* Gastric well-differentiated neuroendocrine (carcinoid) tumor. This tumor is centered in the submucosa.

![Figure 155.51](image2.png)

*Figure 155.51* Gastric well-differentiated neuroendocrine (carcinoid) tumor. Note the uniform nuclear features.
Metastatic neoplasms
Although theoretically any tumor might metastasize to the stomach, those seen in practice are metastatic lobular breast cancer, renal cell carcinoma, melanoma, and hepatobiliary carcinoma. These are best separated from de novo gastric primaries by history, but immunohistochemistry is important as well.

Small bowel
Nonneoplastic conditions
Reactive lesions (gastric metaplasia of the duodenum)
When the esophagus and stomach are injured, metaplasia ensues, often of intestinal type. The duodenum also can undergo metaplasia when injured, but to gastric type mucosa (Figures 155.53 and 155.54). *Helicobacter* gastritis was originally strongly associated with duodenal ulceration [127,240]. It is predominantly the bulb that is damaged. Gastric mucin cell metaplasia supervenes together with Brunner gland hyperplasia. In addition, the area of metaplastic duodenum is then able to support *H. pylori* which further stimulates ulceration in the duodenum. This cycle of events may attract inflammation and impart a nodular appearance to the duodenum ("nodular peptic duodenitis") [172,241]. There may be striking reparative epithelial changes that are occasionally mistaken for adenomas. If PAS staining is done, these foci usually have at least some gastric mucin cell metaplasia as a clue that the process is reparative rather than neoplastic. In any doubtful case, repeat biopsy can be performed following treatment. Peptic duodenitis appears similar to gastric heterotopia, which occurs as a nodule in uninjured small bowel and often consists of oxyntic mucosa. In some cases, it is impossible to suggest whether the endoscopically noted nodule consists of a heterotopic or metaplastic process; although fortunately both are benign.

Infectious enteritis
A host of etiologic agents may affect the small bowel mucosa that should be recognized. It is impossible to be exhaustive, but some merit comment.

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*Figure 155.52* Gastric well-differentiated neuroendocrine (carcinoid) tumor. The lesional cells are reactive with synaptophysin antibodies.

*Figure 155.53* Chronic peptic duodenitis. At low magnification, normal duodenal mucosa is seen at the left (goblet cells are present) but the central portion shows gastric type epithelium that is metaplastic.

*Figure 155.54* Chronic peptic duodenitis. A periodic acid Schiff with alcian blue shows the gastric metaplasia to advantage; it appears magenta.
**Mycobacterium avium complex**

In immunocompetent hosts, atypical mycobacteria show little virulence. However, *Mycobacterium avium* complex (MAI) is a significant cause of opportunistic infection in immunocompromised patients, especially patients with AIDS. Patients with CD4+ cell counts of less than 100/μL are at risk for developing MAI. Symptoms include abdominal pain, fever, weight loss, chronic malabsorption, diarrhea, etc. Disseminated GI tract infection with MAI is common in AIDS patients. Clarithromycin or azithromycin are the preferred agents for MAI prophylaxis.

MAI usually affects both the small and large bowel. Endoscopically, the small bowel mucosa either appears normal or shows a coarse granularity without significant exudate. (implying an attenuated local immunological response). The granular mucosa corresponds to massive infiltration of small intestinal villi by histiocytes loaded with acid-fast bacilli (Figures 155.55 and 155.56).

Unlike for *Mycobacterium tuberculosis*, well defined granulomas are not a feature of MAI. Instead, loose clusters of foamy histiocytes appear with little accompanying inflammation. Apart from the GI tract, MAI infection can affect a wide range of organs including lung, lymph nodes, spleen, liver, bone marrow, and brain.

**Nematode infection**

*Strongyloides stercoralis* is a nematodal infection with a worldwide distribution affecting 30–100 million people. It is endemic in Africa, Southeast Asia and South America and parts of the US (e.g. Kentucky and Eastern Tennessee).

The life cycle of this worm is as follows – the female lays eggs (and can do so without fertilization – parthenogenesis) in small intestinal crypts. The embryonated eggs hatch into rhabditiform larvae which pass into the lumen and are expelled with feces. The rhabditiform larvae develop into filariform larvae (infective form) which penetrate human skin, passing through blood vessels to the lungs, into the upper airways. The patient coughs and the larvae are swallowed and finally reach the small intestine and mature into adult worms. The males are rapidly expelled after fertilizing the females. The female worms can remain in the intestine for decades – and are known in some cases to be present for up to 30 years! In immunosuppressed patients, autoinfection is a major threat as the rhabditiform larvae internally undergo transformation, penetrate intestinal mucosa and disseminates throughout the body. Autoinfection/hyperinfection carries a high mortality rate (up to 80%). Unlike hookworm infection for which eggs are used for identification in stool exams, eggs are not present in the stool in *Strongyloides* infection. Diagnosis is based most frequently on identification of rhabditiform larvae in stool. Intestinal biopsies are used less often for diagnosis. Characteristic findings in the biopsy are the presence of all stages of the worm embedded in mucosal crypts (Figures 155.57 and 155.58). Thus larvae, eggs, and rarely adult worms (recognized by one intestinal tract and a pair of reproductive tubes) can all be seen. Additional changes include villous flattening, crypt hyperplasia, and an inflammatory reaction consisting of lymphocytes, plasma cells, eosinophils. Finding a prominent eosinophilic infiltrate and Charcot-Leyden crystals should prompt a search for a parasitic infestation. Treated worms invoke a brisk immunological response. The small intestine is the most common affected site but rarely stomach and colon can also be involved.

**Whipple’s disease**

Whipple’s disease (WD) is a rare systemic bacterial infection caused by *Tropheryma whipplei* (an actinomycete). There is a striking male predominance of 8–10:1, with white males between the fourth to fifth decades most commonly affected. Patients present with diarrhea, low-grade fever, weight loss, malabsorption, abdominal pain, arthralgia, anemia,
rounded villi with distention of lamina propria by foamy pink macrophages. The macrophages contain PAS positive, diastase resistant rod or sickle shaped bacterial inclusions. The bacterial inclusions can also be present in the extra cellular space of lamina propria, and in epithelial cells, fibroblasts, endothelial cells, and smooth muscle. Lymphatic obstruction gives rise to dilated lacteals containing lipid deposits-a helpful feature which suggests the diagnosis of Whipple's disease on H & E stain (Figure 155.59). Endoscopically, the lesions can present as yellowish-white plaques, as pale yellow shaggy mucosa, or have an erythematous friable appearance.

The classic histological features of intensely PAS positive foamy macrophages, dilated lacteals with large lipid droplets are characteristic of WD.

Apart from histology and special stains, recently, it has been possible to detect the Whipple antigen by immunohistochemical analysis using a polyclonal rabbit antibody produced against a cultured strain of *T. whipplei* [245] (Figure 155.60). The antigen is a component of the bacterial cell wall. This is both a sensitive and specific method of detecting WD. Other tests consist of polymerase chain reaction (PCR) assays for 16S ribosomal RNA genes of *T. whipplei*, and electron microscopy. The bacterium of WD has also been successfully grown in human fibroblast cell line using shell-vial assays.

With electron microscopy, PAS stain and Whipple immunostain it is still possible to see retained bacterial products, months and even years after initiation of therapy despite clinical improvement. Thus, PCR may be a better tool to monitor treatment response as the bacterium has been shown to become undetectable shortly after initiation of antibiotic treatment.

**Other infectious agents**

Other infectious agent known to affect the small bowel include *Yersinia spp.*, which produces necrotizing granulomas and...
Nonsteroidal antiinflammatory drug associated injury

NSAIDs (nonsteroidal antiinflammatory drugs) are well-known to be associated with mucosal damage in the small intestine and may even lead to a peculiar form of strictures called “diaphragm disease” based on its macroscopic appearance [247–249]. The typical injury consists of ulcers which may lead to strictures. Unfortunately the histologic features of NSAID-associated ulcers are not specific although they are usually not associated with abundant chronic inflammation.

GVHD

Patients with GVHD present with secretory diarrhea, abdominal pain, and, at times, hemorrhage. There is a syndrome of upper GI GVHD, presenting clinically as anorexia, dyspepsia, food intolerance, nausea, and vomiting. These syndromes were first recognized in the early 1990s [46,250,251] and endoscopic criteria for recognizing the lesions of GVHD are now available [39]. Patients who have had bone marrow transplants are prone to many infectious causes of enteritis, but many develop upper tract GVHD. The original grading criteria were published by Snover [250] and are summarized as follows:

- Grade 1 – increased crypt apoptosis
- Grade 2 – apoptosis with crypt abscess
- Grade 3 – individual crypt necrosis
- Grade 4 – total denudation of areas of mucosa.

There criteria are simple to apply and correlate well with clinical findings. Unfortunately chronic GVHD results in non-specific features of lamina propria fibrosis and mucosal atrophy. When confronted with such biopsies, both active and chronic components should be graded. Comparison with prior biopsies may be helpful. Of note, a GVHD-like may be seen in small bowel and colon biopsies in response to CellCept® (Mycophenolate mofetil) [252,253]. This medication is widely used for maintenance immunosuppression in solid organ transplantation. Gastrointestinal toxicity, usually manifested as diarrhea, is its most common side effect. These effects have also been reported to be present in upper tract and colonic mucosal biopsies.

Common variable immunodeficiency

Washington and colleagues have reported common GI complaints in patients with common variable immunodeficiency (CVID) and related disorders. Daniels and colleagues documented small bowel biopsy findings in 39 small bowel samples from 19 patients with this condition. Features included a paucity of plasma cells (68%), prominent lymphoid aggregates (47%), increased apoptosis (21%), increased intraepithelial lymphocytes (IELs) (63%) with or without villous blunting (83% of those with IELs), and granulomas (11%). While these features may suggest celiac disease and/or Crohn’s disease, both diagnoses can usually be excluded because of the paucity of lamina propria plasma cells and the likelihood of harboring infectious agents (Giardia, Cryptosporidium, microsporidia). When Giardia is encountered in immunocompetent hosts there are typically fewer organisms present. Not all patients’ biopsies lack plasma cells so clinicopathologic correlation is important.

Malabsorption

Celiac disease

Celiac disease is a relatively common systemic autoimmune disorder induced by gluten proteins found in wheat, barley, and rye. Injury to the small intestine is the hallmark of disease, but manifestations are systemic. Sites of extraintestinal injury include but are not limited to the skin (classically with dermatitis herpetiformis), joints, and uterus such that clinical presentations can be subtle and not GI tract related.

When evaluating patients for celiac disease, it is worthwhile remembering that antigliadin tests are no longer recommended as they produce too many false positives. Presently, antitissue transglutaminase or antiendomysial tests are recommended [254]. These are IgA based tests in general so they yield false negative results in IgA deficient patients. IgG based tests are used in the authors setting.

It is best to evaluate biopsies from beyond the bulb (first portion) since these are less prone to injury from gastric contents. Several biopsies should be obtained since characteristic features may be patchy. Review of these is easiest in well-oriented samples.

There is a range of appearances in biopsies obtained from patients with celiac disease and the constellation of findings has been classified by Marsh [255], and further modified by Rostami and colleagues [256,257], and appears in Table 155.2. What is important about these grading schemes is that they provide a framework for recognizing celiac disease lesions that fall short of mucosal atrophy. Since these observers originally published their findings in the gastroenterology literature rather than pathology literature, many pathologists have remained unaware...
Table 155.2 Schemes for assessment of biopsies in patients with celiac disease.

<table>
<thead>
<tr>
<th>Lesion category</th>
<th>Marsh classification [255]</th>
<th>Rostami modification [256,257]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh 0</td>
<td>Preinfiltrative:</td>
<td>Same as original</td>
</tr>
<tr>
<td></td>
<td>• normal mucosal and villous architecture</td>
<td></td>
</tr>
<tr>
<td>Marsh I</td>
<td>Infiltrative:</td>
<td>Same as original</td>
</tr>
<tr>
<td></td>
<td>• normal mucosal and villous architecture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• prominent intraepithelial lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Marsh II</td>
<td>Hyperplastic:</td>
<td>Same as original</td>
</tr>
<tr>
<td></td>
<td>• same as “infiltrative” but also with enlarged crypts and increased crypt mitoses.</td>
<td></td>
</tr>
<tr>
<td>Marsh III</td>
<td>Destructive lesion:</td>
<td>A. Partial villous atrophy</td>
</tr>
<tr>
<td></td>
<td>• flat mucosa – complete loss of villi</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• lymphocyte infiltration</td>
<td>B. Subtotal villous atrophy</td>
</tr>
<tr>
<td></td>
<td>• enlarged hyperplastic crypts</td>
<td>C. Total villous atrophy</td>
</tr>
<tr>
<td>Marsh IV</td>
<td>Hypoplastic:</td>
<td>Same as original</td>
</tr>
<tr>
<td></td>
<td>• total villous atrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• normal intraepithelial lymphocyte count</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• believed to reflect severe malnutrition and be nonspecific</td>
<td></td>
</tr>
</tbody>
</table>

Figure 155.61 Celiac disease. The villi in this duodenal biopsy are wholly attenuated.

Figure 155.62 Celiac disease. Prominent intraepithelial lymphocytes are a key diagnostic feature.

of subtle findings that suggest celiac disease until recently [258,259], although such findings are by no means specific [260,261]. Of course one has to already know the patient has celiac disease before Marsh grading is relevant since many other conditions produce an identical picture to that termed “Marsh 2”. Essentially subtle or treated lesions of celiac disease display only intraepithelial lymphocytosis, similar in density or more prominent in the tips of the villi than the bases, where intraepithelial lymphocytes are physiologic. As lesions progress, the lamina propria becomes expanded with numerous lymphocytes and plasma cells, the villi become progressively attenuated with epithelial damage, and the crypts become hyperplastic (Figures 155.61, 155.62, 155.63). The cells accounting for the infiltrate are T cells, and there is extensive literature devoted to the phenotype of these T cells, most of which is of value only for research purposes.

Villous atrophy may be caused by a wide variety of disorders in addition to celiac disease and the related condition dermatitis herpetiformis. These include, cow’s milk protein intolerance (pediatric), giardiasis, peptic duodentis, Crohn’s disease, small bowel bacterial overgrowth (stasis and overgrowth usually of anaerobes), eosinophilic gastroenteritis, radiation enteritis, tropical sprue, severe malnutrition, lymphoma, GVHD, hypogammaglobulinemia/common variable immunodeficiency syndrome, and alpha chain disease. A rule of thumb in considering atrophic enteritis is that neutrophils and histiocytes are not a typical inflammatory constituent in celiac disease and their presence should prompt other considerations, particularly bacterial overgrowth (stasis changes) and Crohn’s disease. In reality, there are biopsies for which it is difficult to offer a precise etiology and in that situation a descriptive report is indicated together with a dialogue with the endoscopist.
There remains a troubling subset of cases that defies current medical management and has a presentation resembling celiac disease and these are sometimes termed “refractory sprue” [262–264]. Robert and colleagues reported ten cases of refractory sprue [265] and found that 5 of the 10 refractory patients ultimately developed collagenous sprue as a distinct histologic marker of refractory disease. Additional distinctive findings found in small bowel biopsies in the refractory group were subcryptal chronic inflammation (10 of 10), and marked mucosal thinning in three patients. Other nonspecific findings included acute inflammation and gastric metaplasia. One patient with collagenous sprue developed a B-cell lymphoma of the ileum, and in general collagenous sprue was associated with a poor prognosis. Two of five patients died whereas two others require total parenteral nutrition for survival. In other studies and in the authors experience, such cases may be clonal by gene rearrangement studies and related to T cell lymphomas but these cases are also heterogeneous and rare, so difficult to study well [266]. A diagnostic possibility to ponder when examining biopsies from patients with “refractory sprue” is autoimmune enteropathy, which is further discussed in the following sections.

Refractory sprue can be divided into types. In type 1, the intraepithelial lymphocytes mirror the type normally encountered in the small bowel epithelium whereas those in type 2 have an abnormal (clonal) intraepithelial lymphocyte immunophenotype:

- type 1 refractory sprue: CD3+, CD8+, no clonality on analysis of T cell receptor gene rearrangements
- type 2 refractory sprue: CD3+, loss of CD8, clonality on analysis of T cell receptor gene rearrangements.

Vega and colleagues have also described a patient with “atypical NK-cell proliferation of the GI tract in a patient with antigliadin antibodies but not celiac disease [267]. T cells in this patient’s GI tract expressed CD56, CD7, cytoplasmic CD3 (but not membranous CD3), and TIA-1 but not CD4, CD8, CD10, CD20, CD5, or EBV markers.” These observations were expanded by Mansoor and colleagues [268] in a series of eight patients with lesions resembling those of T cells lymphomas and termed “N-K cell enteropathy”. The patients presented with vague gastrointestinal symptoms and displayed endoscopic zones of superficial erosions, edema, and hemorrhage involving the stomach, duodenum, small bowel, and colon. Their biopsies demonstrated an atypical lymphoid infiltrate with an NK-cell phenotype (CD56(+)/TIA-1(+)/Granzyme B(+)/cCD3(+)), which displaced but did not invade the glandular epithelium. EBV studies were negative and T-cell receptor-γ gene rearrangement showed no evidence of a clonal process. Several of the patients had been diagnosed with lymphomas and treated aggressively but some were followed without treatment. These lesions mimic NK-/T-cell lymphomas on endoscopic biopsies (the clue was the lack of EBV virus). We suspect these lesions may fall within the spectrum of refractory sprue but this cannot be confirmed at this writing.

Lastly, it is worth remembering that olmesartan is associated with a striking celiac disease-like medication effect [269].

**IgA deficiency**

The incidence of IgA deficiency ranges from 1:400 to 1:3000 in healthy blood donors and most IgA deficient individuals are healthy but this condition is associated with protein manifestations [270]. It is believed that these people have a compensatory increase in secretory IgM. However, for the purposes of GI biopsy interpretation, disorders associated with IgA deficiency include giardiasis, nodular lymphoid hyperplasia, celiac disease (in around 2%), milk intolerance and inflammatory bowel disease. When reviewing biopsies from IgA deficient individuals (having serum levels less than 7 mg/dL), IgA-producing cells may be identified on immunohistochemistry but are usually reduced in number. It may be that, at least in some cases, the secretory (J chain) component is defective so that IgA-reactive cells are seen despite a lack of detectable serum IgA. However, since the number of IgA labeled plasma cells is variable in any population of healthy individuals, the disease can only be suggested by the pathologist when the associated disorders are detected.

**Tropical sprue and small bowel bacterial overgrowth**

Aside from infectious intestinal diseases with known etiology, there is a group of gastrointestinal disorders mainly affecting the small intestine of individuals predominantly living in and less often visiting or returning from underdeveloped regions, usually the tropics, and ranging from asymptomatic structural and/or functional abnormalities of the gastrointestinal mucosa (subclinical enteropathy) to a fully symptomatic condition.
highlighted by malabsorption of nutrients with associated nutritional deficiencies responsive to folate and broad spectrum antibiotic treatment (tropical sprue). In addition, tropical sprue has been associated with bacterial contamination of the small bowel. These patients have prolonged transit time through the small intestine, akin to that observed in obstruction [271] and evidence of bacterial overgrowth. The appearance of biopsies from these patients is very much like that in patients in Western countries having small bowel bacterial overgrowth. The findings are similar to those in celiac disease in terms of villous attenuation but with the addition of active inflammation and, at times, features of chronicity such as gastric mucin cell metaplasia and crypt distortion. Both conditions have overlapping features with upper tract Crohn’s disease. Small bowel bacterial overgrowth is relatively common and occurs when small bowel motility is altered and patients present with diarrhea [272,273]. This alteration may be the result of underlying medical conditions such as diabetes or scleroderma (which results in sclerosis of the bowel wall), or from surgery. In addition many patients with so-called irritable bowel syndrome are believed to have this condition. It is best diagnosed by small bowel aspirate and quantitative cultures and specific antibiotic therapy is determined by sensitivity testing of the cultured agent/s, which are generally anaerobes. The morphologic features in small bowel bacterial overgrowth range from normal to Crohn’s disease-like but usually do include a component of neutrophilic inflammation. The pathologist reviewing biopsies may be able to raise this possibility and suggest confirmation but it is difficult to diagnose in isolation from clinical findings.

**Autoimmune enteropathy**

This rare condition is characterized by: (1) small intestinal villous atrophy unresponsive to dietary restrictions; (2) unrelenting diarrhea; and (3) predisposition to autoimmune disease, as initially proposed by Unsworth and Walker–Smith. Though initially thought to affect newborns and young children, adult onset is well-documented in the literature. The pathophysiology is poorly-understood but a proposed mechanism involves loss of self-tolerance and a hypereactive immune system with inappropriate T-cell activation and cytotoxicity. Increased numbers of mucosal CD4+ and CD8+ T cells have been observed by some. Two variants of the disorder are described. The first, termed IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, is fatal, X-linked and characterized by polyendocrinopathy and various autoimmune conditions in association with severe, prolonged diarrhea. The second, termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) syndrome or APS-1 (autoimmune polyglandular syndrome 1) is autosomal recessive and affected patients suffer from autoimmune enteropathy in association with endocrine abnormalities (hypoparathyroidism, adrenocortical insufficiency, diabetes mellitus, thyroid disease), mucocutaneous candidiasis, and skin manifestations such as alopecia and vitiligo, and nail deformities.

The histologic appearance of autoimmune enteropathy varies considerably from case to case. Intestinal biopsies show a picture similar to celiac disease with total or partial villous atrophy, crypt hyperplasia, and expansion of the lamina propria by a lymphoplasmacytic infiltrate. Some cases display intact villous architecture. Active inflammation with or without crypt abscesses may or may not be present. Increased intraepithelial lymphocytes may be seen but often to a lesser degree than in celiac disease. Crypt apoptosis is striking in some cases. Goblet and/or Paneth cells may be absent. Cases lacking goblet cells and/or Paneth cells are easy to recognize as autoimmune enteropathy if the pathologist routinely assesses these components in biopsies whereas the diagnosis can only be listed as part of a differential diagnosis when, for example, prominent apoptosis is the most salient feature (Figure 155.64). The diagnosis should be considered when examining biopsies from adult patients labeled as having “refractory sprue” and from babies and children with intractable diarrhea. Treatment consists of nutritional support and immunosuppressive therapy. With treatment, some patients with absent goblet and Paneth cells regain them.

**Microvillus inclusion disease (microvillous inclusion disease)**

Microvillus inclusion disease is an uncommon congenital enteropathy, producing intractable secretory diarrhea in early infancy [274–281]. It is an inherited disease in an autosomal recessive genetic trait pattern. There are several synonyms used for this disease including Davidson’s disease [275], familial microvillus atrophy, congenital microvillus atrophy, intestinal microvillus dystrophy (a variant of microvillus inclusion disease). The outcome is typically poor, with most patients requiring small bowel transplantation. Rare cases have resolved.

Biopsies of duodenal mucosa show moderate villous blunting without active inflammatory reaction or intraepithelial lymphocytosis. The optimal specimen is a small intestinal biopsy.
in which duodenal biopsy is most commonly used. Rectal biopsy has been proposed as a simple and reliable method for early diagnosis although the findings may be subtle. Architecturally, diffuse intestinal villous atrophy with no inflammatory reaction is a characteristic feature. Due to increased crypt cell apoptosis, either crypt hypoplasia or hyperplasia can be found. Subtle histologic changes in the enterocytes are confined to the villous tips and distal villous lateral borders. Changes are difficult to discern at the base of the villus and in the crypt epithelium; indeed the enterocytes appear normal in these regions. Cytologically, a bubbly vacuolated appearance of the apical cytoplasm with extensive or patchy absence of the brush border is a specific sign for the diagnosis. Typical targetoid cytoplasmic inclusions are occasionally identified in the surface enterocytes.

Instead of a sharp linear brush border that stains with PAS or alkaline phosphatase histochemically, a bright apical cytoplasmic blush is present and is the most easily recognized changes of microvillus inclusion disease. Brush border biomarkers, such as carcinoembryonic antigen (CEA) and particularly CD10 [278], are also useful in the diagnosis of microvillus inclusion disease. CEA and CD10 stains demonstrate the characteristic apical cytoplasmic staining pattern in the enterocytes. Ultrastructurally, identification of apical microvillus inclusions in surface enterocytes in intestinal tract biopsies makes a definitive diagnosis. A variant of this condition (possibly an incomplete form) is called “tufting enteropathy” or “intestinal epithelial dysplasia” and adhesion molecule defects have been implicated [274,280,281].

**Colchicine toxicity**

Colchicine is an alkaloid with antimitotic ability used to treat a variety of medical conditions. Iacobuzio–Donahue and colleagues reported findings in 21 gastrointestinal mucosal biopsies from nine patients receiving oral colchicine therapy [126]. All patients had a history of gout. Four patients with chronic renal failure also had clinical evidence of colchicine toxicity, and the other five patients did not. Distinct morphologic changes, seen as metaphase mitoses, epithelial pseudostratification, and loss of polarity, were seen in biopsy material from four of four (100%) patients with clinical colchicine toxicity. Three of these four cases (75%) also contained abundant crypt apoptotic bodies. These morphologic features were best seen in the biopsies from duodenum (Figures 155.65 and 155.66) and gastric antrum, with relative sparing of the gastric body in the upper GI tract. The distinctive morphologic features were not seen in the five patients without clinical colchicine toxicity.

**Lymphangiectasia**

Primary intestinal lymphangiectasia is usually diagnosed before the age of 3 years. Most patients have growth retardation. Gastrointestinal complaints that vary in severity consist of diarrhea, vomiting, abdominal pain, and steatorrhea. If large segments of the gut are involved, secondary edema resulting from protein-losing enteropathy and malabsorption may occur. The edema is usually generalized, but asymmetric edema is not uncommon. Small biopsies taken in these patients may be nondiagnostic but they simply display multiple dilated lacteals, a finding easy for the pathologist to overlook without knowledge of an often dramatic CT appearance.

**Crohn’s disease**

The clinical features of Crohn’s disease are well-summarized elsewhere in this book. It is typically characterized by foci of glandular destruction, aphthous erosions, serpiginous ulcers as well as areas of transmural inflammation, fibrosis and sometimes granulomas. Because of its transmural nature, fissures, sinuses, and fistulas may occur. Mucosal biopsies, although superficial, can show features that are suggestive of Crohn’s disease (Figure 155.67). Discrete foci...
commonly caused by medications, particularly NSAID rather than Crohn’s disease and finding the features of chronicity is critical; medication induced injury is usually not associated with increased lamina propria inflammation, or pyloric metaplasia. Submucosal fibrosis can also be a sequellae of NSAID damage. Peyer’s patches are a normal component of the terminal ileum, particularly in young individuals, and should not be diagnosed as chronic inflammation. The mucosa over Peyer’s patches may be distorted with flattened villi due to underlying expansion of lymphoid nodules in nonspecific reactive hyperplasia. Yersiniosis can also result in prominent Peyer’s patches.

Behçet’s disease
Behçet’s disease is a systemic disorder consisting of oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test (an exaggerated response to a minor injury of skin) [264,282,283]
The gastrointestinal tract may be affected anywhere, where deep penetrating ulcers lacking specific histologic features are found, but the commonest sites are the terminal ileum and cecum. Establishing the diagnosis requires clinicopathologic correlation and surgical management is often required. Vascularitis is one of the hallmarks, particularly involving veins and can be seen on endoscopic biopsies (Figure 155.69).

Small intestinal findings in ulcerative colitis
Generally the small intestine is normal in patients with ulcerative colitis. However, a subset of patients who have severe pancolitis which extends a short distance into the ileum as well, and the imperfect term “backwash ileitis” has been applied. It is associated with pouch complications in some studies [284] but not others [285] and is believed to reflect the severity of the ulcerative colitis. “Backwash ileitis” is sometimes described as active chronic and sometimes as minimal active, and no real consensus exists. A group of patients with classic ulcerative colitis and severe confluent duodenitis has also been described.
PART 5 Diagnostic and therapeutic modalities in gastroenterology

Small bowel – polyps and neoplasms

Polyps (adenomas, Peutz-Jehgers polyp)

Adenomas

Small intestinal adenomas are usually found in the duodenum, and like their colon counterparts, have three major histologic types: tubular, tubulovillous, and villous. Adenomas in this site appear essentially the same as those in the colon. In patients with FAP, endocrine cells are often a prominent component. Most adenomas occur singly; the presence of multiple adenomas in the small intestine is unusual except in the context of FAP. The majority of FAP patients also develop upper gastrointestinal polyps. Those in the gastric antrum and duodenum are usually neoplastic.

Probably the biggest pitfall for pathologists in interpreting adenomas in the small bowel is the proclivity of reparative lesions to mimic them. When peptic duodenitis has a nodular configuration, it is easily confused with an adenoma. One clue is that peptic duodenitis often has surface gastric mucin cell metaplasia in the atypical focus and adenomas have their initiation point just beneath the surface epithelium [287], whereas reparative lesion have theirs at the base of the mucosa. Unfortunately, there are occasional cases in which it is not possible to distinguish adenomas from reparative processes and these should be designated “indefinite for dysplasia”. This distinction is important, particularly in the area of the ampulla; large ampullary adenomas often warrant pancreatic-duodenectomy based on their high likelihood of harboring an occult invasive carcinoma [288].

Although the ampulla is not usually biopsied since it may result in severe pancreatitis, when biopsies are undertaken for compelling reasons, interpretation is often a source of difficulty for pathologists since it normally has ampullary glands, with their features akin to biliary epithelium, interspersed with disorganized bundles of smooth muscle. When inflammation is a feature, great caution is advised.

When a neoplastic small bowel lesion manifests unusual features, it is important to consider that the process is a metastasis or extends directly from the pancreaticobiliary tree.

Peutz-Jehgers polyps

The WHO has defined Peutz-Jehgers (PJ) syndrome as an inherited cancer syndrome characterized by mucocutaneous melanin
pigmentation and hamartomatous intestinal polyposis preferentially affecting the small intestine [289]. The diagnostic criteria include: (1) three or more histologically confirmed PJ polyps; or (2) any number of PJ polyps in an individual with this syndrome; or (3) appropriate melanin pigmentation in an individual with affected relatives; or (4) any number of polyps with the appropriate mucocutaneous pigmentation. However, our data suggest that finding even one such polyp in the small bowel may be sufficient to establish the diagnosis [290]. In their classical appearance, PJ polyps are easy to recognize on endoscopic biopsies. They are hamartomas and display the type of mucosa typical for the site in which they are found. Thus, in the stomach they have gastric mucosa, and in the small bowel they have small intestinal mucosa. Difficulties arise when biopsies are superficial or when ulceration distorts them. PJ polyps in the small intestine are far more likely than those from the stomach to display the classic arborizing smooth muscle cores from which the mucosa leaves out and must always be assessed for dysplasia (Figure 155.73).

Carcinoma

Adenocarcinomas are the most common malignancies of the small intestine (30%–50% of small bowel malignancies). However, primary adenocarcinomas are still rare accounting for only 2% of gastrointestinal (GI tract) tumors for 1% of GI tract cancer deaths [291]. They present in older adults (median 67 years), with a male predominance and are more common in African Americans than Caucasians.

The majority are sporadic and share with sporadic colorectal adenocarcinomas both clinical risk factors and development from adenomatous polyps. The remaining minority of cases arise in the background of certain predisposing conditions including several of the polyposis syndromes (primarily FAP, but also Lynch syndrome/hereditary nonpolyposis colon carcinoma syndrome [HNPCC], Peutz-Jeghers’ syndrome, and juvenile polyposis syndrome), Crohn’s disease, gluten-sensitive enteropathy (GSE) [292], ileostomy, and ileal conduits among others. Most adenocarcinomas are moderately differentiated, and one third are poorly differentiated. Degree of differentiation and special histologic subsets (mucinous, adenosquamous) have little bearing on prognosis and, as such, we mention them only as comments. The majority of small bowel adenocarcinomas have invaded through the bowel wall by the time of diagnosis.

Residual adenomatous epithelium is found with the majority of resected proximal tumors (those likely to be biopsied prior to resection), but often cannot be demonstrated in large distal small intestinal adenocarcinomas, presumably due to tumor overgrowth. Adenomatous epithelium can be mimicked by tumors metastatic to the GI mucosa. The main differential diagnostic consideration is metastatic disease, as the small intestine is the most common GI site for metastatic disease. Features favoring a metastatic tumor include the presence of multiple lesions, the absence of a precursor adenoma, a histologic appearance of tumor being “bottom heavy” or encroaching from below, and lack of ulceration. Immunohistochemical studies are also helpful in most circumstances. Common metastatic lesions include colonic adenocarcinoma, melanoma, and breast and gynecologic malignancies. Endometriosis is relatively common in the colon, but also can be seen in the small intestine and mimic metastatic adenocarcinoma.

Lymphomas

The GI tract houses more lymphoid tissue than the remainder of combined anatomic sites so it is not surprising that many lymphoid lesions are found there. In fact, the GI tract is most common extranodal site of non-Hodgkin’s lymphomas (NHLs). Secondary disease is common, especially in patients with advanced disease. Primary small intestinal lymphomas, in contrast to gastric lymphomas, are uncommon in the Western world, but still compose 30%–50% of malignant tumors at this site. Primary GI tract lymphomas are defined as an extranodal lymphoma arising in the small bowel with the bulk of disease localized to this site and with the primary clinical manifestations and subsequent therapy related to this site. Lymphomas with a predilection for the small intestine include diffuse large B-cell, followed by MALT (usual and immunoproliferative small intestinal disease [IPSID]), secondary involvement by low-grade lymphomas (primarily mantle cell lymphoma and rarely follicular lymphoma) and enteropathy-like T-cell lymphoma. There is recent evidence of rare follicular lymphomas primarily involving the duodenum. Hodgkin’s disease can involve the GI tract primarily or secondarily but this is an exceedingly rare event [293].

Marginal zone B-cell (MALT) lymphoma

Lymphomas of mucosa-associated lymphoid tissue (MALT) are the most frequent primary lymphomas of the small intestine in the Western world but are much less frequent than gastric
MALT lymphoma. There is a unique form of MALT lymphoma seen in Mediterranean areas and the Middle East referred to as IPSID which includes a spectrum of diseases including α heavy chain disease.

Small intestinal MALT-type lymphoma typically occurs in patients over the age of 50, with a slight male predominance. It is an indolent lymphoma; disease is often localized at diagnosis and may include mesenteric nodal involvement but typically no systemic spread. Long-term disease-free survival and cure are common. Unlike their gastric counterparts and IPSID, small intestinal MALT lymphomas have no clear infectious etiologic associations. Aggressive diffuse large B-cell lymphomas also develop in the intestine both as de novo lesions and through transformation from MALT lymphoma.

Small intestinal MALT lymphomas typically appear as ulcerated, exophytic or annular mass lesions but rarely as small polyps. Deep mural invasion is typical although disease may be confined to the mucosa. The histology of small bowel MALT lymphoma is similar to that of Gastric MALT lymphoma except lymphoepithelial lesions often are less prominent. The lesion typically progresses from an infiltrate between preexisting lymphoid follicles to one in which neoplastic cells erode and eventually over-run the lymphoid follicles resulting in a vague nodularity, or a completely diffuse infiltrate is composed of marginal zone B-cells that have a variable appearance even within the same tumor. They are intermediate size, with irregular nuclei and a rim of variable amounts of pale cytoplasm giving them an overall appearance that ranges from a mature B lymphocyte to a monocytoid appearance. Plasma cell differentiation is not uncommon and may be striking. The presence of moderate nuclear atypia, Dutcher bodies and prominent lymphoepithelial lesions characterized by clusters of neoplastic cells infiltrating and destroying glands are features highly suggestive of lymphoma.

The presence of a large-cell component may represent a transformation of a MALT lymphoma but criteria for diagnosing transformation to large-cell lymphoma are not well defined. When a large-cell component is prominent with clusters and sheets of large-cells, a diagnosis of a large-cell transformation or “composite tumor” has been suggested. When only focal large-cells are present it should be noted. If the tumor is composed exclusively of large-cells, a diagnosis of extranodal diffuse large B-cell lymphoma should be made.

Immunohistochemistry is very useful in the diagnosis of MALT lymphomas; the labeling pattern is CD20+, CD10−, and CD5−. Co-expression of CD43 in CD20 reactive cells is a helpful finding when present but is only seen in about half of cases. The lesional cells express surface and to a lesser extent cytoplasmic immunoglobulin (usually IgM, or IgA, rarely IgG) and show light chain restriction. Cytokeratin antibodies may highlight lymphoepithelial lesions and follicular dendritic cell markers (CD21, CD23 and CD35) help demonstrate the underlying follicular dendritic cell networks in those cases in which the lymphoid follicles have been obliterated by lymphoma.

Ki-67 labeling index is low and can be useful to distinguishing from large-cell lymphoma.

**Follicular lymphoma**

Follicular lymphomas in the small bowel can be encountered as an incidental finding. Duodenal disease often is incidentally found during upper endoscopy for an unrelated condition in an otherwise well patient.

At low magnification, exaggerated lymphoid follicles are noted and the apparent germinal centers appear more monotonous and without typical tingible body macrophages (Figure 155.74).

**Immunoproliferative small intestinal disease**

IPSID (α heavy chain disease, Mediterranean lymphoma, and diffuse small intestinal lymphoma) is a special form of MALT lymphoma restricted to a limited geographic distribution, which is characterized by synthesis of α heavy chain immunoglobulin.

IPSID is generally a diffuse infiltrating lesion; initially the mucosa may appear normal then develop a cobblestone appearance and eventually may form lymphomatous masses. Mesenteric lymph node involvement happens early in the course. The primary site of involvement is the proximal small intestine, but any part of, or the entire small intestine may be affected. The stomach and colon can also be involved.

IPSID demonstrates a histologic spectrum ranging from low to high-grade histology, sub-classified into stages A–C. All stages exhibit some features typical of other MALT lymphomas but usually with more striking plasma cell differentiation.

Stage A is characterized by a lymphoplasmacytic infiltrate with features of a typical MALT lymphoma (reactive follicles with parafollicular clusters of clear cells and lymphoepithelial lesions) which is confined to the mucosa, and expands the lamina propria causing broad villi, but may involve mesenteric
lymph nodes. In stage B disease, the infiltrate becomes nodular, goes beyond the mucosa into the submucosa and has mild cytologic atypia. The macroscopic appearance at this stage is typically abnormal with thickened mucosal folds. Neoplastic cells may completely replace the follicle making distinction from a follicular lymphoma difficult. Stage C is characterized by the presence of large masses and transformation to large-cell lymphoma with numerous centroblasts and immunoblasts. The plasmacytoid differentiation is still evident but there is marked cell atypia including Reed–Sternberg cells. Mitotic activity is increased.

The lymphoma cells are CD20+, CD5−, CD10−, and CD23−. Alpha immunoglobulin heavy chains can be demonstrated in the cytoplasm of the infiltrating plasma cells, centrocytes and transformed blast cells.

The differential diagnostic considerations depend on the stage of IPSID. Early disease (Stage A) may have a similar appearance to gluten-sensitivity enteritis (GSE). Unlike IPSID, GSE has prominent intraepithelial lymphocytes, true villous blunting, and crypt hyperplasia and clinically GSE is usually seen in northern Europeans, and responds to a gluten-free diet. Intestinal T-cell lymphoma, while diffuse like IPSID, infiltrates the surface epithelium and is clearly defined by IHC (CD3+, CD20−).

The nodular lesions of Stage B disease require distinction from reactive follicular hyperplasia, and mantle cell and follicular lymphoma. Reactive follicular hyperplasia is unusual in the proximal small bowel and lacks prominent lymphoepithelial lesions and the typical MALT type neoplastic cell of IPSID with pale/clear cytoplasm. Compared with other low-grade lymphomas, IPSID demonstrates monocytoid cells as well as plasmacytoid differentiation, and lymphoepithelial lesions and lacks the monotonous appearance of mantle cell lymphoma as well as the cleaved cells of follicular lymphoma. Immunohistochemical staining is very helpful in separating IPSID from the other low-grade lymphomas as IPSID is positive for α heavy chain and CD5−, CD10−, and CD23−.

The differential diagnostic considerations in patients with Stage C disease include other high-grade malignancy, especially diffuse large B-cell lymphoma, which can be distinguished by the presence of residual MALT lymphoma with characteristic features and α heavy chain staining.

**Mantle cell lymphoma**

Mantle cell lymphoma (MCL) is a disease of older adults (mean age 55 years) with a male predominance (at least 2:1). It typically is a nodal based disease but extranodal disease is common, particularly in the spleen and bone marrow. GI tract involvement is found in about a third of MCL patients. Any part of the GI tract can be involved, but the ileum is favored.

When MCL involves the GI tract nearly all cases (~90%) have both distal small bowel and colon involvement. Involvement of the stomach and duodenum are also very common, seen in about half of patients [294].

The lymphoma cells are small to medium sized with scant cytoplasm; the nuclei have irregular outlines and indistinct nucleoli. Large transformed cells and proliferation centers are not typically present giving MCL a much more monotonous appearance than other low-grade lymphomas. Mitotic figures are easily identified. The most common architectural pattern is diffuse; however both a nodular pattern and true mantle zone pattern can also be observed. Reactive germinal centers may be intermixed with and compressed by the lymphoma. While displacement and/or obliteration of the glands may also be evident, lymphoepithelial lesions characteristic of MALT type lymphomas are absent.

The tumor cells are mature B-cells that express both CD19 and CD20, and aberrantly express CD5 and CD43. They lack CD10, and CD23. Cyclin D-1 (BCL-1) is virtually always present. Surface light chains are present (usually IgM or IgD) and are typically lambda restricted.

**T-cell lymphomas**

Intestinal T-cell lymphomas are far less common than those of B-cell origin. The majority of T-cell primary GI lymphomas occur in the setting of gluten sensitive enteropathy (GSE) and are specifically referred to as “enteropathy-type T-cell lymphoma” (ETL). ETL is rare (~5% of all GI tract lymphomas). Refractory GSE and particularly ulcerative enteritis (jujenitis) probably represent the first step toward ETL, although not all cases appear to progress to ETL [264]. The prognosis is dismal with a median survival of only 3 months and 5-year survival rates of approximately 10%.

ETL occurs most commonly in the jejunum, alone or in combination with other sites in the GI tract. The affected bowel segment is often dilated and edematous with large circumferential ulcers ulcerated plaques and strictures with intervening areas of normal mucosa. Bulky exophytic or infiltrating masses are not typical but may be seen on occasion. Mesenteric lymph node involvement is common.

The histologic appearance of ETL is quite variable both between individuals and between different sites in the same patient. Three basic types can be discerned, but transition between morphologies in the same patient is common. The most common histologic pattern is that of an infiltrate of pleomorphic medium to large cells followed by an anaplastic type with marked pleomorphism, both of which are associated with fibrosis and admixed inflammatory cells. The third type is composed of monomorphic small to medium sized cells lacking background inflammation and fibrosis. The pleomorphic medium to large-cell type is the most frequent morphology seen and is characterized by irregular nuclei with small nucleoli and moderate amounts of often pale cytoplasm. All the subtypes are associated with destruction of the overlying epithelium by the lymphoma cells. The areas of epithelium most affected are the upper and intermediate villous regions, or in the presence of villous atrophy, the upper aspect of the crypts. In the majority of cases, endoscopically normal background mucosa shows
changes of GSE (intraepithelial lymphocytosis, villous blunting, and crypt hyperplasia).

Most cases are CD3+, CD4−, CD8−, CD7+, CD5−, CD56−, and express cytotoxic granule associated protein TIA-1 often with granzyme B. CD56 has been used to describe two variants of ETL, type A CD56− and type B CD56+ (and CD8+). The immunohistochemical labeling pattern of ETL correlates to some extent with the histologic pattern. Both the medium to large pleomorphic and the anaplastic variants of ETL are usually type A (CD56−) with CD30 positive, but are always ALK1 negative. Most of the type B (CD56+) lymphomas are the small to medium-sized variant.

**Well differentiated neuroendocrine (carcinoid) tumors of small bowel**

Well-differentiated neuroendocrine tumors (WDNTs, carcinoid tumors) of the small intestine account for about one third of small intestine neoplasms. They seem to be over-represented in African-Americans [295]. Small intestinal WDNTs derive from two separate embryonic divisions of the alimentary tract, the foregut (duodenum), and the midgut (jejunum and ileum). These different origins correlate with distinct neuroendocrine differentiation and with the clinical behavior of these tumors.

Duodenal WDNTs are the second most common tumor in that site; the first is adenocarcinomas. The former represents approximately 20% of GI tract WDNTs [296]. Overall, duodenal WDNTs are more common in men (the male-to-female ratio is 1.5:1), with a median age of about 60 years. Two-thirds of duodenal WDNTs are gastrinomas (G-cell tumors); the remaining third are mostly somatostatinomas (D-cell tumors), with a small percentage of undefined type. Only one third of gastrinomas is functional and causes Zollinger–Ellison syndrome (ZES). These duodenal tumors account for half of ZES cases; the remainder are caused by pancreatic endocrine tumors. One third of somatostatinomas are associated with von Recklinghausen disease (NF1). The full somatostatinoma syndrome (i.e., diabetes mellitus, diarrhea, and cholelithiasis), associated with pancreatic islet cell tumors, virtually never occurs with these intestinal tumors, and proximal small intestinal WDNTs almost never produce the carcinoid syndrome. Functional gastrinomas and somatostatinomas present in slightly younger patients than nonfunctional gastrinomas and somatostatinomas, and are slightly more common in females. Nonfunctional gastrinomas are usually located in the bulb, while their functional counterparts are found equally in all parts of the duodenum. A subset of the former has been associated with gastric *H. pylori* infection and long-term use of PPIs. In this setting the tumors are small G-cell tumors (mean 5.4 mm), located in the bulb mucosa and submucosa, demonstrate an insular pattern on histologic exam, and behave indolently. Some cases demonstrate G-cell hyperplasia in the nonneoplastic mucosa [297]. Somatostatinomas typically affect the periampullary region [298].

The few reported cases of high-grade neuroendocrine tumors (small-cell carcinomas) have been seen exclusively in men aged about 50–80 years; they were typically in the periampullary region and had a dismal prognosis. Brenner and colleagues retrospectively studied 64 cases of GI tract small-cell carcinomas and found that only 3.1% of these arose in the small bowel; the most common primary sites being colon (39%) and esophagus (30%) [299].

Distal small intestinal WDNTs primarily involve the ileum, less commonly the jejunum [300], and rarely in association with Meckel diverticula. They account for one fifth of GI tract neuroendocrine tumors and tend to be enterochromaffin cell (EC cell), serotonin-producing WDNTs. The median age of diagnosis is about 60 years and there is no particular sex predilection. The carcinoid syndrome (e.g., watery diarrhea, flushing, and endocardial fibrosis) is seen in 5% to 7% of cases, and jejunoileal WDNTs account for the majority of carcinoid syndrome cases overall. Nearly one third of patients diagnosed with a small intestinal WDNT have a synchronous or metachronous carcinoma (e.g., colon, stomach, lung, or breast).

Duodenal tumors can be readily diagnosed by endoscopic biopsy. The location of jejunoileal tumors makes diagnosis more problematic as they often are not amenable to endoscopy/colonoscopy, and conventional imaging techniques (computed tomography [CT] and barium contrast studies) are not particularly sensitive. In these circumstances, radiolabeled somatostatin analogues (octreotide and lanreotide) used in scintigraphy studies have been proven as sensitive detection methods of both primary and metastatic lesions.

Duodenal WDNTs are typically small polypoid lesions that generally measure <2 cm. They are submucosally based lesions with an overlying mucosa that may be focally ulcerated. A focal, subtle mucosal component may be identified on endoscopic biopsy within the lamina propria. Infiltrative larger tumors can occur but are infrequent. Gastrinomas tend to be smaller than somatostatinomas, and a minority (15%) are multicentric.

In contrast, jejunoileal WDNTs are twice as likely to be multicentric (30%), tend to be large (>2 cm) and often are locally advanced. In addition, they occur with deep bowel wall and mesenteric tumor involvement and cause significant mesenteric fibrosis, subsequent obstruction, and kinking of the bowel. Frank intestinal ischemia may also be seen due to tumor-induced angiopathy. Like duodenal WDNTs, jejunoileal tumors are typically centered in the deep mucosa or submucosa, and the overlying mucosa is typically intact or only slightly eroded.

When referring to jejunoileal WDNTs, the distinction between a benign or malignant WDNT is based upon the presence or absence of metastasis, rather than histology alone. Even clinically malignant tumors show little or no cellular pleomorphism, hyperchromasia, or increased mitotic activity. A WHO grading system is currently in use for neuroendocrine tumors of the stomach, pancreas, and duodenum appears previously in this chapter in the section on gastric neuroendocrine tumors.

Grade 3 tumors are high-grade neuroendocrine carcinomas (large-cell or small-cell types) and are characterized by >20 mitoses /10 HPFs or >20% Ki-67 index.
Survival is significantly poorer for patients with grade 3 tumors compared with those with grade 1 and grade 2 neoplasms. Similarly, survival for patients with grade 2 tumors is worse than for those with grade 1 neoplasms [301].

WDNTs, are characterized by a monotonous proliferation of small, bland, polygonal cells with moderate amounts of cytoplasm. They also have round, regular nuclei with "salt and pepper" chromatin. Pleomorphism and significant mitotic activity are conspicuously uncommon. Morphologic features of the cells do not differ by cell of origin (immunohistochemistry is required for this distinction). WDNTs demonstrate variable architectural growth patterns. These do not have prognostic significance but may be characteristic of certain WDNTs subtypes. The main architectural patterns are insular or nested (type A), trabecular (type B), and acinar (type C). These patterns often overlap and multiple patterns are typically seen within a single tumor. Small intestinal WDNTs are generally submucosal (based just below the mucosa); they typically are not well circumscribed, and tumor cells frequently extend in small groups into the mucosa and into the bowel wall.

Duodenal G-cell tumors typically can manifest a variety of architectural growth patterns, while somatostatinomas often have characteristic features of prominent acinar growth pattern with frequent intraluminal psammoma bodies. Jejunoileal WDNTs, like G-cell tumors, do not display any consistent characteristic growth patterns. They typically exhibit prominent nested growth, with more trabecular and acinar growth peripherally. These tumors are often larger, extend deeply into the bowel wall, and can be associated with significant fibrosis.

Although WDNTs tumors can show immunohistochemical evidence of multiple hormone production, this information is typically not clinically significant. The vast majority of small intestinal WDNTs are positive for chromogranin and synaptophysin, and these markers are useful in confirming the diagnosis of WDNTs. Specific cell types (G cells, etc.) can be identified by immunohistochemical labeling, but the utility of this is limited because functional status correlates poorly with immunohistochemistry.

Duodenal WDNTs are generally indolent (overall 4% mortality); however, two-thirds of somatostatinomas and one half of functional gastrinomas behave aggressively. Poor outcome in duodenal tumors is best predicted by invasion beyond the submucosa and lymph node, or distant metastases. Jejunoileal WDNTs have a worse prognosis than those of the duodenum, with a 20% mortality rate. Survival has been negatively correlated with distant metastases (liver), tumor multiplicity, mitotic rate, invasion beyond submucosa, and female gender. Pathologic features associated with outcome are size, depth of invasion beyond submucosa, mitotic activity, and lymph node involvement.

Both low and high-grade neuroendocrine tumors in the small bowel sometimes arise in association with typical adenomas.

Mesenchymal tumors
Gastrointestinal stromal tumors of the small intestine
Overall, GISTs of the small bowel should be regarded with more concern than those in the stomach, which more often behave in a benign than malignant fashion [302,303]. They are not typically diagnosed on biopsies.

Gangliocytic paraganglioma
These are rare tumors, the vast majority of which are found in the duodenum in adult patients (average age, about 54 years [304–309]). The typical presentation involves abdominal pain, gastric outlet obstruction, or bleeding. There are isolated reports of an association with neurofibromatosis, but most cases are sporadic. These lesions typically have their epicenter in the submucosa with minor extensions into the mucosa which are occasionally biopsied. Excised tumors are 3–4 cm with a soft yellowish cut surface. They have infiltrative borders.

These tumors display a histologic constellation of three cell types: (1) spindle cells with the appearance of nerve sheath cells; (2) ganglion-like cells; and (3) epithelioid cells arranged in nests ("endocrine" pattern), trabeculae or papillary structures. The proportion of the cell types is variable and hence these lesions are prone to causing diagnostic problems.

On immunohistochemistry, the tumors are reactive with S100 protein in spindle and "supporting/sustentacular" cells, synaptophysin in ganglion-like cells, and neuron specific enolase staining in all three cell types [304,307]. About half of cases display keratin in the epithelioid cells. A variety of hormones can be demonstrated in various fractions of gangliocytic paragangliomas, including somatostatin, human pancreatic polypeptide, serotonin, gastrin, glucagon, insulin, and vasoactive intestinal peptide.

In spindle cell predominate lesions, the differential diagnosis is with GIST and nerve sheath tumors – the S100 protein positivity excludes GIST, finding the admixture of other cell types excludes nerve sheath tumors. Epithelioid lesions are distinguished from carcinoid tumors and carcinomas again by the admixture of the other cell types.

Gangliocytic paragangliomas are benign in the majority of cases. There are rare reports of regional metastases [305,306] but not of tumor-associated deaths.

Colon
Nonneoplastic conditions
Normal histology in the colon reflects function of the specific site. Liquid stool from the small intestine enters the cecum and water is progressively absorbed such that it has the consistency of feces by the time it has reached the descending colon. The colonic mucosa produces abundant mucus that lubricates the surface and facilitates the passage of fecal material. The differences in the normal histology of the right and left colonic mucosa reflect these functions of absorption and lubrication. In
the crypts of the right and transverse colon, absorptive cells predominate, although the larger goblet cells are more conspicuous. The lamina propria in these proximal segments of the colon is more cellular than that of the distal colon and rectum, and includes abundant plasma cells (involving the full thickness of the mucosa), lymphocytes and eosinophils. Paneth cells may be found in the cecum and right colon. In contrast, goblet cells increase sharply in number, and absorptive cells are fewer in the left colon and rectum. The lamina propria is much less cellular, with fewer eosinophils. Plasma cells are present only beneath the surface epithelium more distally.

Lymphoid aggregates are normal and prominent intraepithelial lymphocytes are normally found over lymphoid aggregates. Macrophages are normally present, and play a role in the processing and presentation of antigens. They aggregate in the superficial lamina propria, where they phagocytose cellular debris from normal apoptosis of surface epithelial cells. Surface apoptosis is more prominent in the left colon and rectum than in the proximal colon.

Although eosinophils are present in the lamina propria of nearly all right colonic biopsies, their numbers vary greatly, particularly between geographic regions, being generally more numerous in warmer areas in the US [310]. Paneth cells are abnormal outside of the right colon; their presence in the left colon is metaplastic, usually in response to chronic inflammation or injury.

**Effects of bowel preparation and other artifacts**

Bowel preparation for sigmoidoscopy and colonoscopy may induce a number of mucosal injuries that must be recognized to avoid misinterpretation. Hypertonic enemas, generally used before sigmoidoscopy, may injure the mucosal surface, resulting in flattened or absent surface epithelium, loss of epithelial mucin, or slight neutrophilic inflammation. The lamina propria may be edematous or hemorrhagic [311].

The two most commonly used preparations for full colonoscopy are sodium phosphate and balanced electrolyte solutions containing polyethylene glycol (PEG). Sodium phosphate bowel preparations (e.g., Fleet enema) are preferred by many patients, and thus are currently the most common bowel preparation in adult patients. Oral sodium phosphate preparations are strong osmotic laxatives that induce a number of endoscopic and histologic changes. The most common endoscopic change is the presence of what appear to be small aphthous lesions: small foci of pale mucosa surrounded by erythematous rings that look like shallow erosions (an aphth is a “spot”). These aphthous-like lesions have been described in up to a quarter of patients after sodium phosphate bowel preparation. Histologically these are usually large lymphoid aggregates, although some authors have described edema, hemorrhage or acute inflammation [312–314]. The lesions disappear when colonoscopy is repeated with an alternate bowel preparation, and so are clinically unimportant. Oral sodium phosphate bowel preparation is also believed to induce foci of neutrophilic cryptitis (focal active colitis [FAC]) in about 3% of patients. Whereas apoptosis is normal in the surface epithelium, scattered apoptotic bodies at the bases of crypts are found after sodium phosphate bowel preparation. These apoptotic bodies have been counted at about 1 per 10 well-oriented crypts [314].

**Other endoscopic and biopsy-related artifacts**

During the course of colonoscopy, gas is induced to insufflate the bowel for better visualization of the mucosa. Small amounts of this gas may infiltrate tissue and appear as small clear bubble-like spaces in the mucosa or superficial submucosa, often in or near lymphoid aggregates. Because these spaces resemble adiopcytes; this phenomenon has been termed “pseudolipomatosis” [315]. Biopsy forceps can also induce tissue trauma, resulting in mucosal hemorrhage, crushing of epithelium that may resemble dysplasia, and an artifact in which the epithelium is squeezed entirely out of crypts leaving empty crypts. This squeeze artifact is common on the edges of mucosal biopsies and usually readily recognized. However, when a large area is involved, it may be mistaken for ischemic injury.

**Focal active colitis**

FAC is the term used to describe focal neutrophilic infiltration of colonic crypts. It may consist of one focus in a single biopsy, or multiple foci. Since focal inflammation is a feature of Crohn’s disease, studies of FAC have examined whether it antedates subsequent development/diagnosis of Crohn’s disease. In two studies [316,317] of adult patients with FAC in colon biopsies, only a very few developed Crohn’s disease. Many seemed to have a clinical course that resembled infectious diarrhea, although this may have had no relationship to the FAC and may simply have reflected a common indication for endoscopy. However, in group of pediatric patients with FAC, a higher proportion (27.6%) went on to develop Crohn’s disease [152]. In Greenson’s studies, no adult patient with FAC developed Crohn’s disease and the only endoscopic abnormalities were aphthous or aphthous-like ulcers, possibly artifacts of bowel preparation. In contrast, in the pediatric group, 2 of 17 patients with normal colonoscopy developed Crohn’s disease, compared with 6 of 11 with abnormal colonoscopy. Thus, it seems that in adult patients without history or endoscopic features suggestive of Crohn’s disease, FAC can be safely ignored whereas it should probably be followed when it is found in biopsies from pediatric patients.

**Lamina propria macrophages**

Macrophages are a normal constituent of the colonic lamina propria, where they serve roles in antigen processing and phagocytosis of surface epithelial cells that have undergone apoptosis. CD68 immunostaining highlights a gradient in their distribution, with more macrophages in the upper lamina propria, fewer deeper [318]. Pigmented macrophages are referred to as melanosis coli and those containing mucin as muciphages.
When muciphages are present in otherwise normal biopsies, the usual gradient is reversed, as they tend to accumulate in the lower part of the mucosa. Muciphage aggregates are found associated with crypt rupture from any cause, and so are seen in many settings [318]. Ultrastructural study supports degenerated epithelial cells as the source of the mucin [319]. Muciphages must be distinguished from the macrophages of Whipple’s disease, mycobacterial infection, and from carcinoma but it is not usually necessary to perform a full workup since aggregates of muciphages are very common in colorectal mucosa, present in 40% of otherwise normal rectal biopsies [320]. They are presumed to reflect occult and clinically unimportant epithelial injury, such as trauma related to stool passage, or subclinical infection.

The term melanosis coli is a misnomer. The brown pigment that accumulates in lamina propria macrophages in this condition is lipofuscin, not melanin (Figure 155.75). Although it is most often seen in right colonic biopsies, it can be found throughout the colorectum, appendix and terminal ileum. It is extremely common and detected in the majority of elderly individuals. In one study of 200 patients, of men and women in the age group of 20 to 54 years, 32% and 44% were affected, and above the age of 75 years, 76% and 67%, respectively [321]. Lipofuscin accumulates by phagocytosis of apoptotic epithelial cells [322–324]. There is a strong association with anthraquinone and other laxatives because they induce apoptosis [325–327], but melanosis may be a result of any process associated with apoptosis, such as nonsteroidal antiinflammatory drug (NSAID) use. Many patients with melanosis have not used laxatives, including patients with ulcerative colitis and Crohn’s colitis [328].

**Ulcerative colitis**

As discussed in detail elsewhere in this text, ulcerative colitis is a chronic crypt destructive inflammatory process of unknown cause characterized by a predominantly mucosal based disease and clinically associated with exacerbations and remissions of bloody diarrhea. The initial presentation may be indolent in onset or may be severe and acute presenting with toxic hemorrhagic colitis. In children, initial biopsies may be nondiagnostic since they are likely to be brought to medical attention before histologic features of chronicity are evident (whereas adults wait until they have been symptomatic for months to years before seeking attention) [152,329,330].

The gross endoscopic appearance of ulcerative colitis varies with the degree of activity, duration of disease and response to therapy. It is characterized by diffuse disease with rectal involvement extending proximally. In the more active phases the mucosa is typically erythematous, bloody and friable with a granular appearance. Quiescent disease may appear granular with areas of punctuate erythema. Pseudopolyps (mucosal remnants) and inflammatory polyps may be seen in active disease and postinflammatory polyps in active or quiescent disease. In all cases, the normal submucosal vascular network is lost and is an important clue to the endoscopist indicating chronic colitis. In patients who have had repeated bouts of colitis, the normal haustral folds may be absent. The transition between normal and abnormal mucosa is generally gradual but may be abrupt. Except for the occasional presence of focal cecal or periappendiceal involvement as “skip areas”, there is no loss of disease continuity, and no skip lesions are seen in ulcerative colitis.

On biopsies, crypt architectural distortion and increased mucosal chronic inflammation are the two characteristic histological findings (Figures 155.76, 155.77, and 155.78). Neutrophils, the hallmark of active disease, are located within crypt epithelium (cryptitis) and crypt lumina (crypt abscesses) with fewer within the lamina propria around the crypts. Architectural distortion results from prior mucosal destruction and imperfect repair leading to decreased numbers of crypts and branched, malformed regenerated crypts (“crypt destructive...
Ulcerative colitis must be distinguished from infectious colitis, medication induced colitis, ischemic colitis and Crohn's disease. Longstanding infectious colitis may display the features of ulcerative colitis including increased chronic inflammation, neutrophils, basal plasmacytosis, and diffuse colonic involvement. A predominance of neutrophils within the lamina propria rather than within the crypt epithelium and overall architectural preservation supports infectious over ulcerative colitis. The initial episode of ulcerative colitis may histologically appear similar to infectious colitis, therefore infectious etiologies should be excluded prior to confirming a diagnosis of ulcerative colitis. Medications, particularly nonsteroidal antiinflammatory drugs (NSAIDs) may present with focal acute colitis or ulcers throughout the colon. Histologically, NSAID ulcers are typically abrupt with no significant inflammation in the adjacent mucosa and minimal chronic inflammation. Chronic ischemic colitis can be mistaken for ulcerative colitis particularly because ischemia due to low vascular flow often affects the left colon and because it may be intermittent. As such, abrupt episodes of ischemia can result in mucosal ulceration which, following reperfusion, may become inflamed and show all of the architectural features of ulcerative colitis. Features that support ischemia include the age of the patient, location, involvement of the muscularis propria, and importantly, the lack of neutrophils destroying crypt epithelium. Crohn's lesions characterized by crypt destruction are typically patchy, with areas that appear involved and uninvolved within single biopsies and among different fragments from one area. Crohn's colitis typically lacks the diffuse crypt destruction characteristic of ulcerative colitis.

Once a patient is treated, the characteristic distribution of ulcerative colitis may become altered. Thus, a patient may display iatrogenic rectal sparing, something that should be remembered by pathologists interpreting biopsies from treated patients (the usual case). Most patients have mild to moderately active disease, which does not require colectomy.

Longstanding ulcerative colitis is associated with an increased risk of dysplasia (Figure 155.79) and adenocarcinoma, even in patients with well-controlled, quiescent disease. Periodic colonoscopic exams are used to survey for dysplasia and adenocarcinoma. Routine surveillance with biopsies is recommended annually for patients with extensive disease of more than eight years’ duration because there is an increasing annual incidence of adenocarcinoma. Biopsies are generally taken from the cecum, ascending, splenic flexure, transverse, hepatic flexure, descending, and sigmoid colon, and rectum. The pathologist should record evidence of colitis, activity, and the presence or absence of dysplasia. As noted above, these surveillance biopsies often lack the typical distribution of ulcerative colitis but this should not prompt a diagnosis of Crohn's disease but rather of treated ulcerative colitis [331–333].

**Crohn's disease**

The biopsy features of small intestinal Crohn's disease are addressed previously though patients may also have colitis alone.
or in conjunction with small bowel and/or disease elsewhere in the GI tract.

Colonic mucosal biopsies, although superficial, can show features that are suggestive of Crohn’s disease. Discrete foci of inflammation often associated with neutrophils within crypts (cryptitis) adjacent to histologically normal crypts are common. Aphthous erosions or ulcers, characterized by focal surface epithelial necrosis associated with a mixed chronic inflammatory infiltrate, sometimes associated with underlying lymphoid aggregates, are typical early lesions. Variability of inflammation within a single biopsy and among several biopsy fragments from the same anatomic location is also typical. The areas of inflammation show architectural changes of chronic crypt destructive colitis while adjacent crypts may appear normal. Fissures may be apparent. Granulomas are infrequent but, when present, are usually poorly formed, and associated with chronic inflammation.

If submucosa is present in the biopsy, there may be significant submucosal chronic inflammation while the overlying mucosa, may only be slightly expanded by chronic inflammatory cells, a feature absent in infectious or ulcerative colitis. Pyloric metaplasia (mucinous glands, reminiscent of the antral or pyloric mucosa) indicates repeated bouts of inflammation and repair.

Crohn’s colitis must be distinguished from infectious colitis, medication associated colitis, and ulcerative colitis. The endoscopic finding of focal aphthous erosions of early Crohn’s colitis may be similar to erosions caused by medications, bowel preparation, and infections. Erosions of Crohn’s disease are associated with a chronic inflammatory infiltrate. Infectious colitis is characterized by a predominance of neutrophils rather than lymphocytes and plasma cells. Medication (NSAIDs and others) induced erosions usually have negligible acute inflammation; typically only a few neutrophils are found in the area of erosion. The more advanced changes of Crohn’s colitis, particularly discrete ulcers and masses seen endoscopically, must also be distinguished from medications and infection. NSAID ulcers may be multiple and deep. They tend to be on the top of mucosal folds and are circumferential rather than longitudinal. Biopsies often show fibrosis with only minimal inflammation. NSAID strictures may form; when these are circumferential they are termed, “diaphragms”. Bowel wall thickening and heaped up masses may be seen in *Yersinia* infection, particularly in the terminal ileum and right colon. The presence of marked inflammation histologically with numerous granulomas and the clinical information of a mass or stricture may lead to a diagnosis of Crohn’s in a patient with *Yersinia* or histoplasmosis. Features that suggest infection over Crohn’s disease include numerous granulomas, granulomas centered in lymphoid follicles, and granulomas with central necrosis. Any specimen with numerous granulomas should suggest infection over Crohn’s disease.

Fulminant Crohn’s colitis is difficult or impossible to distinguish from fulminant ulcerative colitis in a mucosal biopsy specimen since many of the distinguishing features are deep to the mucosa. Furthermore, in fulminant (toxic) ulcerative colitis inflammation may become transmural. In resection specimens, the most important features are the presence of transmural lymphoid aggregates and the presence of occasional poorly formed granulomas at all levels of the bowel wall. The effects of treatment can also cause diagnostic difficulty as treated ulcerative colitis may show areas of involved and uninvolved mucosa and variable degrees of disease activity. It is important to assure that there is re-review of original pretreatment material, if possible, to help distinguish between ulcerative colitis and Crohn’s since patients with ulcerative colitis, but not Crohn’s disease, are candidates for ileal pouch anal anastomosis (IPAA).

**Pouchitis**

The classic histologic features in acute pouchitis includes neutrophilic inflammation and in chronic pouchitis features of chronicity with villous atrophy. These findings are the same as those found in ulcerative colitis or Crohn’s disease [334,335]. Pyloric metaplasia is also seen in some examples, and appears identical to that in the ileum in Crohn’s disease [336–338]. Some patients develop striking villous atrophy, and this may be the precursor to the dysplasia that develops in a few patients [339–342]. Occasionally a patient who was presumed to have ulcerative colitis prior to IPAA develops pouch complications that are indistinguishable from Crohn’s disease. The conclusion of surgical and endoscopic colleagues is generally that the pathologist has misdiagnosed the resection specimen with ulcerative colitis when the patient in fact has Crohn’s disease. In some instances this may be the case. Since patients with Crohn’s disease in whom a continent pouch is attempted have a high rate of complications, many quite serious, most surgeons avoid creating continent pouches in these individuals (in patients with “indeterminate colitis”, severe pouch complications are documented about 20% of the time and about 8%–10% in ulcerative colitis). However, there is a small set of patients who indeed
had ulcerative colitis by all evidence develop an idiosyncratic Crohn’s like disease in their continent pouch and it requires revision [343].

**Infectious colitis**

Acute self-limited colitis (ASLC) is used here to invoke features of colitis secondary to various bacteriologic etiologies, with the exception of enterohemorrhagic *Escherichia coli* which produces an ischemic colitis appearance as described below. In ASLC neutrophils and crypt abscesses tend to appear in the upper half of the mucosa and prominent neutrophils in the lamina propria [344]. The basal plasmacytosis seen in ulcerative colitis and Crohn’s colitis is lacking [345]. Glandular architecture is preserved. Erosions and lamina propria edema may be seen. The course is self-limited and correlates with pertinent stool cultures. As ASLC heals (often when biopsies are taken), there are reactive epithelial changes but crypt architecture remains intact.

As for specific infectious agents affecting the colon, bacterial colitis is often a result of *Campylobacter sp.*, or *Aeromonas sp.* but culture is required for precise typing. Cytomegalovirus (CMV) infection, distinguished by its inclusion bodies, may be encountered in many settings in which patients are immunosuppressed as can various parasites. The ova of *Schistosomases* can be encountered (Figure 155.80 and 155.81) and *Strongyloides* is occasionally found on colon biopsies.

Colonic spirochetosis is a peculiar condition in which numerous unusual Warthin–Starry reactive organisms carpet the colon surface (Figures 155.82, 155.83, 155.84). It has been associated with abdominal pain, appendicitis, chronic diarrhea, and rectal bleeding in some cases, but in the majority of cases, spirochetosis is an incidental finding with no clear clinical correlates. The anaerobic intestinal spirochetes *Brachyspira aalborgi* and *Brachyspira pilosicoli* seem to be responsible for most cases of spirochetosis. *B. pilosicoli* colonizes the intestinal tract of many animal species, especially pigs, and can be found in approximately 30% of feces from persons in developing countries. Koteish and colleagues have reported a retrospective analysis of colonic spirochetosis in 14 cases including four children and 10 adults seen at the authors hospital [346]. Two men had HIV infections. All children and both HIV-infected men had abdominal complaints, diarrhea, or both. Most other adults underwent colonoscopy for polyp screening (four), follow-up of Crohn’s disease (one). Histologically, spirochetosis was identified in all parts of the colon and was not strongly associated with active inflammation, mucosal injury, or changes of chronicity. Genotype analysis of 13 cases showed that 11 resulted
from *B. aalborgi* and two from *B. pilosicoli* infections. Only two patients were treated specifically with antibiotics, with complete resolution of abdominal symptoms in one patient with follow-up. Follow-up biopsy results were available for two patients who did not receive treatment; one showed persistent spirochetosis, and the other was negative. Spirochetosis in this series had a male predominance, was generally caused by *B. aalborgi*, and occurred in two distinct clinical settings: children who often have abdominal symptoms and adults who typically are asymptomatic. While treatment information remains limited, treatment seemed to ameliorate symptoms in some cases.

It is well known that a large number of infectious processes can mimic idiopathic inflammatory disease. Generally, the features of *Campylobacter, Salmonella*, and *Shigella* are distinguished from irritable bowel disease (IBD) by the proclivity of responding neutrophils to involve the lamina propria more than the glands, and the lack of architectural distortion and basal plasmacytosis, but overlapping features do occur. Epithelioid granulomatous inflammation may accompany *Yersinia pseudotuberculosis* and aggregates of macrophages may accompany *Yersinia enterocolitica*. To the extent that the morphologic features of pseudomembranous colitis (Figure 155.85) and enterohemorrhagic *E. coli* colitis mimic inflammatory bowel disease, these must also be considered (although these mimic ischemic effects more than they mimic IBD). The proclivity for GI histoplasmosis to mimic IBD has been emphasized by Lamps and colleagues [347] (Figures 155.86 and 155.87). The presentation of IBD and GI histoplasmosis can be identical (fever, malaise, GI bleeding, diarrhea, nausea and vomiting, ulcers, fissures, perforation, colitis) and the histologic presence of granulomas and full thickness inflammation can lead to an interpretation of Crohn’s colitis. The disease may be seen in nonendemic areas.

**Figure 155.83** Spirochetosis. The hair-like structures emanating from the surface are the organisms.

**Figure 155.84** Spirochetosis. This Warthin-Starry silver stain highlights the organisms.

**Figure 155.85** Pseudomembranous colitis. A pseudomembrane is seen at the center of the field.

**Figure 155.86** Histoplasmosis. This poorly-formed necrotizing granuloma was found in an immunosuppressed person and contains the organisms.
Malakoplakia, which is usually found in the genitourinary tract, can also be found in the GI tract and reflects a curious response to degenerating bacteria which assume a targetoid appearance when ingested by macrophages (Michaelis Gutmann bodies).

Ischemic colitis

The biopsy features that are classically associated with ischemic colitis include marked surface injury, mucin loss in crypts, “atrophic microcrypts”, and hyalinization of the lamina propria such that the normal loose connective tissue punctuated with plasma cells, lymphocytes, and eosinophils is replaced with dense eosinophilic matrix and the residual glands become more closely spaced (lamina propria “collapse”) [348] (Figure 155.89). In older patients, ischemic disease is typically attributable to atherosclerotic mesenteric vascular disease. In the setting of global hypoperfusion or splanchnic constriction the “watershed” zones are prone to vascular insufficiency. The classic “watershed zone” is at the splenic flexure, an area supplied by the distal-most reaches of both the superior mesenteric artery and the inferior mesenteric artery but not by more proximal branches of either source. As such, any vascular compromise from hypovolemia or splanchnic shunting during vigorous to extreme exercise or global hypotension (such as after trauma) can affect this zone (Griffith’s point) more substantially than others in the colon. A similar “watershed zone” is present in the ileocecal region (Sudeck’s point) [349].

There are many etiologies for ischemic colitis. For example, distance running is known to be associated with varying degrees of colonic ischemia. Indeed, approximately a quarter of both runners were found to manifest occult blood in their stool following a marathon [350] and more extensively documented
colonic ischemia has also been reported in such athletes [351–353]. In contrast to the effect of splanchnic constriction in athletic settings, hypovolemia seldom leads to ischemic colitis in young trauma patients [354].

Certain infectious agents are also known to produce an ischemic insult. These include, enterohemorrhagic (Verotoxin producing) E. coli [355–371] and C. difficile. The prototype infectious agent for producing ischemic colitis is E. coli O157:H7, which first came to attention in the early 1980s [360,372]. It is a primary cause of severe hemorrhagic diarrhea and the serious complication of, hemolytic uremic syndrome develops in up to 20% of patients. Ground beef and other bovine products have been implicated as sources. Since E. coli is ubiquitous in stool, the hemorrhagic strains must be specifically sought by stool cultures using Sorbitol–MacConkey medium from which sorbitol nonfermenting colonies are selected and assayed for the specific organism with either an enzyme immunoassay or a latex agglutination assay [373]. Unfortunately, about 3%–18% of toxin producing E. coli are able to ferment sorbitol and thus appear as “ordinary” E. coli on culture plates even though they may still be responsible for outbreaks [361].

The key pathogenetic mechanism underlying the manifestations of enterohemorrhagic E. coli is the direct effect of its cytotoxin on endothelium [374], which results in gastrointestinal manifestations if the process is limited, but in hemolytic uremic syndrome if it becomes systemic. Endoscopic biopsies taken from infected patients may display ischemic colitis features with prominent fibrin thrombi, findings that allow the pathologist to suggest pertinent laboratory evaluation [362] but which are by no means specific. An immunohistochemical test has been developed although there is limited experience with it in tissue diagnosis [365].

In younger patients with ischemic colitis, a variety of drug associations can be causitive, including illegal drugs (cocaine [375–380]), over the counter decongestant medications [381–384], oral contraceptives [385,386], NSAIDS [387,388], kayexalate (given for hyperkalemia in renal patients and suspended in a sorbitol solution that induces osmotic ischemia) [389], the migraine headache medication sumatriptan [390,391], and alosetron (Lotronex) [392–400].

Other causes of ischemic intestinal disease in young adults include coagulopathies [401], anorexic behavior [402], and vasculitides (see later). A 2001 report from the Mayo Clinic of 39 young adults with ischemic bowel disease included 13 (of 25) women taking oral contraceptives, four patients with vascular thrombi, four taking vasoactive drugs, four with hypovolemia, and two with vasculitis. No etiology was demonstrated in the remaining 19 patients [403].

In older patients, the differential diagnosis is often between pseudomembranous and ischemic colitis. The diagnosis of ischemic colitis often requires careful clinicopathologic correlation. The process may resolve spontaneously. Involvement is segmental and the splenic flexure area is particularly vulnerable. In early cases there is desquamation and necrosis of the mucosa, particularly the superficial mucosa. Pseudomembranes are often seen microscopically although the endoscopic appearances of ischemia and pseudomembranous colitis differ. Hemorrhage and hemosiderin-laden macrophages are seen in the lamina propria. Fibrin thrombi may be seen as the process progresses. Chronicity is evidenced by crypt atrophy and hyalinized lamina propria. Dignan and Greenson have published helpful criteria to distinguish ischemic colitis and pseudomembranous colitis [348]. These criteria allow distinction in most but not all patients where this differential diagnosis arises. C. difficile is often the etiologic agent in pseudomembranous colitis, but not all pseudomembranes are caused by this bacteria and not all infestations with C. difficile result in pseudomembranes. Cases are typically associated with antibiotics (see Chapter 62).

**Findings in systemic diseases**

**Scleroderma**

This connective tissue disorder can result in hypomotility and intestinal pseudo-obstruction, classically associated with sclerosis of the inner circular layer of the muscularis propria. Since the pathologic process is mural, there are no specific biopsy changes. However, the resulting stasis from the obstruction can result in bacterial overgrowth.

**Vasculitis**

It is very difficult to make a diagnostic determination of vasculitis on colonic biopsies since if ischemic ulcers are present, any inflammation in walls of small vessels may be secondary rather than primary. The systemic vasculitides are clinically diverse, multisystem diseases and their unifying pathologic feature is inflammation of blood vessel walls. Vasculitides may be categorized according to vessel size. Small vessel vasculitides includes systemic lupus erythematosus (SLE), microscopic polyangiitis, Wegener granulomatosis (WG), the Churg–Strauss syndrome, the Henoch–Schönlein syndrome, Adamantiaides–Behçet disease, and rheumatoid vasculitis. Medium-sized vessel vasculitides includes systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), thromboangiitis obliterans, and Kawasaki disease, whereas large-vessel vasculitis refers to Takayasu arteritis and giant-cell arteritis. However, there may be considerable overlap among the various syndromes. In addition, both Crohn's disease and ulcerative colitis itself may result in vasculitis, though it is more common in Crohn's disease where an arteritis may be seen.

Intestinal vasculitis may accompany a variety of systemic vasculitides such as polyarteritis nodosa, Churg–Strauss syndrome, Henoch–Schönlein purpura, lupus, and rheumatoid arthritis [403–408]. Among the angitides, PAN, SLE, and Henoch–Schönlein are those most commonly accompanied by gastrointestinal complications. Key features of the vasculitides affecting the GI tract are summarized in Table 155.3.

Isolated venulitis of the GI tract has been reported using several terms (lymphocytic phlebitis, necrotizing and giant-cell
Table 155.3 Summary – vasculitis affecting the GI tract.

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Vessel size typically affected</th>
<th>Microscopic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henoch–Schönlein syndrome (also termed anaphylactoid purpura Schönlein–Henoch syndrome)</td>
<td>• Most common vasculitis in children characterized by purpuric skin eruption, fever, arthralgia, visceral symptoms. Seasonal incidence (peaks in winter) • Renal involvement in up to half • Skin purpura, intestinal, renal, or pulmonary hemorrhage</td>
<td>Small</td>
<td>• Necrotizing vasculitis (small vessel), histologically indistinguishable form small vessel forms of polyarteritis • IgA immune deposits in vessel walls</td>
</tr>
<tr>
<td>Polyarteritis nodosa (periarteritis nodosa, polyarteritis)</td>
<td>• Necrotizing vasculitis (medium and small-sized arteries) • Involvement of the aorta is unknown • Can involve any organ • In descending order: kidneys, muscles, nerves, viscera, heart. In children, heart most common site</td>
<td>Medium (arteries)</td>
<td>• Focal segmental necrotizing arteritis with fibrinoid necrosis is hallmark of acute lesions, which have a proclivity for micro-aneurysm formation. • Healing lesions have vessel wall sclerosis • Characteristic feature: coexisting acute and healing lesions with intervening segments of unaffected artery</td>
</tr>
<tr>
<td>Lupus vasculitis</td>
<td>• Vasculitis affecting patients known to have Lupus</td>
<td>Medium</td>
<td>• Variable and nonspecific histology</td>
</tr>
<tr>
<td>Wegener's vasculitis</td>
<td>• A necrotizing granulomatous vasculitis that in classic form affects the lungs and kidneys • Most affected (75%) are c-ANCA (antineutrophil cytoplasmic antibody) positive</td>
<td>Small</td>
<td>• The lesions have geographic necrosis, granuloma formation, and vasculitis • All three components are only found in 20%–30% of extra-pulmonary cases, so diagnosis requires clinicopathologic correlation</td>
</tr>
<tr>
<td>Churg-Strauss vasculitis (allergic granulomatosis and angiitis)</td>
<td>• A subset or “overlap syndrome” of polyarteritis nodosa • The pathologic diagnostic criteria require systemic and pulmonary necrotizing vasculitis with an eosinophilic infiltrate and extra-vascular granulomas • Clinical diagnostic triad: history of asthma/allergy, peripheral blood eosinophilia, and pulmonary and systemic vasculitis with eosinophilic infiltrate</td>
<td>Medium</td>
<td>• Like PAN with an eosinophilic infiltrate. • When changes are limited to an isolated organ system, the condition is known as limited/isolated Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Buerger's disease (thrombangitis obliterans)</td>
<td>• Nonarteriosclerotic segmental inflammatory occlusive disease of medium-sized and small arteries and veins usually affecting limbs with occasional visceral involvement • Strong association with smoking, male sex (9 : 1) • Usually in young men (under 40 y). Begins with Raynaud's phenomenon</td>
<td>Medium</td>
<td>• Diagnostic only in early stages with clinically evident thrombophlebitis • Inflammatory thrombi of arteries and veins with “endovascular” microabscesses with scattered giant cells • Later stages less diagnostic and organizing thrombi are seen • The end stage is nondiagnostic with fibrotic occluded vessels</td>
</tr>
</tbody>
</table>

Amyloidosis

Amyloidosis can affect the colon just as it may affect other regions of the GI tract (Figures 155.70, 155.71 and 155.72). Since it imparts a thickened basement membrane, it may have overlapping features with collagenous colitis. In contrast to the collagen in the latter, which is punctuated with nuclei of fibroblasts and entrapped endothelial cells, the thick basement membrane in amyloidosis contains no nuclei.

Common variable immunodeficiency

Colonic mucosal findings in common variable immunodeficiency (CVID) are similar to those found in the small bowel.

granulomatous phlebitis, idiopathic myointimal hyperplasia of mesenteric veins, mesenteric inflammatory venoocclusive disease, intramural mesenteric venulitis, idiopathic colonic phlebitis) [406,409]. The terms describe a pattern of injury but the etiology remains unknown.

On biopsies, vasculitis involving the GI tract vessels results in ischemic changes that cannot be distinguished from other causes of ischemia. Clinical correlation in collaboration with the endoscopist may clarify the diagnosis. For example, the angiographic features of PAN are characteristic and the diagnosis can be made prospectively by noting ischemic features on mucosal biopsy.
Radiation colitis/proctitis
Radiation colitis may be acute or chronic. The acute phase occurs hours to days following irradiation and shows an edematous dusky pattern with loss of the vascular pattern at endoscopy. On biopsy, nuclear pyknosis, karyorrhexis and enlarged nuclei are seen with diminished mitotic activity and mucin. These changes are reversible over a 1–2 months time course. Chronic radiation colitis develops weeks to years following therapy. Hyalinized connective tissue is seen in any of the bowel wall layers accompanied by atypical fibroblasts, telangiectasia, vessel wall hyalinization, phlebosclerosis, and atrophy on the muscularis propria. The changes may be most evident in the submucosa and not detected by mucosal biopsy [410–412]. Stromal changes may be striking and occasionally, epithelial changes are seen as well [412]. Hyalinized vessels aligned parallel to the surface epithelial basement membrane are very common in rectal biopsies from men who have had irradiation for prostate cancer (Figure 155.93).

Lymphocytic and collagenous colitis
The term “microscopic colitis” has been applied to biopsies of patients with symptomatic colitis in whom there are no endoscopic or radiologic anomalies but in which specific microscopic features are found. It was coined by Read in 1980 to describe patients who had chronic diarrhea, normal colonoscopy, and a normal barium enema, and mucosal inflammation in their colonic biopsies [413]. Most patients have one of two types of microscopic colitis: collagenous and lymphocytic colitis. Both entities feature an inflamed lamina propria and surface injury, but seem to be distinct entities that differ in their demographics, disease associations, and clinical course.

CVID is the second most common immunodeficiency syndrome after select IgA deficiency. The hallmark of CVID’s presentation is persistent sinusal infections, but many such patients have GI tract complaints attributable to small intestinal atrophy, chronic giardiasis, pernicious anemia, and colitis. Such patients are at risk for development of small bowel lymphoma and gastric carcinoma. Since CVID is a chronic disease, injury to the colon in patients with this condition is lifelong. As such, although they do not have plasma cells (Figures 155.90 and 155.91), other features of their disease mimic “quiescent” ulcerative colitis (they can display marked crypt distortion). Apoptosis is often a prominent feature, mimicking GVHD (Figure 155.92). CVID is also associated with lymphocytic colitis.
abdominal pain, fatigue, or weight loss. Collagenous colitis is more common in women, with a female to male ratio of 6–8:1, and a median age at diagnosis of 55 years. However, the age range is broad, and many cases are diagnosed in patients under the age of 45 years. 40% of patients have an associated disease. The most common of these are rheumatoid arthritis, thyroid disorders, celiac disease, and diabetes mellitus. There may also be an association with the use of NSAIDs [415–417].

Lymphocytic colitis was separated as a specific form of microscopic colitis by Lazenby and colleagues in 1989 [415,418]. Like those with collagenous colitis, patients with lymphocytic colitis have chronic watery diarrhea and normal colonoscopy. There is a broad age range at diagnosis, ranging from young adults to elderly patients, with a mean in the sixth to seventh decade. In sharp contrast to collagenous colitis, men and women are equally affected. Some patients report abdominal pain and/or weight loss. Lymphocytic colitis has a stronger association with celiac disease than collagenous colitis. Of patients with celiac disease, about a third have histologic features of lymphocytic colitis on biopsy. Of patients with lymphocytic colitis, as many as a quarter may have celiac disease.

These two microscopic colitides share many histologic features, including increased lamina propria cellularity, primarily attributable to plasma cells, but also lymphocytes and eosinophils (Figures 155.94–155.96). The crypts are nondistorted or minimally distorted. There is surface epithelial injury associated with infiltration by lymphocytes, and degenerative features such as cytoplasmic vacuoles, loss of mucin, nuclear irregularity, pyknosis, flattening.

The key diagnostic distinction between collagenous colitis and lymphocytic colitis is the deposition of an abnormal layer of collagen between the surface epithelium in the former. This can be variable, and tends to be more pronounced in the proximal colon and less so in the rectosigmoid. The lower border is irregular, with strands of collagen extending into the underlying...
lamina propria and incorporating dilated capillaries and fibroblast nuclei. Eosinophils are quite often prominent in collagenous colitis, both in the lamina propria and within surface and crypt epithelium [418]. Scattered neutrophils are often found in collagenous colitis but are not a feature of lymphocytic colitis. When neutrophils are prominent, it suggests superimposed infectious colitis. In collagenous colitis, the surface epithelium tends to separate from the basement membrane beneath, leaving stretches in which abnormal collagen is exposed. In lymphocytic colitis the surface lymphocytosis is usually more prominent, eosinophils are less common, and prominent crypt epithelial lymphocytosis is often a feature.

The abnormal subsurface collagen that is diagnostic of collagenous colitis is not always thick enough to be appreciated on routine H & E stain. There is no minimal thickness required for the diagnosis of collagenous colitis. In normal colonic mucosa, the trichrome stain marks the basement membrane lying at the base of the surface epithelium, forming a smooth, thin line. When collagen is deposited beneath this epithelium, the trichrome stain has an irregular lower border, with strands of collagen extending into the adjacent lamina propria and trapping capillaries. It is this abnormal pattern, rather than the absolute thickness of the collagen that is the key feature in collagenous colitis. The abnormal collagen deposition is not always evident on routine stains and a trichrome stain should be obtained when microscopic colitis is suspected. An abnormal collagen band alone is insufficient for the diagnosis of collagenous colitis, but must be present in the appropriate context. Occasionally, thick bands of collagen may be seen in the colonic mucosa as a result of healed ischemia, radiation injury, ulcerative colitis, or mucosal prolapse [419].

**GVHD**

The features of GVHD of the colon are similar to those found elsewhere with varying degrees of apoptosis and crypt drop-out. Grading is helpful for comparison among biopsies taken over time:

- **Grade 1:** increased crypt apoptosis (Figure 155.86)
- **Grade 2:** apoptosis with crypt abscess
- **Grade 3:** individual crypt necrosis
- **Grade 4:** total denudation of areas of mucosa.

Like GVHD elsewhere, it can have a chronic phase in which crypt distortion appears but it lacks the active inflammation and prominent basal plasmacytosis that characterize ulcerative and Crohn’s colitis. It typically accompanies bone marrow rather than solid organ transplant. The diagnosis of GVHD requires the proper clinical setting so correlation with the clinical impression is critical. The differential diagnosis includes entities resulting in apoptosis, such as viral infection, autoimmune disease, NSAID use, and medications. For example, mycophenolate mofetil (Cellcept), administered to solid organ transplant patients, can result in colon biopsy findings that are identical to those of GVHD [252], and chemotherapy or other prolonged injury can produce similar features. The endoscopist should remember that phosphasoda bowel preparation itself can result in prominent apoptosis and this preparation should be avoided when GVHD is a consideration.

**Diversion colitis**

Occasionally a surgeon finds it necessary to create or leave a bypassed segment of bowel so that it is not in continuity with the fecal stream. If the rectum is left as a blind opening continuous with the anus, it is called a “Hartmann’s pouch”. In these circumstances, so called diversion colitis may develop. The colitis that may follow diversion of the fecal stream is usually mild, occurring as subclinical disease in approximately 70% of patients. However, in severe cases, the features may closely resemble either ulcerative or Crohn’s colitis creating diagnostic confusion if the surgery was prompted by preexisting IBD. Regression of diversion colitis generally follows restoration of the normal continuity of the fecal stream. Some authors have reported that lymphoid follicle hyperplasia is a typical finding although others have reported variable histology [420–425]. If diverted colon is reconstructed into another anatomic structure (such as a neovagina), it is still prone to diversion colitis [426–428] The hypothesis is that the condition results from absence of luminal short-chain fatty acids (the preferred metabolic substrate of colonic epithelium) secondary to a change in the bacterial milieu based on the reported reversal of the condition upon the instillation of these compounds into the diverted segment [426,429].

**Diverticular disease associated conditions**

In the early 1990s, clinicians first noted a small subset of patients with diverticular disease (usually involving the sigmoid colon) who developed segmental colitis in the area of diverticular disease [430,431]. The pathologic findings sometimes closely mimicked ulcerative colitis [430] or Crohn’s disease [432]. Although a small number of patients indeed subsequently had manifest ulcerative colitis or Crohn’s disease following their episode of diverticular disease associated colitis, with recognition of the latter as a seemingly discrete diagnostic entity, caution should be exercised in making a diagnosis of idiopathic IBD affecting only the sigmoid colon in patients with diverticular disease. Cases may display features of chronicity, including basal plasmacytosis and crypt distortion although most show mild active colitis. Those cases of diverticular disease displaying granulomas may even have granulomas in resected lymph nodes [433]. Patients with diverticular disease associated colitis usually respond to antibiotics.

**Colon – polyps and neoplasms**

**Elastosis/elastofibromatous change**

There is a subset of polyps of the GI tract in which the submucosa and muscularis mucosa exhibit a focal or diffuse increase of elastin fibers. This elastosis or elastofibromatous change is most commonly manifested as a colonic polyp found during screening colonoscopy. Gastric and small intestinal cases are
less frequent and associated with ulcers or an inflammatory process. Histologically, elastosis appears as finely granular and/or fibrillar amphophilic material, sometimes with a fibrous component (elastofibromatous change) (Figures 155.97, 155.98, and 155.98) [434]. The changes occasionally appear centered around blood vessels and often are mistaken for amyloid, but are negative for Congo red stain and strongly positive for elastin stain. These lesions are probably incidental and of no clinical consequence.

Filiform polyps/post-inflammatory polyps
Filiform polyps (also called postinflammatory polyps) are essentially a subtype of polyps associated with prior mucosal injury found in patients who have had any type of prior ulceration. They consist of fingerlike projections of submucosa covered by mucosa on all sides. They reflect healing of undermined mucosal and submucosal remnants and ulcers and are typically multiple. To the endoscopist, they appear long and finger-like [435]. They are diagnosed by noting that they consist of two protruding layers of mucosa plastered together with only one intervening layer or no intervening layer of muscularis mucosae. This is because they reflect regrowth of mucosa over an area of ulcer that has damaged the muscularis mucosae.

Mucosal prolapse conditions
This category of lesions encompasses a host of processes in diverse GI tract sites, but prolapse changes often appear as polyp on endoscopic examination in the colon. Well-defined colonic prolapse conditions include solitary rectal ulcer syndrome, localized colitis or proctitis cystica profunda, inflammatory cloacogenic polyp, prolapsing folds associated with diverticular disease of the colon, and fibrin cap polyps of the colon. So-called myoglandular polyps are presumably part of the same spectrum [436,437]. In some gastrointestinal sites, prolapse is virtually physiologic. For example, the ileocecal valve is prone to prolapse and if there is abundant submucosal fat in the prolapsed area, this is termed “lipoma of the ileocecal valve” but is probably not neoplastic. These conditions are all benign and are occasionally mistaken both clinically and microscopically for carcinomas.

Solitary rectal ulcer syndrome
Solitary rectal ulcer syndrome describes a pattern of mucosal changes (some of which are polyps without ulceration) localized to the terminal rectum and imparted by mucosal prolapse. It occurs at all ages, with a peak incidence between 20 and 40 years. There may be hamatochezia, pain, tenesmus, and sometimes lower abdominal pain. Inability to evacuate the rectum or a “foreign body” sensation are described and it usually occurs in those who strain when defecating, especially young women. At endoscopy ulcers are seen in 20%–70% of patients, usually on the anterior or anterolateral rectal wall but a mass-like lesion can also be found, raising the possibility of a neoplasm. Sometimes defecation studies are used to evaluate these patients as they are believed to have difficulty coordinating the smooth muscle during the defecation process in part associated with failure of the puborectalis sling to relax at the proper time.

The pathologic changes on biopsies consist of hypertrophy of the muscularis propria with splaying of fibers which course into the mucosa and are seen throughout the lamina propria. The proliferated smooth muscle is accompanied by variable fibrosis and the glands become entrapped and distorted. As the process progresses, there is surface ulceration and glands can herniated into the submucosa, accompanied by wisps of lamina propria) [438–442]. Thus lesions can have a “polypoid phase” or an ulcerated phase. Often crypts become “diamond-shaped” [443,444]. A caveat is that mucosal prolapse changes adjacent to carcinomas are the same as those of isolated mucosal prolapse, so multiple biopsies of large “solitary rectal ulcers” are important to exclude sampling error [445]. “Colitis cystica profunda” is part of the same spectrum of disease and implies that glands have prolapsed into the submucosa.
These polyps are considered hamartomatous. In the colon they display colonic type mucosa and have irregularly shaped and dilated glands accompanied by lamina propria that is expanded with edematous granulation tissue (Figure 155.101). Dysplasia is rare in sporadic juvenile polyps.

Juvenile polyposis has been recognized since 1975 [452] and criteria for diagnosis consist of: (1) more than five juvenile polyps of the colorectum; (2) juvenile polyps throughout the GI tract; or (3) any number of juvenile polyps in a patient with a family history of juvenile polyposis. These are encountered in a number of syndromic settings. These syndromes are described in detail in Chapter 79.

When juvenile polyps are biopsied from syndromic patients, smaller ones are identical to the typical sporadic ones. However, larger ones display an increase in the relative amount of epithelium compared to stroma, are multilobulated with rounded or finger-like lobes, and are more likely to display true dysplasia. Both types of juvenile polyps are prone to surface erosions with attendant reactive epithelial changes. In general, the pathologist is cautioned against diagnosing dysplasia when active inflammation and erosions are a feature.

Peutz-Jehgers polyps
Peutz-Jehgers polyps are most common in the small intestine. Their manifestations in the colon are similar to those in other sites in that they are characterized by site specific (colonic) mucosa with arborizing smooth muscle. Unfortunately, since mucosal prolapse is common in the colon, it is difficult to prospectively diagnose Peutz-Jehgers’ syndrome on the basis of a colonic polyp in isolation.

Cronkhite–Canada polyps
Cronkhite and Canada reported a series of patients in 1955 who had polyposis, pigmentation, alopecia and onychotrophy [453]. There have been only a few subsequent reports of this condition...
Although Burke and colleagues were able to amass polyps from nine patients from the consultations files of the AFIP for histologic analysis [454] and Ward has provided excellent reviews of the literature [454–457].

Cronkhite–Canada syndrome is characterized by diffuse polyposis occurring in patients with unusual ectodermal abnormalities, including alopecia, onychodystrophy and skin hyperpigmentation. The most common presenting symptoms include diarrhea, weight loss, nausea, vomiting, hypogeusia and anorexia. Paraesthesias, seizures and tetany, apparently related to electrolyte abnormalities, have also been reported. Nail dystrophy (thinning, splitting and separation from the nailbeds), essentially a reflection of protein loss, is one of the features. Both scalp and body hair alopecia may be present. Diffuse hyperpigmentation of the skin, manifested by light to dark brown macular lesions, is seen most frequently on the extremities, face, palms, soles, and neck. Microscopic examination of biopsied skin reveals abnormally increased melanin deposition with or without increased melanocyte proliferation.

Cronkhite–Canada syndrome is distinguished by the diffuse distribution of polyps throughout the entire GI tract, except for characteristic sparing of the esophagus.

It is not possible to diagnose this syndrome solely on basis of the histologic features of an associated polyp. However, the Cronkhite–Canada polyp is characterized by its broad sessile base, expanded edematous lamina propria, and cystic glands [454] (Figures 155.102 and 155.103). Similar features are found in the lesions of juvenile polyposis. The only distinguishing feature reported between Cronkhite–Canada and colonic juvenile polyposis was the pedunculated growth of the latter [454]; a feature that did not hold for gastric lesions. Unlike Cronkhite–Canada polyps, juvenile polyps sometimes have areas of dysplasia, but this is not typical. Therefore the diagnosis of Cronkhite–Canada polyps, (especially in the stomach), requires correlation with the presence of the ectodermal changes characteristic of this syndrome. The question of whether polyps in Cronkhite–Canada syndrome possess malignant potential remains controversial.

**Other conditions**

**Endometriosis**
Endometriosis is well known to be found in a variety of sites and affects the GI tract in up to 40% of patients with pelvic endometriosis and about a third of these patients have mucosal lesions amenable to biopsy [458]. The sigmoid colon is the most common site.

On gross examination, endometriosis appears as it does in other sites, as firm areas which may contain cysts filled with brown fluid. Most examples of endometriosis affect the serosa or muscularis propria and are accompanied by abundant fibrosis and adhesions, though submucosal examples are also reported. Endometriosis of the colon resembles examples found elsewhere, consisting of endometrial-type glands and stroma associated with hemosiderin deposition and a fibroblastic response (Figures 155.104 and 155.105). The endometrial-type epithelium changes with the menstrual cycle. A stromal decidual reaction may be found in endometriotic foci in pregnant patients.

**Vascular lesions**
As biopsy of vascular ectasias in not always wise, these are not often seen in biopsy material. When they bleed, they are...
germline defects in the adenomatous polyposis coli (APC) gene, the gatekeeper of colorectal neoplasia, and have hundreds to thousands of colon adenomas and essentially all develop colon cancers if no prophylactic colectomy is performed. Adenomas of the colorectum generally pose few diagnostic problems to the pathologist, and endoscopists usually recognize and remove them readily. Differential diagnosis can occasionally be difficult when reparative changes in the epithelium resemble adenomas and when dysplasia is encountered in the setting of inflammatory bowel disease.

Adenomas have dysplasia by definition. It is usually low-grade with regular nuclei showing maintained nuclear polarity (their long axes are perpendicular to the basement membrane. Typical adenomas display elongated “pencillate” nuclei that are similarly hyperchromatic throughout, in contrast to normal mucosa that shows reduced nuclear hyperchromasia at the surface. Apoptotic bodies are usually prominent in sporadic adenomas. Adenomas may contain foci of clear cell change, squamous-like morules akin to those seen in the endometrium that have also been referred to as “microcarcinoids”, and Paneth cell differentiation, none of which matter in an adenoma, but which may inform some of the variation in the appearances of invasive carcinomas. Prominent intraepithelial lymphocytes and reduced numbers of apoptotic bodies are encountered in colorectal adenomas from patients with hereditary nonpolyposis colorectal carcinoma (Lynch syndrome) but it is not known whether finding these features prospectively predicts the diagnosis. High-grade neuroendocrine (small-cell) carcinomas may arise in the background of ordinary-appearing adenomas, but this is rare and discussed further on.

Adenomas have their initiation point near the surface of the mucosa, such that tiny adenomas only affect the upper half of the mucosa and grow in a “top-down” fashion (Figure 155.106). Genetically altered cells in the superficial portions of the mucosa managed with various oblitative techniques but not sampled for histology. However, there are a variety of vascular lesions occasionally encountered on colonic biopsies. Kaposi's sarcoma is sometimes encountered in patients with HIV/AIDS. Other lesions occasionally seen include incidental hemangiomas and lymphangiomas, Dieulafoy's lesions (usually these are found in the stomach but rarely in the colon), and vascular malformations. Angiosarcomas tend to be deeper and diagnosed on resections.

Adenomas
It is estimated that more than half of the Western people will develop a benign colorectal tumor (adenomatous polyp) during their lifetime, and that ~10% of such tumors will progress to malignancy. Familial adenomatous polyposis patients have
spread laterally and downward to form new crypts that first connect to preexisting normal crypts, and eventually replace them. This is a useful feature in separating adenomas from reactive lesions and colitis-associated dysplasia, both of which seem to display “bottom-up” growth. Also, adenomas usually display prominent apoptosis and may contain scattered neutrophils. The presence of prominent apoptosis can be a helpful diagnostic feature.

When endoscopists biopsy “polyps”, sometimes the pathologist sees nothing to account for a polyp. If recut sections are performed in such instances, about 10% of such cases can be shown to harbor an adenoma on additional sectioning and if tissue blocks are re-embedded and recut, up to 20% can be found to harbor adenomas. Each laboratory should probably determine its own protocol for further evaluating sampling in which the endoscopist notes a polyp and no lesion is seen on evaluated slides. In our hospitals, we perform no recuts if a separate sample from the same patient has an adenoma whereas we perform additional sectioning if this might alter the patient’s follow-up and thus recut the sample/s of “polyps” that are negative for adenoma.

Adenomas may undergo striking mucosal prolapse changes, which can cause a host of diagnostic problems. Neoplastic glands can herniate into the submucosa and, similarly, strands of muscularis mucosae can proliferate into the lamina propria and simulate submucosa. When neoplastic glands from adenomas prolapse into the submucosa, this can occasionally impart an appearance similar to that of invasive carcinoma, especially if the glands become obstructed and inspissated mucus dissect into the surrounding connective tissue, termed “pseudoinvasion”.

Criteria to diagnose high-grade dysplasia (Figure 155.107) in colon adenomas are not established, despite the fact that a finding of high-grade dysplasia in an adenoma is a reason to intensify post polypectomy follow-up. Fortunately high-grade dysplasia and large adenoma size generally go hand-in-hand so observer variation in thresholds for high-grade dysplasia are less important than they might seem. Although we have no validation, we generally reserve a diagnosis of high-grade dysplasia in colorectal adenomas for lesion that have cribriform architecture and/or loss of nuclear polarity rather than only cytologic atypia or stratification of nuclei to the surface. Some pathologists resist use of the designation of high-grade dysplasia in colorectal adenomas to forestall overtreatment by surgical colleagues who harbor the erroneous notion that high-grade dysplasia should prompt a colectomy. When carcinomas arise in adenomas of the colon, invasion of the lamina propria is considered biologically equivalent to high-grade dysplasia (since the lamina propria of the colon is believed to lack lymphatic access, “intramucosal carcinoma” in the colon is thus staged as Tis rather than T1, so some observers do not report this invasion either. We report intramucosal carcinoma in adenomas as such and include a note that it is biologically equivalent to high-grade dysplasia (Tis) and that complete polypectomy should be curative unless additional sampling discloses deeper invasion.

Adenomas with “villous features” are supposed to prompt closer surveillance than those without but there are no real criteria for when an adenoma has “villous features” – some colleagues are averse to reporting either high-grade dysplasia or “villous features” as there are no universal criteria for diagnosing them and they correlate with lesional size regardless, a piece of information the pathologist is usually unaware of at the time of interpretation of mucosal sample.

Pathologic evaluation and diagnosis of early colorectal cancers treatable by endoscopic polypectomy

Carcinomas are believed to develop in about 1 in 25 adenomas left in situ. When these are found in endoscopically removed polyps, a management decision must be made, and the role of the pathologist is important. To justify colectomy, the risk of the patient having a metastasis must be higher than the risk of the patient undergoing surgery to remove a segment of the colon. Criteria to make this decision have appeared in the literature since the 1980s and have largely stood the test of time. Although early studies made a point that there were levels of invasion akin to those in a melanoma, other protocols have proved more reliable and more readily assessed in biopsies.

The diagnosis and treatment of colorectal cancers by endoscopic polypectomy have become commonplace. “Malignant polyps” are adenomas that contain any amount of invasive carcinoma, which is defined as a tumor that has gone through the muscularis mucosae into the submucosa. They also include polypoid carcinomas, in which the entire polyp head is replaced by carcinoma. By definition, malignant polyps exclude...
adenomas containing intraepithelial carcinoma or intramusosal carcinoma because these polyps lack biologic potential for metastasis. Polyps containing invasive carcinoma comprise about 5% of all adenomas. The chance that an adenoma contains invasive carcinoma increases with polyp size, and the incidence of invasive carcinoma in adenomas >2 cm ranges from 35% to 53%. Therefore, any polyp >2 cm in diameter should be approached with the suspicion that it might harbor an invasive cancer. When technically possible, these polyps should be removed intact, rather than piecemeal, with as great a margin as possible at the base or stalk. Identification of the resection margin is necessary for determining both the adequacy of the excision and the closest approach of the tumor, a parameter that predicts the risk of tumor recurrence.

Malignant polyps often constitute a form of early carcinoma (pathologic T category pT1) curable by endoscopic polypectomy alone. However, the incidence of an unfavorable outcome (i.e., lymph node metastasis or local recurrence from residual malignancy) for malignant polyps treated by polypectomy alone varies from 0% to about 20% in the literature [459]. Pathologic evaluation is critical in defining polyps with an increased risk of residual or recurrent disease, and the subsequent clinical management of the patient may be based, in part, on the findings. The histopathologic parameters that are known to be associated with a significantly increased risk of adverse outcome are:

- A high tumor grade including poorly differentiated adenocarcinoma, signet ring cell carcinoma, small-cell carcinoma, or undifferentiated carcinoma. It remains unclear in the literature whether poorly differentiated carcinomas (that are apparently confined to the lamina propria) have the biologic potential to metastasize.
- A tumor ≤ 1 mm from the resection margin (some authors advise ≤ 2 mm) can be assessed by making two small dots (one at the leading edge of the tumor and the other at the nearest cauterized margin) and measuring the distance between them with a ruler. Of note, cauterized tissue contracts, a process that can pull the normal tissue margins together and give a false impression of positive margins.
- Involvement of a small (thin-walled) vessel, presumably lymphatic, by the tumor (Figures 155.108 and 155.109). In the presence of one or more of these features, the risk of an adverse outcome following polypectomy is estimated to be about 10% to 25%. If one or more of these high-risk features is found on pathologic examination, further therapy may be indicated. Optimal management is decided on an individual basis, but segmental resection of the involved colonic segment, local excision (e.g., transanal disk excision for a low rectal lesion), or radiation therapy may be considered. In the absence of high-risk features, the chance of adverse outcome is extremely small, and polypectomy alone is considered curative.

In the pathologic evaluation of malignant polyps, assessment of small vessel invasion is hampered by interobserver variability. In fact, small vessel invasion may be impossible to diagnose definitively in some cases and, ultimately, may be judged as being indeterminate. An absolute diagnosis of vessel invasion is dependent upon finding carcinoma cells within an endothelial-lined space. Contraction artifact in the tissue, tumor-induced stromal sclerosis, and extracellular pools of mucin secreted by tumor cells may all complicate the evaluation of vessel invasion. The dilemma may or may not be resolved by the examination of additional tissue levels of the specimen, review by a second
observer, and/or immunohistochemical staining for endothelial markers. In published cases in which the malignant polyps have lacked definitive evidence of high-risk features (but the patients have died of their disease), lymphatic invasion had been judged (on blinded review) as indeterminate because of a lack of interobserver agreement. This suggests that even the suspicion of small vessel invasion on pathologic examination should be considered as potentially important. When there were no adverse features at all, there were no adverse events in this study.

**Small-cell carcinomas of the colon**

These tumors are morphologically identical to those in the lung. They are typically found in the right colon where they are often associated with an ordinary adenoma or typical colorectal adenocarcinoma. They are not found associated with carcinoid tumors. The prognosis is poor and patients often have metastases at the time of surgery. The small-cell component usually proliferates off the lower portions of the lesion and is thus not detected on biopsies. Like small carcinomas in other sites, these express neuroendocrine markers (chromogranin and synaptophysin). Additionally, like small-cell cancers elsewhere in the body, about a quarter stain using CD117/c-kit antibodies [460] but lack kit mutations. Carcinoid tumors and conventional colorectal cancers do not display CD117/c-kit labeling.

**Serrated polyps**

**Hyperplastic polyps, traditional serrated adenomas, sessile serrated adenomas**

In addition to hyperplastic polyps and adenomas, a third class of colonic polyp distinguished by serrated or star-like glandular morphology is now recognized. Although referred to generally as "serrated polyps", this diagnostic category includes lesions with different cytological and molecular features and they are further categorized as: (1) hyperplastic polyps (HPs) (Figure 155.110); (2) sessile serrated adenomas (SSAs, also known as sessile serrated polyps) (Figure 155.111); (3) sessile serrated adenomas with cytological dysplasia (mixed hyperplastic/adenomatous polyps [MHAP's] (Figures 155.112, and 155.113); and (4) traditional serrated adenomas (TSA's), (Figure 155.114). Initially HPs were regarded as benign and metaplastic. However, there is now considerable evidence implicating at least a subset of what has traditionally been called HP in the development of a subset of colorectal carcinomas. Initially, case reports and small series of adenocarcinomas associated with “giant” or “large” HPs (usually defined as >1 cm) appeared. Additionally, some studies link hyperplastic polyposis syndrome with an increased risk for colorectal cancer. The term “serrated polyposis” is preferred over “hyperplastic polyposis” due to the common occurrence of sessile serrated adenomas in this setting.
ble HPs of the left colon, but differ by larger size, a higher proliferative index, the presence of serrations extending to their bases, dilated architecture of the glands at the bases, and a tendency to have mismatch-repair defects. The authors recommended the term “sessile serrated adenoma” for such polyps, which were previously referred to as “serrated adenomas”. Both terms are somewhat unsatisfactory to some, as the lesions lack the “pencillate” nuclei that typify SAs. The term “sessile serrated polyp” has also been used to describe such polyps, a term that has been adopted into the 2010 WHO classification. To those unfamiliar with serrated polyps, using the term “adenoma” implies the need for more careful follow-up than the term “polyp” although the 2010 WHO endorsed the two terms equally [236].

Classical hyperplastic polyps account for the 75% of all serrated polyps. They are typically an incidental finding during routine screening colonoscopy. They may be single or multiple, typically in the rectosigmoid colon, and usually measure less than 5 mm. Three distinct types are recognized, namely microvesicular, goblet cell rich, and mucin-poor. These subtypes bear no clinical significance and, as a result, it is not necessary to subclassify them in daily practice. Typically hyperplastic polyps have serrated architecture that is limited to the upper crypt with glands that taper down near the base and have prominent neuroendocrine cells. Some examples show a thickened (but regular) collagen table. Microvesicular hyperplastic polyps have frequent BRAF mutations while KRAS mutations are identified more frequently in the goblet-cell-rich type.

SSAs account for approximately 9% of colonic polyps [462] and 15%–25% of all serrated polyps. SSAs are more commonly located on the right colon, are broad-based, and may reach several centimeters in size. The endoscopic appearance may be subtle with coloration similar to that of the adjacent mucosa and may give the impression of a thickened mucosal fold. Histologically, these polyps are characterized by serrated crypt architecture that extends to the deep crypts, papillary invaginations, and dilated crypt bases oriented parallel to the muscularis mucosae. Contrary to hyperplastic polyps, neuroendocrine cells are few and far between and the collagen table is usually thin.

Loss of MLH1 (by promoter methylation rather than germ-line mutation of mismatch repair genes) occurs at the point of cytological dysplasia [463] but is not seen in nondysplastic SASs/polyps so the molecular parallels of sporadic and syndromic lesions are not as straightforward as in the setting of conventional adenomas versus FAP. When serrated polyps are studied for molecules in the Wnt pathway, most (67%) SSAs show aberrant nuclear labeling for β-catenin and a decreased staining with CDX2 (predominantly confined to the crypt bases) when compared to hyperplastic polyps [464,465]. Aberrant nuclear β-catenin labeling is always seen in the background of BRAF activating mutations and correlates with neoplastic progression as it is seen in 100% of SSAs that have acquired conventional dysplasia. As a result of these findings, Yachida and colleagues suggested activation of the Wnt pathway as a

![Figure 155.113](image1.png)  
*Figure 155.113* Sessile serrated adenoma with associated dysplasia and invasive carcinoma. In this immunohistochemical preparation for the mismatch repair protein MLH1, there is (nuclear) loss in the high-grade dysplasia and carcinoma component.

![Figure 155.114](image2.png)  
*Figure 155.114* Traditional serrated adenoma. There is serrated architecture of the epithelial cells as well as traditional epithelial dysplasia like that of an ordinary adenoma.

The WHO defining criteria for diagnosis of serrated polyposis syndrome include [236]:

1. The presence of 20 or more serrated polyps (of any size) spread throughout the colon, or
2. At least five serrated polyps proximal to the sigmoid colon with two or more measuring more than 10 mm, or
3. Any number of serrated polyps in an individual who has a first-degree relative with serrated polyposis.

In 2003, Torlakovic and colleagues [461] published an important set of observations that has set the stage for a radical change in how pathologists address colorectal polyps. In their work, the authors noted that there is a subset of polyps that tends to occur on the right side of the colon. These polyps superficially resem-
The key practical issue is how to manage patients with the various serrated polyps; the main clinical decisions are how to address incompletely excised polyps, whether to perform pan-colonoscopy when index lesions are identified on proctoscopy, or sigmoidoscopy, and whether long-term endoscopic surveillance is needed. Guidelines promulgated in 2012 should allow better data to accumulate [469].

Colitis

Associated dysplasia and colon carcinoma
Criteria for grading dysplasia in the setting of inflammatory disease were developed in 1983 [470] and these remain useful. Presently dysplasia in ulcerative colitis is separated into low and high-grades (Figures 155.115, 155.116 and 155.117) and cases in which the findings are unclear are diagnosed as “indefinite

An uncommon and recently described variant of TSA is the “filiform serrated adenoma” [468]. This polyp is characterized by left sided location, elongated, filiform projections lined by serrated epithelium, edematous stroma, and columnar cells with abundant eosinophilic cytoplasm. These polyps may be seen associated with areas of conventional tubular adenoma, high-grade dysplasia, SSA, or hyperplastic foci. These polyps are molecularly more similar to SSAs as they have a high frequency of BRAF mutations (50%) and minority possess KRAS mutations (21%). Unlike SSAs, they are predominantly microsatellite stable or have only low levels of microsatellite instability (MSI-L).

As with every entity in pathology, some serrated polyps defy current classification. Diagnosis in some cases requires correlation with site and polyp size but there are no hard and fast rules for these examples. However a number of features may be helpful in this setting:

1. If the overall morphology is that of a hyperplastic polyp but the lesion is located on the right or transverse colon, we hesitate to diagnose it as such, especially if large (>5 mm). In these instances a diligent search for neuroendocrine cells (rare to absent in SSAs), serrations deep in the crypts, and subtle crypt dilation is warranted. Finding one dilated crypt is sufficient to classify it as a SSA.

2. Although SSAs can occur on the left colon, they are uncommon in that site. Some hyperplastic polyps may display reactive epithelial changes and mild, uniform crypt dilation. They usually display prominent neuroendocrine cells and serrations are limited to the upper parts of the crypts. If these are features of a small (<5 mm), left sided polyp, it is best classified as a hyperplastic polyp.

3. Large (>5 mm), left sided “hyperplastic” polyps may be diagnosed as such with the caveat that these probably require closer endoscopic follow-up (interval uncertain) than that of small (<5 mm) hyperplastic polyps.

4. Some observers are more comfortable with the term “serrated polyp with features of SSA” for examples that do not entirely fulfill SSA criteria. These are typically followed as SSAs.
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Mesenchymal tumors

Benign fibroblastic polyps (perineuriomas) of the colon

These are incidental lesions detected in adult patients undergoing screening colonoscopy. As such the mean age in the reported series was 61.5 years. They present as small polyps at endoscopy (size range, 0.2–1.5 cm). These lesions have also been called “perineuriomas” of the colon and are often found intimately associated with serrated polyps.

The polyps consist of an expansion of the lamina propria by a monomorphic spindle cell population lacking mitotic activity or necrosis. Some literature supports colectomy in the presence of any degree of dysplasia; others recommend resection only in the setting of high-grade dysplasia in flat mucosa. Dysplasia associated lesion or mass (DALM) lesions are typically irregularly shaped and raised, without a discrete stalk. The dysplasia may be found at any location in the crypt, a difference from an adenoma in which the dysplasia begins at the surface and moves down the crypt. Endoscopically, DALM lesions are often difficult to remove, in some instances because they are contiguous with an underlying invasive adenocarcinoma. Because sessile irregular DALMs are likely to harbor an adenocarcinoma, colectomy is sometimes recommended. While distinguishing between an adenoma and a DALM lesion is important, in some cases this distinction is difficult or even impossible. However, available evidence for both ulcerative and Crohn’s colitis supports treating the lesion in the same fashion as a sporadic adenoma (polypectomy) if it is discrete, and endoscopically adenoma-like [471,472]. In daily practice, we diagnose such lesions as “polypoid low- (or high-grade) dysplasia VERSUS sporadic adenoma” and write a note explaining the basis for the favored alternative. As a general rule, lesions arising in the field of inflammatory disease that have an unusual endoscopic appearance are probably best regarded as “DALMs”. In other words, the gross appearance probably yields more information than the microscopic one. Adenocarcinomas detected during surveillance have a significantly better prognosis than those found in individuals with clinical symptoms. Total colectomy is then indicated. Resection with subsequent ileoanal anastomosis allows the patient to have relatively normal bowel function by maintaining the anal sphincter following colectomy.

Leiomyomas

If a brightly eosinophilic spindle cell lesion with bland cytologic features is arising in association with the muscularis mucosae, it is, in all likelihood, an incidental leiomyoma, readily managed by simple polypectomy. Most spindle cell tumors of the wall of the GI tract are GI stromal tumors (except in the esophagus where leiomyomas preeminate) but muscularis mucosae-associated tumors of the colorectum are usually leiomyomas.

Miettinen and colleagues [474] studied 88 such tumors of the muscularis mucosae of the colon and rectum. The lesions, except one, were removed by snare polypectomy as incidental lesions at cancer or polyp surveillance; one small tumor was an incidental finding in the rectal resection specimen. The tumors had a significant male predominance (overall 2.4:1) and were found in adults (38 to 85 years, median 62 years). The lesions were typically small (range 1 to 22 mm, median 4 mm) and located predominantly in the rectum and sigmoid (72%).
**GISTs of the colon**

GISTs are most common in adults in the sixth decade and arise in the ascending and descending colon and usually present with pain or a mass. Except for small subserosal lesions, they are typically transmural tumors with intraluminal and outward-bulging components. Morphologically they are heterogeneous with spindle cells in fascicles, palisades or storiform arrangement, and sometimes an organoid pattern; a minority has epithelioid cells in varying proportions.

Most (75%) colon GISTs are CD117 positive and 60% have CD34, with c-kit mutations in exon 11 in about a third of cases. Some have taken a size of 5 cm and five mitoses per 10 HPF as thresholds for malignancy [475,476], but Miettinen and colleagues found lower levels [477]. In their series, tumors smaller than 1 cm did not recur, whereas in larger tumors 20% with minimal mitoses and all with more than five mitoses per 50 HPF metastasized or died of disease. Interestingly, the few cases with skeinoid fibers had a better prognosis. These tumors are not commonly encountered on mucosal biopsies as they are typically mural, but when they are, performing an immunohistoch- emical panel is prudent.

**Neural tumors**

Ganglioneuromas occur in two general settings: (1) as solitary isolated lesions, and (2) syndromically as multiple lesions that either produce multiple exophytic polyps (“ganglioneuromatous polyposis”) or poorly demarcated transmural proliferations (“ganglioneuromatosis”) [478]. In solitary examples, there is no gender predominance and lesions have been detected in adults from ages 20–90 years old with a peak incidence between the ages of 40 and 60 (mean age of 48 years). The majority are found in the colon, usually on the left side. Most patients are asymptomatic and the lesions are detected during routing colonoscopy. Solitary lesions are not associated with genetic syndromes. In contrast, ganglioneuromatous polyposis is associated with familial adenomatous polyposis and diffuse ganglioneuromatosis is associated with multiple endocrine neoplasia type IIb and with NF1. Diffuse ganglioneuromatosis is found in virtually all patients with MEN IIb and often antedates the development of the endocrine neoplasms. Patients with MEN IIb and ganglioneuromatosis present with diverse gastrointestinal symptoms which may include constipa- tion, diarrhea, difficulty feeding, projectile vomiting, and crampy abdominal pain. Most syndromic GI tract ganglioneuromas are found in the colorectum and in younger patients than sporadic isolated ganglioneuromas (mean ages of about 35 years).

Polypoid isolated ganglioneuromas are small sessile or pedunculated polyps that grossly resemble juvenile polyps or adenomas and are 1–2 cm. The polyps in ganglioneuromatous polyposis are multiple (20–40) and display greater variability than sporadic ones, ranging from 1 mm to over 2 cm. Some are filiform. Diffuse ganglioneuromatosis results in a poorly demar- cated whitish thickening that may be transmural.

At low magnification, polypoid sporadic ganglioneuromas often resemble juvenile/inflammatory polyps in that they have disturbed crypt architecture and expanded lamina propria. At higher magnification, the lamina propria is expanded by collections of spindle cells within fibrillary matrix and irregular nests and groups of ganglion cells (Figure 155.119). Sporadic exam- ples may also have submucosal extension and a plexiform arrangement involving the submucosal nerve plexus such that they superficially resemble neurofibromas (differing by the presence of many ganglion cells). The ganglioneuromas in ganglioneuromatous polyposis show overlapping features with sporadic ganglioneuromas but tend to be more variable and have more numerous ganglion cells and filiform architecture. In diffuse ganglioneuromatosis, the process is centered around the myenteric plexus and is either diffusely intramural or transmu- ral and consists of fusiform expansions or confluent transmural ganglioneuromatous proliferations.

Sporadic ganglioneuromas are treated by polypectomy and seldom recur. Patients with syndromic ganglioneuromas must be carefully followed based on their specific syndromes. Those with NF1 may develop other neural lesions, including malig- nant peripheral sheath tumors and those with MEN IIb may develop endocrine neoplasms. Polypoid ganglioneuromas may herald Cowden’s disease, tuberous sclerosis, familial adenomatous polyposis, and juvenile polyposis whereas the diffuse type is the type most likely associated with NF1 and MEN IIb. This type may cause strictures requiring resections but the gangli- oneuromas are all themselves benign.

**Schwannomas**

Like gastric schwannomas, those of the colon differ from those encountered in the somatic soft tissues by lacking a capsule and having a prominent lymphoid cuff [479,480]. They consistently display strong diffuse S100 protein and lack CD117/c-kit. These
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the fourth to the seventh weeks of gestation and the upper two thirds is endoderm-derived whereas the lower one third is ectodermally-derived; the dentate or pectinate line is where these zones meet.

The anus can also be divided into the mucosa-lined anal canal and the more distal epidermis-covered anal margin. Where the skin meets the canal, apocrine glands may be prominent. Cancers arising in the anal margin are regarded as skin cancers and are treated with local excision. The anal canal extends proximally from the anal verge to the rectal mucosa. Most of the anal canal is lined by squamous mucosa, which is present between the anal verge and the dentate (or pectinate) line. The dentate line is a visually identifiable border between the more distal squamous mucosa and a transitional area of squamous and nonsquamous mucosa. The adjacent nonsquamous lining can consist of either transitional (urothelium-like) or rectal glandular mucosa [486,487]. Anal ducts and glands are found at the transition zone and lymphatic spaces are often prominent in these zones. Therefore, it is important for pathologists to remember that a biopsy from the anatomic (clinical) anus can display glandular, transitional, or squamous mucosa.

The anus can be the site for the host of conditions affecting the skin, a topic beyond the scope of this chapter, but, for example, various keratoses can be found in the anal area. When typical seborrheic keratoses present in this area, they raise the possibility of condyloma based on their site despite their lack of viral cytopathic changes. In patients who have received radiation treatment, the usual radiation-associated changes are seen [488] including hyalinized vessels and collagen.

Hidradenoma papilliferum
This cystic and papillary apocrine neoplasm generally arises in the perianal skin and vulva. The characteristic affected individual is a white woman over the age of 30. The typical sites include labia majora, perineum, and perianal skin [489–491], although extra-genital sites appear as case reports. Rare reports of malignant change in these are often contested.

The lesion forms a large epithelial-lined cyst in the mid-dermis displaying elaborate papillary infoldings that are formed...
correlated with clinical ones. Anal biopsies are not commonly performed in Crohn’s disease due to the risk of procedure related morbidity [498].

**Polyps**

**Fibroepithelial polyps**

These lesions are also called anal tags and excising them is generally not suggested unless they are uncomfortable or interfere with personal hygiene since removing them may be extremely painful and, in the case of those associated with Crohn’s disease, may result in poor healing and additional morbidity. They are essentially projections of anal mucosa and submucosa. When one arises at the leading edge of an anal ulcer or fissure, the term “sentinel tag” is applied. They are often submitted to the pathologist as hemorrhoids but lack vessels, features of hemorrhage, and organized thrombi. They are essentially the same lesion as skin tags (acrochordons).

Fibroepithelial polyps have received little attention in the pathology literature [499,500] but consist of myxoid or collagenous stroma covered by squamous epithelium at the edge of ulcers. Immunohistochemistry can be helpful in confirming an impression of HSV proctitis.

**Crohn’s disease**

In ulcerative colitis, involvement of the anal canal is typically nonspecific and unrelated to the inflammatory disease. In contrast, in Crohn’s disease the anal canal itself is affected in about 25% of patients with classic small intestinal disease and in up to 80% of those with colonic involvement. Anal disease may be the initial manifestation in about a third of patients with Crohn’s disease. Biopsies may display a patchy active chronic inflammatory process but fissures, fistulas, and striking chronic inflammatory infiltrates are the hallmark. However, unless granulomas are detected, biopsy features are not specific and must be correlated with clinical ones. Anal biopsies are not commonly performed in Crohn’s disease due to the risk of procedure related morbidity [498].

**Syphilis proctitis**

*Treponema pallidum* is the causative agent of syphilis, a sexually transmitted disease characterized by primary, secondary, and tertiary stages. The primary stage presents with a chancre, a painless firm, red lesion at the site of inoculation, which heals after 3–6 weeks. The secondary stage, characterized by a maculopapular rash, is the result of spirochete multiplication within the skin and mucous membranes and occurs 2–10 weeks after the initial stage. Condyloma lata (raised, broad-based plaques) may be seen during this stage and may provoke concern for
HPV infection, especially in the anal area. Condyloma lata displays acanthosis that can be striking, surface erosion, broadening and elongation of rete ridges, exocytosis and neutrophils in the most superficial layers, and spongiosis [501]. Vessels may show endothelial swelling and proliferation and may be encircled by a cuff of plasma cells [501]. Although not widely available, an antibody to Treponema pallidum can be used to confirm the diagnosis [502–504] Figures 155.124 and 155.125). The antibody cross reacts with the agent of “intestinal spirochetosis”.

Endoscopically, syphilitic proctitis may present granular, friable, erythematous, thick, or ulcerated mucosa [505–507]. There is often a clinical concern for carcinoma because of mass lesions (that vanish upon treatment of the infection) and patients are often not forthcoming about their sexual practices or they are not asked about them [508,509]. On histologic exam of anal mucosa one sees ulceration, granulation tissue, and massive associated mucosal and submucosal lymphoplasmacytic infiltration that tends to be angiocentric. Although silver stains can highlight the spirochetes, these are frequently not identified. Definitive diagnosis requires serologic confirmation with rapid plasma reagin (RPR), fluorescent treponemal antibody-absorption test (FTA), or immunolabeling.

Lymphogranuloma venereum proctitis
Chlamydia trachomatis, serotypes L1, L2, and L3, is the causative agent of lymphogranuloma venereum (LGV), although other subtypes of this organism can cause cervicitis, endometritis, urethritis, and trachoma [510]. Recently, outbreaks have been reported in men who have sex with men (MSM) [510]. Traditionally, LGV initially presented with a penile papule followed by a secondary stage featuring tender inguinal lymphadenitis (Bubos). However, in the MSM population, the presentation at all stages may include rectal discharge and proctitis with a tertiary stage of anorectal strictures, perirectal abscesses, genital elephantiasis, penile deformities, and esthinomene (a chronic ulcer) [510]. The diagnosis can be established by serology or PCR and the infection is treated with doxycycline.

The histologic findings in LGV are relatively nonspecific and overlap with those of syphils proctitis and thus the diagnosis must be confirmed by laboratory testing. Depending on the stage of the disease, biopsies may demonstrate mucosal ulcers, prominent chronic inflammation, and fibrosis. Biopsies showing rectal mucosa may display distorted crypt architecture and lamina propria fibrosis [511].

Neoplasia
Introductory
The bulk of anal neoplastic pathology encountered in daily practice revolves around the diagnosis of squamous carcinoma and its precursors even though such tumors are relatively rare. Resection specimens should be rarer still since most cancers are treated with radiation and chemotherapy. As such, biopsy diagnosis is particularly important. Resected anal specimens are handled differently from colorectal ones; size rather than the depth determines the T status in anal cancers (T1 is ≤2 cm, T2 is 2–5 cm, T3 is >5 cm, and T4 encompasses invasion into adjacent organs [485].

Anal squamous intraepithelial neoplasia
The vast majority of anal squamous intraepithelial neoplastic lesions, like those in the uterine cervix, are related to sexually transmitted human papillomavirus (HPV) infections of the various subtypes, and these are presumed to be the precursors to invasive anal squamous cell carcinomas. The number of individuals in the population exposed to HPV is high; for example,
3% and 12% of US male and female blood donors, respectively, had positive HPV16 serology in one study [512]. Given the enormous number of individuals and the relatively small number of patients who develop cancers (estimated at 5260 new cases of anal cancers and about 12,200 new cervical cancers in 2010) progression rates must be quite low [513]. However, individuals infected with HIV are extremely likely to have anal HPV lesions [514,515], so this is the group in whom screening is presently being evaluated, akin to mass cervical screening. Anal HPV lesions in HIV-positive patients can be advanced. One study found that 37% (118/319) of excised condylomas in men who have sex with men (MSM) harbored high-grade anal intraepithelial neoplasia or squamous carcinoma. In the same study, HIV seropositive men were twice as likely to have high-grade AIN or squamous carcinoma when compared with HIV negative patients [516]. At least half of the homosexual male HIV population has anal HPV lesions [514,515], and low-grade lesions progressed to high-grade lesions in about 20% of such patients in 2 years in one study [515], but it seems that very few of these in situ lesions progress to invasive carcinoma; patients most at risk for progression to invasion are those with immunosuppressed states [517]. The main reason to treat these lesions is the aggressive nature of carcinomas once invasion ensues. The effect of highly active antiretroviral therapy (HAART) on these lesions remains unclear, but is not necessarily beneficial [518].

Like the uterine cervix, the anal canal has a transformation zone. This zone cannot be visualized without the use of anoscopy, so a procedure is required even for cytologic screening. In biopsies obtained from this area (anoscopically at the dentate/pectinate line), it is typical to find fragments of rectal-type mucosa adjoining, or separate from, the lesions in question. The histology of anal squamous intraepithelial lesions is quite similar to that found in the uterine cervix, and is associated with the same HPV types as cervical lesions. Such lesions had been classified as anal intraepithelial neoplasia (AIN) I, AIN II, and AIN III, but now, as for the cervix, most observers prefer to separate low- and high-grade lesions, with the AIN II subsumed under high-grade (Figures 155.126 and 155.127). HPV 16 and 6 are the most common genotypes detected in association with high-grade and low-grade lesions, respectively [519].

Interestingly and similarly to some colon cancers, Zhang and colleagues reported high rates of DNA methylation in cases of squamous cell carcinoma and high-grade AIN. DNA methylation of the genes IGSF4 and DAPK1 was specific for high-grade AIN and squamous cell carcinoma as methylation of these genes was absent in cases of low-grade AIN and in normal mucosa [520]. Current treatment options for AIN include electrofulguration, infrared coagulation, immunomodulation therapy with Imiquimod 5% cream, and surgical excision.

Bowen's disease is an eponymous term used for squamous carcinoma in situ at the anal margin (the outside part that can be seen by the clinician, in contrast to lesions seen at the transition zone, inside the canal, at the dentate line) where it presents macroscopically as a brownish plaque. In other words, Bowen's disease is essentially an AIN lesion that arises in perianal skin [236]. The terminology is sometimes complicated by the fact that lesions may not be restricted to one area. Biopsies of Bowen's disease display full thickness dysplasia with jumbled nuclei, disorderly maturation, mitoses at all levels, and dyskeratosis, sometimes extending into skin appendages (pilosebaceous units). Like AIN, it is strongly associated with HPV. It is more likely to progress to invasive cancer than the AIN lesions, but most cases still do not progress. The squamous precursor lesions encountered on anal area biopsies are summarized on Table 155.4.

**Anal squamous cell and other carcinomas**

Carcinoma of the anal canal accounts for 1.5% of digestive-system cancers in the United States, with an estimated 5260 new
Endoscopic mucosal biopsy – histopathological interpretation

CHAPTER 155

... cells, and the other is characterized by small-cells. Many tumors show more than one morphologic subtype but the majority of these neoplasms are diagnosed on small biopsies, which are likely not representative of the entire tumor morphology. The bladder and anus share a common embryologic origin, thus giving rise to the similar (i.e., transitional or cloacogenic) morphology. The biology and prognosis of keratinizing and nonkeratinizing tumors of the anal canal are essentially the same, so prior concern about subclassification of anal tumors is probably not warranted (and we do not devote effort to this subclassification). Furthermore, pathologists do not always reproducibly separate the categories, further limiting their utility [525].

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Gross appearance</th>
<th>HPV type</th>
<th>Microscopic features</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condyloma acuminata</td>
<td>Protuberant “genital wart”, cauliflower-like lesion</td>
<td>6,11</td>
<td>Exophytic lesion with prominent surface viral cytopathic changes</td>
<td>Aggressive transformation vanishingly rare</td>
</tr>
<tr>
<td>Bowenoid papulosis</td>
<td>Multiple brownish to reddish papules</td>
<td>16, 18, 33, 34</td>
<td>Histologically similar to Bowén's disease (below, carcinoma in situ) but the clinical presentation different (multiple papules versus a plaque)</td>
<td>• Sometimes resolves spontaneously, can recur</td>
</tr>
</tbody>
</table>
Tumor differentiation, however, should be included in the report as poorly differentiated neoplasms are associated with a higher risk of death than well to moderately differentiated examples [522]. It is also worthwhile to attempt to separate high-grade neuroendocrine (small-cell) carcinomas from squamous cell carcinomas of the anus, although these tumors are rare in this site. Adenocarcinomas of the anal canal are clinicopathologically like rectal cancer and are treated as such.

Although the presence of anogenital condylomata has been shown to increase the likelihood of anal cancer, there is little, if any, risk associated with the presence of hemorrhoids, fissures, or fistulae. Furthermore, a history of inflammatory bowel disease has now been shown not to predispose patients to anal cancer, in contrast to prior anecdotal views [526].

Women with anal cancer were more likely than women with colon cancer to have a history of genital warts or infection with herpesvirus or Chlamydia trachomatis. As compared with men with colon cancer, men with anal cancer were more likely to have engaged in homosexual activity, to have practiced receptive anal intercourse, and to have a history of genital warts or gonorrhea. Frisch and colleagues compared 417 patients with anal cancer to 534 patients with adenocarcinoma of the rectum and 554 normal control subjects [527]. On multivariate analysis, the relative risk of anal cancer in women was highest among those with 10 or more sexual partners, and those with anal warts, genital warts, gonorrhea, or cervical neoplasia. The risk was also elevated in women who had been tested for HIV infection and those whose sexual partners had a history of a sexually transmitted disease. A history of receptive anal intercourse, either before the age of 30 or with multiple partners, was also associated with an increased risk of anal cancer; however, <10% of the women with anal cancer reported such risk factors. Among heterosexual men in the study, multivariate analysis showed a significantly elevated risk of anal cancer in association with 10 or more sexual partners or a history of anal warts, syphilis, or hepatitis. Data from the Surveillance, Epidemiology, and End Results program revealed that the relative risks of anal cancer and vaginal cancer were 4.6 and 5.6, respectively, in women who had been given a diagnosis of invasive cervical cancer, as compared with the expected rate according to age-matched controls [528].

The emerging relation between cervical and anal cancer, the known association of both cancers with sexual activity, and the established link between HPV and cervical cancer led to speculation that anal cancer might also be caused by HPV. Frisch and colleagues found HPV DNA in 88% of 388 patients with anal cancer but none in the 20 control patients with rectal adenocarcinoma [527,529]. As is the case for cervical cancer, HPV type 16 is the subtype most frequently associated with anal cancer and was found in 73% of patients with invasive anal cancer in that study. HPV16 is more likely to be associated with high-grade anal intraepithelial neoplasia, whereas other types of HPV are more often isolated in patients with low-grade anal intraepithelial neoplasia. The presence or absence of detectable HPV in patients with cancer of the anal canal, however, does not impact the prognosis [530].

HIV-positive patients are two to six times as likely as HIV-negative persons to have anal HPV infection, regardless of sexual practices. These individuals are also seven times as likely as HIV-negative persons to have persistent HPV infection, a risk inversely related to the CD4 lymphocyte count. Moreover, HIV-positive patients who have low-grade anal intraepithelial neoplasia are twice as likely as HIV-negative persons to have progression to high-grade anal intraepithelial neoplasia. Whether or not HIV infection itself has a direct effect on the development of anal cancer remains unknown. The estimated incidence of anal cancer in the HIV population, however, is between 35 and 100 per 100,000. Since anal HPV DNA has been detected in 55% and 23% of 285 HIV-seropositive and 204 HIV-seronegative homosexual men, respectively [514], the rate of progression is probably quite low, and ongoing studies will clarify this.

Several case-control studies have shown that a history of smoking increases the risk of anal cancer by a factor of 2 to 5, independent of sexual activities [531].

Anal squamous carcinoma was classified by the 1989 WHO in the following types [532]:

(a) squamous cell (cloacogenic)
   (i) large-cell keratinizing
   (ii) large-cell nonkeratinizing (transitional)
   (iii) basoloid
(b) giant condyloma (verrucous carcinoma).

An exception to the usual striking epithelial changes is the rare verrucous carcinoma, which displays broad-based squamous papillae that are sheet-like in a sclerotic background. They are often accompanied by many neutrophils and a peculiar pattern of abnormal keratinization at all levels of the markedly thickened epithelial proliferation. Verrucous carcinoma has been termed the “giant condyloma of Buschke–Löwenstein” and may involve the external genitalia and perianal skin. It resembles a condyloma, but is, if anything, cytologically blander with less striking viral cytopathic changes. Koilocytes with nuclear cavities are not seen. Metastases from verrucous carcinomas are vanishingly rare and, when present, should prompt a diagnosis of squamous cell carcinoma. The primary tumors are treated by local excision, but this can be challenging since the lesions can be quite large and locally invasive.

Because the reproducibility of diagnosing most of these subtypes is not particularly good [525], and because it bears little impact on outcome (with the exception of attempting to separate verrucous carcinoma and poorly differentiated carcinomas), we do not devote much effort to separating anal squamous carcinoma into subtypes. Providing a diagnosis of invasive carcinoma is all that is clinically relevant, and awareness of the subtypes is simply a construct to avoid misdiagnosis of squamous carcinoma variants as something else. As such, the 2010 WHO classification simply “lumped” together the subsets of squamous carcinoma [236].
Rare high-grade neuroendocrine (small-cell) carcinomas can be encountered on anal biopsies, some of which can reflect spread from prostatic (or other) primary lesions. Unfortunately, these can be difficult to distinguish. For example, most prostatic small-cell carcinomas lack “prostate” markers [533] (although some lesions do express prostate markers), and about 45% have ERG gene rearrangements [534]. Imaging studies are sometimes the best tool to determine the primary site when a small-cell carcinoma is biopsied from the anus. Anal small carcinoma can be associated with squamous cell carcinoma.

Rarely, adenosquamous carcinomas can be encountered in the lower GI tract and the anus is no exception. The tumors appear similar to adenosquamous carcinomas elsewhere in the body with areas of both squamous and glandular differentiation. When there is ambiguity, a mucicarmine stain helps in identifying intracellular mucin. Fifty-eight percent of the cases are encountered in the sigmoid, rectum, and anus. Patients with localized disease have an overall survival similar to those with colorectal adenosquamous carcinoma but survival in the setting of regional and distant disease is significantly lower. Individuals with distal disease (sigmoid, rectum, and anus) have a better prognosis than patients with proximal tumors [535].

Paget’s disease
Extra-mammary Paget’s disease typically affects apocrine gland-rich sites such as the perianal zone. It presents as a slowly growing erythematous eczematoid plaque that may extend internally to the dentate line. On biopsies, part or all of the squamous epithelial thickness is infiltrated by large pale cells, some of which may have signet cell features, and some of which may be large and pink (Figures 155.129 and 155.130). If the epithelium is crushed or altered in any way, it can be difficult to separate the Paget cells from atypical keratinocytes or from melanoma. Fortunately an immunohistochemical panel resolves most doubtful examples. True Paget’s disease is a lesion with apocrine cell differentiation, and the proliferating cells express Cam 5.2, CEA, gross cystic disease fluid protein (GCDFP), and CK7 and have mucin [536,537]. Merkel cells can also have CK7, a feature the pathologist must consider when evaluating these stains. However, about half of cases showing adenosquamous cells in squamous mucosa reflect Pagetoid extension of an underlying typical colorectal cancer into squamous epithelium and such lesions lack GCDFP and are often CK20+ and CK7−. Even though the occasional microsatellite unstable colorectal carcinoma lacks CK20 [538], most such tumors are found in the right colon rather than the rectum. The best way to determine whether any given case of anal Paget’s disease is associated with an invasive cancer is by a careful clinical examination!

The “true” Paget’s disease cases that are epidermotrophic apocrine neoplasms have a high local recurrence rate and can eventually become invasive. Those reflecting epidermotropism of “ordinary” adenosquamous carcinomas behave as the associated cancers; thus stage is the primary prognostic marker.

Adenocarcinoma, including anal gland adenocarcinomas
Most adenocarcinomas arising in the anus are of the rectal type and arise in the upper zone of the anus (which is normally lined by columnar mucosa). These are identical to true rectal carcinomas and are managed as such. On biopsies, they appear identical to rectal adenocarcinomas, and their immunohistochemical profile is similarly identical, namely CK20+, CK7 (usually) negative. These tumors are characterized by “pencillate” nuclei, abundant necrosis, and the usual overall pattern of colorectal carcinoma, with frequent association with an adenoma. Like rectal cancers, some are mucinous, particularly those associated with fistula tracts [539] and some can be poorly differentiated. Anal adenocarcinomas generally pose few diagnostic problems, although the differential diagnosis is with prolapse polyps (inflammatory cloacogenic polyps) with prominent colitis cystic profunda, which are distinguished by their diamond-shaped

Figure 155.129 Anal Paget’s disease. Glandular cells proliferate in the squamous mucosa.

Figure 155.130 Anal Paget’s disease. At high magnification, intracellular mucin is apparent in these Paget’s cells.
glands, fibromuscular mucosal stranding, and bladder cytology. Anal adenocarcinomas with poorly differentiated morphology have a worse prognosis that well-differentiated lesion [540].

A subset of anal adenocarcinomas (and squamous carcinomas for that matter) arises in association with chronic anal fistulas. Most of these fistula-associated adenocarcinomas are clinically unsuspected and arise from long-standing tracts (10–26 years). Patients often have a history of Crohn's disease and previous anorectal surgery [539].

There is a rare subset of anal canal adenocarcinomas believed to arise in association with, or display differentiation towards, anal ducts/anal glands. These are called anal gland (duct) carcinomas. They are sufficiently rare that the AFIP was only able to amass seven convincing cases [541]. These tumors are composed of tubules originating from ducts that open onto the mucosal surface. They are intramural, without a luminal in situ component (Figure 155.131), although they may exhibit pagetoid spread. They have variable overlying surface ulceration. On immunohistochemical staining, they are typically CK7+ and CK20−, akin to the anal glands and ducts. Many have behaved aggressively [542].

**Mesenchymal tumors**

**GIST of the anus**

True GISTs of the anus are rare [477]. When found, they display the typical staining pattern of GIST. Staining for S100 protein should also be performed to distinguish from the 40% of melanomas that express CD117/c-kit. Small leiomyomas that appear similar to those found in the esophagus are far more common and tend to occur in women and express hormone receptors. Small leiomyomas may also arise from the muscularis mucosae if the upper part of the anus above the dentate line.

**Melanoma and nevi**

As melanocytes are normal residents of the anal canal and anal verge, it follows that both melanomas and nevi can be encountered (albeit rarely) in this area. Anal melanoma usually affects white adults. However, as for subungual and esophageal lesions, individuals with pigmented skin can also be affected. Patients present with a mass and often with rectal bleeding, which, typically, is initially attributed to hemorrhoidal bleeding [543]. The lesions may be sessile or polypoid. Unless overt pigment is present, a panel immunohistochemical approach is usually warranted to exclude poorly differentiated carcinomas and lymphomas. Confirmation that the lesion is primary is best accomplished by the identification of an in situ component (Figures 155.132 and 155.133). The outcome has generally been poor, with a 5-year survival reported in 10% to 45% of cases [543–545]. Some surgeons have advocated sphincter-sparing surgery with adjuvant therapy, rather than operations requiring colostomy [546].

Melanomas often are CD117/c-kit+ on immunohistochemistry, which does not always correlate with kit mutations.

![Anal melanoma](image1.png)

![Anal duct/Anal gland carcinoma](image2.png)

![Anal melanoma](image3.png)
However, approximately 20% of mucosal melanomas (about 20%) so harbor kit mutations [547]. Some response to imatinib has been reported in melanomas with targetable kit mutations [548].

Like melanomas, melanocytic nevi are rare in this area and only sporadic examples are reported in the literature. Some cases may not be recognized clinically and are incidental findings associated with hemorrhoidectomy specimens. Histologically, they appear similar to nevi elsewhere in the body as collections of bland melanocytes that show maturation towards the deep aspect of the lesion.

References are available at www.yamadagastro.com/textbook

Further reading

Gastric secretory testing

Physiology of gastric acid secretion
The stomach anatomically and physiologically is divided into distinct regions: the cardia, body, and antrum as described in more detail in Chapter 4. The primary site for gastric acid secretion is in the body of the stomach and the primary site for regulation of gastric acid secretion is in the antrum. The regulation of gastric acid secretion is described in more detail in Chapter 23. The cephalic or neural phase of gastric acid secretion involves vagal efferent innervation of the stomach and is regulated by the release of acetylcholine [1]. The vagal pathway involves enteric neurons that innervate the gastric mucosa (Figure 156.1). The gastric mucosa contains the regulatory paracrine and endocrine cells, namely the histamine-containing enterochromaffin-like (ECL) cells, the somatostatin-containing D cells, and the gastrin-containing G cells. These cells contain peptides, which help to regulate the secretion of acid from the parietal cell. Acetylcholine, released from vagal efferent neurons, stimulates gastric acid secretion by acting at specific muscarinic (M3) receptors expressed on the parietal cell. The ECL cell comes under neural control through activation of the receptor for pituitary adenylate cyclase activating polypeptide (PACAP) [2,3]. Prior to the ingestion of food, there is neural release of acetylcholine and presumably also PACAP that results in a small increment in gastric acid secretion as well as salivation. Following food ingestion, this small amount of gastric acid assists in the digestion process and allows proteins present in meals to be degraded to aromatic amino acids which in turn stimulates gastrin release. Immediately after meal ingestion there is some neutralization of the gastric acidity followed by gastric acid stimulation and intragastric acidification.

Gastric hormonal and secretory testing
Measurement of serum gastrin
Gastrin was first isolated in 1964 by Gregory and Tracy [4]. The human gastrin gene is localized to chromosome 17 and its mRNA transcribes a prepropeptide form, which undergoes a series of posttranslational processing steps to yield a propeptide which can be cleaved to several forms of gastrin. In the human, the major forms of circulating gastrin are 17 or 34 amino acids in length (G17 and G34, respectively) as shown in Figure. 156.2a. As developed by McGuigan in 1967, a radioimmunoassay using a double antibody technique can be used to measure serum gastrin measurements in humans [5]. The receptors for gastrin have been cloned and referred to as cholecystokinin (CCK) B/gastrin or CCK2 receptors and are distinguished from the CCKA or CCK1 receptors based on the structure of the heptahelical, G protein receptor structure as shown in Figure. 156.2b [6–8]. The specific receptor that triggers gastrin release from the gastric antrum is not known. As described below, the release of gastrin in humans can be achieved by a peptone meal or a standard meal and is the basis for these serum tests in various disease states. The antral G cell
plays a key role in sensing luminal contents as well as releasing gastrin. In organ culture from patients with duodenal ulcer (DU) and non-DU patients it was shown that there is a greater amount of antral gastrin released in DU patients compared to non-DU patients whereas there was less somatostatin released by the non-DU patients [9]. Gastrin is released by luminal Ca++ as well as by an increase in luminal pH suggesting the potential for multiple luminal sensory inputs [9]. The authors in this study showed that oral administration of 2 g of calcium carbonate produced a significant increase in gastric acid secretion within 2 h and a concomitant increase associated with an increase in serum gastrin levels. These results suggested the presence of a Ca++-sensing receptor on the human G cell. An intragastric pH of <3.0 will generally suppress gastrin release whereas, in conditions of hypochlorhydria or achlorhydria such as with atrophic gastritis, hypergastrinemia is typical. Since it was discovered that about 40% of gastrin release is not coupled to vagal stimulation, other mediators are thought to be important, such as gastrin-releasing peptide (GRP). GRP is a neurocrine peptide present in the central nervous system and in the enteric neurons of the gastrointestinal tract. GRP belongs to the larger group of amphibian bombesin peptides sharing similar -COOH terminal amino acids. Antral GRP is released by enteric neurons. In contrast, somatostatin suppresses gastrin release, presumably through its type 2 receptor.

Administration of pentagastrin in humans
Card and Marks demonstrated that during histamine-stimulated gastric acid secretion the relationship between the number of parietal cells in the stomach and the maximal acid output (MAO) are linear [10]. Thus, the MAO could approximate the relative numbers of parietal cells. The relationship between exogenous gastrin administration and maximal gastric acid secretion was reported in 1964 in a canine model [11]. Thereafter, pentagastrin (2.7–6000 ng/kg/h) has been routinely used to determine MAO, and the use of histamine for this purpose was largely abandoned. Non-DU patients required 2.8 times more pentagastrin than DU patients (246.8 ng/kg vs 92.1) suggesting that DU patients are more responsive to the effects of pentagastrin [12]. In normal volunteers, pentagastrin has been infused for 24 h to simulate the levels of hypergastrinemia observed in patients with Zollinger–Ellison syndrome. Pentagastrin (1 μg/kg/h) infused in 39 subjects over a 25-h period resulted in maximal gastric acid output [13]. Pentagastrin coadministration with proton pump inhibitor (PPI) is noted to enhance the effects of the PPI by recruiting pumps that are subsequently inhibited.

Gastrin in Zollinger–Ellison syndrome
Zollinger and Ellison first described this syndrome in 1955 as a recurrent, often fatal peptic ulcer disease associated with gastrointestinal bleeding. Zollinger–Ellison syndrome, caused by the excessive release of gastrin from a gastrinoma, is described in greater detail in Chapter 57. Zollinger–Ellison syndrome is characterized by the presence of hypergastrinemia and gastric acid hypersecretion. Gastric acid and gastrin testing is therefore critical in the establishment of the diagnosis and to enable adequate control of the symptoms. Zollinger–Ellison syndrome is associated with elevated levels of serum gastrin [14]. Gastrinoma tumors secrete gastrin in response to stimulation with infused calcium [15], presumably mediated by a calcium-sensing receptor (CaSR) present in gastrinoma tumors [16]. In a study comparing provocative tests for Zollinger–Ellison syndrome including (1) rapid calcium infusion (2 mg Ca++/kg/min); (2) secretin (2 clinical units (CU)/kg/bolus); (3) long calcium infusion (12 mg Ca++/kg/3 h); and (4) a combination test consisting of a rapid calcium infusion followed immediately by secretin, administration of rapid calcium followed by secretin provided greatest provocation of gastrin stimulation in Zollinger–Ellison syndrome [17]. The calcium infusion test is a provocative test for the diagnosis of gastrinomas, insulinomas, and intestinal carcinoids but is less reliable for the diagnosis of the latter [18]. The CaSR is a sensing receptor for extracellular Ca++, aromatic amino acids, and pH. The expression of this receptor on antral
Figure 156.2 Structure of gastrin (a) and amino acid structure of the cholecystokinin (CCK) 2 receptor (b). Note that the receptor is a heptahelical, G protein coupled receptor with a long NH2 terminus and a long third intracellular loop.
G cells may explain the dual function of this cell to both sense and regulate gastrin release [19].

Measurement of serum gastrin is indicated in patients suspected clinically of having Zollinger–Ellison syndrome. A markedly elevated serum gastrin level (>1000 pg/mL) in the absence of achlorhydria is highly specific for the diagnosis of Zollinger–Ellison syndrome [20]. When interpreting the results of fasting serum gastrin levels, physicians should be aware of the variability in measurement among several commercially available gastrin assay kits, resulting from the limited specificity of antibodies used in these assays, which either measure only single gastrin form (G17) or overreact with sulfated gastrins and several nonspecific plasma proteins. When gastrin is very elevated, the sera should be diluted such that the level measured falls within the linear portion of the standard curve during radioimmunoassay. Falsely high or low concentrations of gastrin measurement have been demonstrated if the degree of hypergastrinemia is moderate (50–400 pg/mL). This can lead to either unnecessary investigations in normal patients, or misdiagnosis and undertreatment of patients with Zollinger–Ellison syndrome [21]. A comparison of the provocative tests is shown in Figure 156.3 [22]. The secretin test is comparatively more sensitive for establishing a diagnosis of Zollinger–Ellison syndrome. Patients with Zollinger–Ellison syndrome who have undergone prior gastric acid reducing surgery require a higher dose of PPI therapy [23]. In patients undergoing a curative gastrinoma resection both the secretin test and fasting serum gastrin determination can be used to establish the early diagnosis of recurrent disease whereas the calcium provocative test and imaging studies fail to detect recurrences [24].

Other causes of hypergastrinemia

**Antral G cell hyperplasia**

Antral G cell hyperfunction or hyperplasia can lead to hypergastrinemia associated with either normal or elevated gastric acid secretion. The primary differentiation between this disorder and Zollinger–Ellison syndrome is an exaggerated gastrin secretion in response to a protein meal. This disorder was of major interest in the 1970s to the 1990s until the discovery of *Helicobacter pylori*, which established that hypergastrinemia occurred with infection and that eradication resulted in normalization of the serum gastrin levels. Infection with *H. pylori* results in elevations in gastric juice ammonia levels hence antral gland pH, which is thought to predispose to hyperfunction by the antral G cell. In an animal model, the effects of elevated luminal ammonia in the presence of gastritis resulted in antral G cell hyperfunction [25]. Currently, hypergastrinemia attributable to G cell hyperfunction or hyperplasia is more likely to be found in conjunction with PPI use [26] as well as patients who have undergone vagotomy.

**Retained gastric antrum syndrome**

The retention of the distal gastric antrum occurring in gastric resections such as with the Billroth II gastrectomy removes this region of the gastric antrum from direct communication with the remainder of the gastric lumen, thereby circumventing the inhibitory pathways that normally reduce gastrin levels resulting in hypergastrinemia [27]. This diagnosis should therefore be considered in any patient presenting with a history of gastric acid reducing surgery. These patients are at greater risk for the development of recurrent episodes of peptic ulcer bleeding. Patients with retained gastric antrum syndrome exhibit elevated serum gastrin, gastric acid hypersecretion, a negative meal stimulation test, a negative pentagastrin stimulation test, and a negative calcium provocative test. This condition can therefore be distinguished from Zollinger–Ellison syndrome and G cell hyperfunction by the negative results of the provocative testing. Sodium Pertechnetate Tc-99m scanning can also be used to confirm the diagnosis; in one series this scan was found to have a 100% specificity [28].

![Figure 156.3](image-url) The effects of secretin infusion (left), calcium (center) and standard meal (right panel) on serum gastrin in patients with Zollinger–Ellison syndrome. The secretin test is positive in 87%, the calcium infusion in 56% and the standard meal in 25% of patients. Data from [22].
**Gastroparesis**

In patients in whom a reduction in gastric motility results in delayed gastric emptying, such as in patients with diabetes, there is retention of gastric contents. The most likely cause is due to vagal autonomic neuropathy that results in a reduction in emptying, as discussed in detail in Chapter 55. Patients with scintigraphy-proven gastroparesis have been found to manifest increased serum levels of CCK and oxytocin as well as gastrin [29]. Results suggest that impaired gastric emptying should be considered in the differential diagnosis of hypergastrinemia. It has been suggested that changes in meal-induced gastric emptying rate combined with the measurement of serum gastrin predict the development of autonomic neuropathy in type II diabetics [30].

**Atrophic gastritis and hypochlorhydria (pernicious anemia)**

Atrophic gastritis is being recognized more frequently as more patients undergo upper endoscopy especially in elderly patients and in middle-aged women [31]. Patients with atrophic gastritis, with or without resulting pernicious anemia exhibit hypergastrinemia, again reflecting the absence of negative feedback reflecting lack of acid production [32]. The net result of prolonged hypergastrinemia associated with chronic atrophic gastritis and pernicious anemia is ECL cell hyperplasia and gastric neuroendocrine tumors (type I gastric carcinoids). Of note, treatment of a small number of patients with netazepide (YF476), an oral gastrin receptor antagonist, reduced gastric carcinoids without a direct effect on serum gastrin levels [33,34].

**Chronic renal failure and uremia**

Hypergastrinemia is common in patients with chronic renal failure and in patients undergoing hemodialysis, who typically exhibit hypochlorhydria despite the presence of hypergastrinemia [35]. Although the mechanism for hypergastrinemia in renal failure is not known, uremic patients have a 30–50-fold increase in volatile aliphatic amines in the gastric juice, which in turn induces the antral G cells to release gastrin [36]. The hypergastrinemia associated with chronic renal failure can induce the growth of gastric mucosa and parietal cell hypertrophy and the development of ECL cell hyperplasia, but not the development of gastric neuroendocrine tumors [37]. Gastrin is metabolized in the kidney where it is excreted. Furthermore, CCK2 receptors are expressed in the kidney [38]. Using In-111-labeled minigastrins, the authors reported high affinity and rapid renal clearance in rats [39]. Gastrin may also exert an effect on the kidney by interacting with CCK2 receptors expressed on kidney proximal tubular cells to increase natriuresis and diuresis, the mechanism of which has not been completely clarified [40]. Whether these mechanisms are relevant to the hypergastrinemia that occurs in renal failure is unknown, although regression of this hypergastrinemia has been demonstrated following renal transplantation [41].

**Use of proton pump inhibitors**

Use of PPIs can result in hypergastrinemia, defined as a fasting serum gastrin >100 pg/mL. In contrast, the less potent histamine H2 receptor antagonists typically cause only a minor increase in serum gastrin [42]. On average the fasting serum gastrin associated with PPIs increases in the 200–300 pg/mL range, although the elevation depends on the dose of PPI used, and there is a wide variation in the hypergastrinemic response, with some patients showing little gastrin elevation. While there was initially some concern about the induction of hypergastrinemia by PPIs given the link to the development of ECL cell carcinoid tumors in rats, no such association has been observed in patients, and in general, it was felt that if achlorhydric doses of PPIs were not used then significant hypergastrinemia could be avoided [43]. As previously noted, fasting serum gastrin typically returns to normal 7–10 days after discontinuation of PPIs. Discontinuation of PPIs is also associated with rebound gastric acid hypersecretion. This probably reflects the increase in parietal cell mass from the trophic effects of hypergastrinemia [44]. Long-term use of PPI has been reported to worsen oxyntic mucosa gastritis and the resulting gland atrophy has been considered a potential risk factor for neoplastic changes in the gastric mucosa.

**Secretin provocation testing**

The measurement of serum gastrin following intravenous infusions of secretin in Zollinger–Ellison syndrome and DU patients are useful to confirm the diagnosis of Zollinger–Ellison syndrome when the fasting serum gastrin levels are only modestly elevated [45]. This is accomplished by measuring fasting serum gastrin at baseline, followed by rapid injection of secretin (2 U/kg) intravenously and measurement of serum levels of gastrin at 2, 5, and 10 min. In Zollinger–Ellison syndrome patients, the rise in gastrin occurs rapidly generally within 5 min, thereby obviating the need for the collection of additional samples. A positive secretin test for the diagnosis of Zollinger–Ellison syndrome is defined by an elevation of gastrin of at least 200 pg/mL above the baseline level. The secretin test has an overall sensitivity of ~90% but appears to be less sensitive for small duodenal gastrinomas [20]. Secretin receptor expression occurs in all gastrinomas and accounts for the stimulation of gastrin release as shown in a study of 54 patients with Zollinger–Ellison syndrome [46]. Porcine secretin previously used for the diagnosis of Zollinger–Ellison syndrome is no longer available in the US. Use of human recombinant secretin has been approved by the US Food and Drug Administration (FDA) for this purpose. Synthetic secretin for the diagnosis of Zollinger–Ellison syndrome appears to perform in a manner identical to porcine secretin [47], though the availability of even this secretin in the US is limited. Glucagon has been used as an alternative stimulus in this setting and yields a similar response to that seen with secretin in Zollinger–Ellison syndrome patients [48]. Glucagon is administered i.v. at a dose of 20 μg/kg plus 20 μg/kg/h for 1 h, with measurement of serum gastrin at 1 and 3 min preceding glucagon infusion and 3, 5, 10, 20, 30, 40, 50, and 60 min after administration.
Pepsinogen and other investigative tests of gastric function

Though still investigational, determination of serum pepsinogen (PG) has shown promise for clinical use. PGs are a family of gastric aspartic proteases secreted from the chief cell zymogen granules and converted in the gastric lumen by H+ to pepsin to initiate the digestive process of proteins (see Chapter 23). Pepsin I and II are active at an intraluminal pH < 3.5 and are irreversibly inactivated at pH > 5 and at higher pH values (>7) are denatured [49]. PG secretion is stimulated by agents that activate chief cell intracellular calcium such as CCK and GRP or by activating cyclic adenosine monophosphate (cAMP) such as forskolin, vasoactive intestinal polypeptide (VIP), and PACAP [50]. Secretin infusion also stimulates PG secretion, presumably through its ability to stimulate cAMP in the chief cell [51]. Measurement of PGs I and II in the serum may serve as noninvasive surrogate biochemical markers of gastric acid secretion. The serum PG I is always high in patients with nonatrophic gastritis, while it is low in patients with atrophic gastritis. In contrast, serum PG IIC is elevated in both. Hence, a combination of low PG I and low PG I/II ratio is a marker of significant gastric atrophy and can serve to detect patients at risk for gastric cancer [52,53].

Serum PG I elevations are found in patients with gastrinoma. This is highly specific, especially in combination with an elevation in basal acid output (BAO), positive secretin testing, and radiological imaging. PG I is low in patients with chronic renal failure. Simultaneous measurement of serum PG I and serum creatinine are useful in the assessment of elevated serum gastrin levels [54]. Serum PG levels may be useful to evaluate the extent and recurrence risk for gastric cancer. In one study, the ratios of PG I/PG II were evaluated in 107 patients with gastric cancer. In patients with a low (<2.0) ratio, the prognosis was worse than patients with a ratio of >2.0 [55]. Serum PG is significantly diminished after eradication of H. pylori [56]. In clinical practice, serum PG can be used as a biomarker of gastric inflammation and the status of the gastric mucosa. In atrophic gastritis, elevated levels are associated with an increased risk of gastric cancer. In H. pylori infection, the serum PGs I and II are typically increased. The treatment of H. pylori reduces both PG I and PG II, and increases the PG I to PG II ratio [57]. Measurement of serum PGs for the evaluation of dyspepsia is of limited value [58]. Various other noninvasive indirect tests were developed for gastric acid measurement. These include urinary and serum dye based tests to detect hypochlorhydria, hydrogen breath testing utilizing magnesium or calcium carbonate, and a pH sensitive radio telemetry Heidelberg capsule [59–61]. However, none of these tests received widespread acceptance for clinical use and remain experimental.

Gastric acid secretory testing

There are generally two methods for assessing gastric function: quantitatively measuring the amount of acid present in the stomach and qualitatively assessing intragastric pH. The former method is more accurate since it takes into account both the [H+] present in the gastric juice and the volume of gastric juice produced over a given time period, generally expressed as mmol H+ per hour. Measurement of intragastric pH using indicator paper to estimate the pH was reported by Sippy in 1959 [62]. In the early 1970s, pentagastrin infusion largely replaced the use of histamine for the determination of peak gastric acid output [63] which demonstrated that gastric output of acid during the first hour after stimulation by the peptide is a valid measurement of the amount of maximal secretory capacity of the stomach. A newer intragastric titration method was developed to assess the gastric acid secretory rate through measurement of the buffer content and the rate of net gastric acid secretion in humans fed a standard meal using a sodium bicarbonate infusion to "clamp" the intragastric pH [64]. Lewin and coworkers in 1973 used intragastric BAOs and MAOs to document gastric acid hypersecretion in patients with Zollinger–Ellison syndrome [65]. Other methods that have been used include constant duodenal perfusion with a nonabsorbable marker, [14C] polyethylene glycol (PEG), to quantify emptying into the duodenum. By manipulating the intragastric pH, gastric acid and pepsin outputs can be calculated [66]. A modification of intragastric titration has been developed using glucose (5.8%) as the test meal to inhibit gastric emptying, since intragastric glucose will not stimulate gastrin release [67]. Technetium scanning has also been used to estimate gastric acid secretion but has not been generally clinically adopted [68].

Yamaguchi et al. assessed gastric acid secretion in 1987 in gastric juice collected under direct endoscopic observation [69]. Endoscopic gastric analysis was compared to standard, nasogastric analysis, in patients with Zollinger–Ellison syndrome. Excellent agreement was observed between the two groups, and the former was found to yield greater reproducibility for measurement of gastric acid output and measuring gastric juice volume [70] (see Figure 156.3). More recently, capsule endoscopy (Smartpill), a noninvasive measuring device for gastric acid secretion, has been developed [71] (see Figure 156.5). This method appears to be as accurate and as reproducible as nasogastric tube-measured gastric acid output. Measuring MAO was shown in one study to have a small but significant benefit over measuring BAO alone [72].

Indications for gastric acid secretion testing

Gastric acid secretory measurement is important to confirm gastric acid hypersecretion in the management of patients with fasting hypergastrinemia. It helps differentiate high acid output diseases like Zollinger–Ellison syndrome, antral G cell hyperplasia, retained gastric antrum syndrome, and gastric outlet obstruction, from conditions causing achlorhydria such as pernicious anemia, vagotomy, chronic atrophic gastritis, and gastric cancer. Gastric acid secretory measurement can also guide therapy in Zollinger–Ellison syndrome patients. Gastric pH testing may also serve as a screening tool to identify patients
with gastric atrophy who are predisposed to gastric carcinoma among high-risk populations [73].

Methods of gastric acid measurement

Nasogastric tube-based acid aspiration test

The aspiration port of a gastric tube is placed in the most dependent portion of the gastric fundus, and the position of the tube is confirmed by fluoroscopy or by the observation of recovery of >90% of instilled water. Gastric acid is then aspirated either manually or using a suction device connected to a nasogastric tube. The volume of the gastric content is measured and its acidity determined by titrating to a pH of 7 using neutralizing alkaline agents and chemical indicators or pH meters [74,75]. BAO is determined by aspirating gastric acid in 15 min increments for an hour. The upper limit of normal BAO is approximately 10 mmol/h in men and 5 mmol/h in women. MAO is the total acid secretion during a period of 60 min (calculated as a sum of four 15 min collections) after parenteral administration of pentagastrin. PAO is determined by adding the sum of the two largest 15 min collections following gastric stimulation and then multiplying by 2. MAO and PAO correlate with the total parietal cell mass. In Zollinger–Ellison syndrome, BAO is typically above 10 mmol/h; and MAO >45 mmol/h [76].

Several other modalities have been utilized to stimulate gastric acid. These include a nonpharmacological test meal. However, the latter is fraught with poor precision and poor reproducibility in addition to the technical challenges of titrating gastric acid mixed with food. The use of histamine, a gastric acid stimulant, was abandoned due to its H1 receptor mediated side effects of nausea, palpitations, and hypotension [10,77]. Pentagastrin, a rapidly acting stimulant, is better tolerated and yields reproducible results [78]. Tetragastrin has properties comparable to pentagastrin [79]. GRP, a neuropeptide that stimulates antral G cells, can simultaneously assess gastrin secretion and gastric acid stimulation [80]. At higher acid output states, the correlation between the BAO and intragastric pH appears more linear, and therefore pH more closely reflects the level of acid secretion (Figure 156.4) [81], but this remains largely a research tool at present.

Endoscopy-based gastric acid measurement tests

Quantitative test

This test involves aspiration of gastric secretion into a standard container under direct endoscopic visual guidance both during basal conditions and after intravenous injection with gastric stimulants pentagastrin or tetragastrin. The volume of aspirate is measured and acidity determined by titration as described above. BAO, MAO, and PAO are calculated as with gastric tube-based methods. This test subjects the patients to a prolonged upper endoscopy procedure which is uncomfortable, with potential need for large doses of sedatives and analgesics [69,82,83]. The endoscopic method is similar in outcome with the nasogastric test (see Figure 156.4).

Ambulatory intragastric pH tests

Conventional nasal catheter based pH monitoring

Intranasal placed catheter systems containing pH-measuring electrodes have been used for esophageal pH monitoring. These catheters have also been adapted to measure intragastric pH. A standard dual channel pH probe with two electrodes is placed, either with manometric guidance or using fluoroscopy, and connected to a recording device directly or indirectly by radiotelemetry. It can record intragastric pH for up to 24 h [84]. The position of the probe is vital as different parts of the stomach yields different pH values. Although the optimum location for measuring gastric pH remains to be determined, it is usually done at 10 cm below the upper margin of lower esophageal sphincter [85]. Placement of the probe can be very challenging, requiring multiple manipulations of the probe and repositioning of patients. In addition, the pH probe tends to move, depending on various factors, including body position, bolus size, bolus composition, and when the patient talks. It is also uncomfortable and conspicuous, leading most patients to modify their daily activities and/or diet that interfere with accurate gastric acid assessment [73]. Integrated esophageal and gastric acidity values can be calculated from 24-h pH recordings, which have been used to evaluate esophageal and gastric disorders and to predict therapeutically responses to antisecretory therapy. Measurement of...
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Ambulatory gastric pH testing has several drawbacks, most notably, the inability to determine the volume of gastric acid secretion. In addition, the acidity of gastric contents may be influenced by food, gastric emptying, and dilution effect of saliva and intestinal secretions [73].

Capsule endoscopy

Capsule endoscopy, a wireless pH-sensing capsule, may also be used to determine gastric acid output non-invasively. It appears to be as accurate and as reproducible as nasogastric tube-measured gastric acid output. As shown in Figure 156.5, gastric acid output is stimulated by Ensure, as reflected by the negative slope of the pH curve. This slope reproducibly and accurately predicts gastric acid secretion.

Special considerations: Zollinger–Ellison syndrome and gastric acid hypersecretion

Zollinger–Ellison syndrome is a rare digestive disorder characterized by increased production of stomach acid. The diagnosis of Zollinger–Ellison syndrome is made clinically in the patient with

in-vivo gastric autotitration can be performed using gastric pH measurements [86].

Wireless capsule pH measurement

A wireless pH monitoring system (the Bravo wireless pH capsule, Medtronic, Shoreview, MN) was developed to enable longer pH monitoring time than the conventional catheter based techniques that were better tolerated. The Bravo pH monitoring system utilizes a radio telemetry pH-sensing capsule, which is typically attached to the gastric mucosa. The oblong capsule (6 mm × 5.5 mm × 25 mm) has an antimony pH electrode and a reference electrode located at its distal tip with an internal battery and a transmitter. The capsule simultaneously measures pH and transmits data, via a radiofrequency signal, to a pager-sized receiver clipped onto the patient’s belt [87]. Although it was initially developed for monitoring esophageal pH, several investigators adapted its use for intragastric pH monitoring by placing it endoscopically in the gastric wall under direct vision. The placement of capsule can also be done using a delivery catheter. The capsule records gastric pH for 48 h and is usually spontaneously eliminated within 1–2 weeks [88]. High early dislodgment (before 48 h) rates were seen in the earlier studies, but Chang and colleagues developed a clipping technique, which reduced the early capsule dislodgement rate from 70% with conventional delivery system to 20% [89]. The advantages of the Bravo system compared with traditional pH monitoring with a catheter include good tolerability due to less pharyngeal discomfort, lack of restriction of activities of daily life, and longer ambulatory monitoring of pH. Moreover, it does not significantly increase the endoscopy procedure time after an initial learning curve [87–89]. However, ambulatory gastric pH testing has several drawbacks, most notably, the inability to determine the volume of gastric acid secretion. In addition, the acidity of gastric contents may be influenced by food, gastric emptying, and dilution effect of saliva and intestinal secretions [73].

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Zollinger–Ellison syndrome is a rare digestive disorder characterized by increased production of stomach acid. The diagnosis of Zollinger–Ellison syndrome is made clinically in the patient with
elevated fasting serum gastrin in the absence of achlorhydria with either a positive secretin test or histologically proven neuroendocrine tumors (NET). Physical examination is not revealing in the majority of cases. The diagnosis is made biochemically when the fasting serum gastrin is elevated (>100 pg/mL) in the absence of achlorhydria. Typically, patients with gastrinoma have levels of serum gastrin >500 pg/mL, and a level >1000 pg/mL in the absence of achlorhydria is virtually diagnostic of Zollinger–Ellison syndrome. Hypochlorhydria and achlorhydria can result in false-positive secretin testing [73]. Some patients with acid peptic disease have idiopathic gastric acid hypersecretion defined as a basal acid output >10.0 mmol/h in the setting of normal gastrin levels; however, a significant proportion have basal acid outputs >15.0 mmol/h, which is within the range found in Zollinger–Ellison syndrome. Although idiopathic gastric acid hypersecretion is more common than Zollinger–Ellison syndrome, it is important that these two disorders be differentiated because of differences in treatment and natural history.

Once the diagnosis of Zollinger–Ellison syndrome is made, the control of gastric acid secretion is usually the most important step in the management of these patients [90]. In practice, this can be achieved by maintaining the level of acid secretion to <10 mmol/h. The majority of patients will require continued gastric acid antisecretory medications, even following curative gastrinoma resection [90]. For patients with MENI syndrome, GERD, or prior gastric acid reducing surgery, the BAO should be maintained at <1–2 mmol/h (see Chapters 56 and 57).

### Pancreatic function testing

The pancreas contains both endocrine and exocrine elements each of which can be tested by either invasive secretory tests or serum biochemical markers. Various tests have been developed to measure the exocrine secretory function of the pancreas to diagnose primary or secondary pancreatic insufficiency. However, the role of functional analysis has diminished over time due to the advent of highly sensitive noninvasive imaging modalities including computed tomography imaging (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and invasive endoscopic ultrasound (EUS) [91]. Currently, functional evaluation of the pancreas is indicated to diagnose chronic pancreatitis if imaging findings are inconclusive, and in the assessment of the need and efficacy of pancreatic enzyme substitution therapy in patients with known chronic pancreatitis.

### Exocrine pancreas

The pancreatic exocrine function tests fall into two categories, direct and indirect.

### Direct tests

Direct tests of pancreatic secretory function involve the collection of pancreatic secretions after intravenous administration of a secretagog or a combination of secretagoggs. These tests are based on the principle that maximal volume, bicarbonate secretion, and enzyme secretion are related to the functional mass of the pancreas. Secretagoggs stimulate cAMP, which in turn results in secretion [92].

#### Secretin and cholecystokinin tests

The most common secretagoggs used for the stimulation of pancreatic secretions have been secretin, CCK, or a combination of both. The secretin test provides measurement of volume and bicarbonate secretions whereas CCK stimulates digestive enzymes including amylase, trypsin, and lipase. The combination provides comprehensive information about both ductal and acinar function of the pancreas [93], providing the most sensitive and specific measurement of exocrine pancreatic functions. The duodenal secretions can be collected by either a nasally placed catheter or during endoscopy [94].

Physiologically, CCK is secreted into the blood from intestinal (L cells) endocrine cells following meals. Certain luminal sensing receptors, presumably in the duodenum, results in CCK release by endogenously released peptides such as the luminal CCK-releasing factor (LCRF). Using dispersed human intestinal mucosal cells, LCRF (5–200 nM) was demonstrated to induce CCK release, an effect inhibited by the L-type calcium-channel blockers [95]. Although the LCRF test is not commercially available or approved for human use, it has the potential for explaining the physiological basis for CCK release.

#### Nasal catheter aspiration

For this test, a double-lumen nasoduodenal tube is used for the collection of pancreatic secretions. Gastric intubation is required to remove acidic gastric secretions that might interfere with the accurate quantification and assess of alkaline pancreatic secretions. Secretagoggs are administered via continuous intravenous infusion during which the duodenal juice is collected over ice by fractional collection. The pancreatic secretions lost distally into the jejunum can be quantified by constant perfusion of nonabsorbable marker such as cobalamin or PEG through the duodenal tube [96].

#### Endoscopic aspiration

The endoscopic collection of duodenal fluid occurs under direct visual guidance at 0, 15, 30, 45, and 60 min after intravenous administration of the secretagog [96,97]. The direct tube-based pancreatic function tests are no longer used outside research facilities as these are invasive, cumbersome, time consuming, and expensive. Their use is limited mainly to validate new pancreatic function tests.

#### Secretin-stimulated magnetic resonance pancreateography (S-MRP)

**Direct test** This tubeless direct test involves the quantification of pancreatic secretions during MRCP after intravenous secretin administration. The duodenal filling is reduced significantly after chronic pancreatitis and it is sensitive enough to diagnose patients with mild exocrine pancreatic insufficiency. The test
correlates well with the direct duodenal intubation secretin test and has the added advantage of providing morphological information of the pancreatic ducts [98].

**Indirect test** Indirect pancreatic function tests involve the measurement of pancreatic secretions in duodenal samples after nutrient ingestion, products of pancreatic enzyme action on ingested substances, pancreatic enzymes in the stool, or serum markers of pancreatic insufficiency. Previously, these have required duodenal intubation but have been supplanted by so-called tubeless tests.

These tubeless tests can be subclassified into genetic tests, fecal tests, and oral tests.

**Fecal tests**

**Fecal fat analysis** Fecal fat analysis is a nonspecific test for malabsorption, and is helpful in the diagnosis of steatorrhea due to either pancreatic exocrine insufficiency or a small bowel disorder. It involves the quantification of fat in stool samples collected over 72 h in a patient ingesting a standard fat diet containing 70–100 g/day of fat. Normally, 7% or less of ingested fat appears in the stool. Major limitations of this test include poor patient compliance with diet and stool collection, and the cumbersome processing of stool samples needed. In order to overcome these difficulties, microscopic analysis for the presence of fat in a single stool sample by Sudan staining is commonly used in routine clinical practice to diagnose steatorrhea. This simple qualitative analysis is almost as sensitive as quantitative measurements of stool fat. However, as steatorrhea occurs only with advanced pancreatic insufficiency, this test is not sensitive to identify mild to moderate disease. Of note, as mentioned above, it is not specific for pancreatic disorders requiring subsequent evaluation to distinguish between maldigestion and malabsorption [99,100].

**Fecal chymotrypsin analysis** This test involves the quantification of the pancreatic enzyme chymotrypsin activity in a single stool sample. Although the test is easy to perform in a clinical setting, it has several limitations. Some of the chymotrypsin secreted by the pancreas is inactivated during intestinal passage. Furthermore, the activity of this enzyme in the stool becomes diluted in patients with diarrhea. Hence in order to improve the specificity of the test, at least 3 U/g of stool should be used to define normal. However, this significantly compromises the sensitivity of this determination in diagnosing mild to moderate pancreatic insufficiency thereby limiting its utility in clinical practice. Pancreatic enzyme supplements should be discontinued for at least 48 h before obtaining the stool sample to avoid false-negative results in these patients. Conversely, this test may be used to confirm compliance among patients on pancreatic enzyme replacement therapy in which case the stool levels of chymotrypsin would be elevated [101].

**Fecal elastase activity** Elastase is another pancreatic enzyme, which can easily be measured in a single stool sample. As compared to chymotrypsin, this enzyme remains relatively stable during intestinal transit and its fecal concentration accurately reflects the amount secreted by the pancreas. Moreover, the assay used to measure fecal elastase involves human monoclonal antibodies and hence oral pancreatic enzyme replacement therapy does not interfere with the test. These advantages make this a practical and useful test in routine clinical practice. Normal fecal elastase concentration is considered to be that above 200 μg/g of stool. Levels below 50 μg/g are quite specific for pancreatic insufficiency, as long as the sample is not diluted by watery diarrhea. The sensitivity of the test is also high in cases of moderate to severe pancreatic insufficiency [102,103].

**Oral test**

**13C-mixed triglyceride (13C-MTG) breath test** This test is based on the principle that intraduodenal hydrolysis of a 13C-labeled substrate (13C-MTG), given along with an oral test meal, by pancreatic lipase produces 13C marked metabolites, which are absorbed from the gut and then metabolized in the liver, leading to the release of 13CO2 that is eliminated in the breath. The amount of 13CO2 expired can be determined by either mass spectrophotometer or near infrared analysis, and correlates with exocrine pancreatic function. Levels of 13CO2 recovered at 6 h if below 58% are highly suggestive of fat malabsorption. This test can provide an alternative to fecal fat analysis [104] (Table 156.1).

**Endocrine pancreas**

Neuroendocrine tumors are a heterogeneous group of peptide and/or biogenic amine-secreting tumors characterized by combinations of argentaffin cells possessing granules that stain positively for peptides and chromogranins, synaptophysins or neurotensins and are covered in more detail in Chapter 88 [105]. These tumors are distinguished both biochemically and clinically by their normal peptide products.

**Glucagonomas**

Glucagonomas arise from the pancreatic α cells and lead to an elevation of the serum glucagon level. Classically, the “glucagonoma syndrome” comprises a distinctive rash, weight loss, stomatitis, glossitis, mild diabetes, hypoaminoacidemia, and a normochromic normocytic anemia, as well as a susceptibility to deep vein thrombosis and neuropsychiatric disturbances. Patients may have normal serum glucose levels despite very elevated serum glucagon levels [106,107]. Preproglucagon, also designated as enteroglucagon, normally produced in the cells in the intestine, is a growth factor for gut mucosa, explaining the association of glucagonomas with mucosal thickening and villous hypertrophy throughout the small intestine [108–110]. Markedly elevated fasting plasma levels of pancreatic glucagon, often in excess of 1000 pg/mL (normal <150 pg/mL) are generally characteristic, and a level >1000 pg/mL is virtually diagnostic of a glucagonoma. There are no specific provocative studies to confirm an elevated glucagon level [111].
Insulinomas

Insulinomas are tumors of pancreatic β cells that secrete excessive amounts of insulin and may clinically manifest with hypoglycemia [112]. Insulinomas occur more often in women and are usually diagnosed in patients in the fourth and fifth decades [113–118]. While serum glucose concentrations may drop as low as 30–35 mg/dL after a 3-day fast (especially in women), insulin levels decrease proportionally [119] but remain elevated in insulinoma patients. There are several ways to relate glucose and insulin concentrations during fasting, such as the simple insulin (U/mL) to glucose (mg/dL) ratio. In normal subjects, this ratio is below 0.3 as fasting continues, whereas in patients with inappropriate insulin secretion, the ratio will almost invariably rise above 0.3 [120]. Thus, elevated insulin concentrations are not necessary to establish the diagnosis, and a value of 25–40 (U/mL) at a time when the glucose concentration has fallen to less than 40 mg/dL is considered diagnostic. Provocative testing with tolbutamide, leucine, glucagon, and calcium is sometimes used, but false-positive and false-negative results are common. Proinsulin is composed of two amino acid chains that are connected by a 33 amino acid connecting peptide, termed the C peptide. Both insulin and the C peptide are secreted in similar equimolar amounts. Normally proinsulin in the fasting plasma is <20% of the total insulin whereas it is increased to 25%–75% with insulinoma [121]. Aggressive insulinomas are more often associated with the highest levels of proinsulin (50%–75%) [122]. Patients with insulinoma have increased amounts of circulating proinsulin but a normal or elevated level of C peptide that can be measured in either blood or urine, and this is useful to exclude the surreptitious use of insulin in some patients [123]. In one study, the diagnosis of insulinoma was established by a glucose level of 40 mg/dL with a serum insulin level of 6 mU/mL, a C peptide level exceeding 200 pmol/L, and negative screen for sulphonlyurea [124]. Since nearly all insulinomas can be successfully removed at surgery, early recognition and confirmative testing is useful in achieving a cure.

VIPomas

These neuroendocrine tumors are relatively rare and result in a condition that is often referred to as pancreatic cholera (watery diarrhea, hypokalemia achlorhydria syndrome) because they hypersecrete VIP or peptide histidine isoleucine [125]. Interestingly, gastric acid secretion is usually low or absent, even after stimulation with pentagastrin, and this is thought to be related to the role of VIP in stimulating the D cells to release the inhibitory peptide, somatostatin. Patients with pseudopancreatic cholera syndrome and laxative abuse can be distinguished by a normal VIP level (<170 pg/mL) [126]. VIP is relatively unstable at room temperature, so blood should be centrifuged.

Table 156.1 Exocrine pancreas function tests.

<table>
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<tr>
<th>Test</th>
<th>Advantages</th>
<th>Challenges</th>
<th>Clinical use</th>
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<tr>
<td>Secretin and cholecystokinin stimulation test</td>
<td>Most sensitive and specific</td>
<td>Requires nasal catheter or endoscopy</td>
<td>Validate new pancreatic function tests</td>
</tr>
<tr>
<td>Secretin stimulated magnetic resonance pancreatography</td>
<td>Provide additional morphological information of the pancreatic duct</td>
<td>Requires expensive radiological test</td>
<td>Diagnose mild exocrine insufficiency</td>
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<td><strong>Indirect tests</strong></td>
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<tr>
<td>Qualitative fecal fat analysis</td>
<td>Readily available</td>
<td>Not specific for pancreatic insufficiency</td>
<td>Diagnose malabsorption</td>
</tr>
<tr>
<td>Fecal chymotrypsin</td>
<td>Simple test requiring single stool sample</td>
<td>Poor specificity due to dilution in stool, and crossreactivity with exogenous enzymes</td>
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<tr>
<td>Fecal elastase</td>
<td>Do not crossreact with exogenous supplements</td>
<td>Loss of specificity due to dilution by watery diarrhea</td>
<td>Screen for moderate to severe pancreatic insufficiency</td>
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<td><strong>Oral tests</strong></td>
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| 13C-mixed triglyceride (13C-MTG) breath test | Noninvasive | Limited availability | Not specific for pancreatic insufficiency | Alternative to fecal fat analysis test for diagnosis of malabsorption |
immediately and the serum frozen. Levels >900 pg/mL are commonly observed in VIPomas [127]. Similar to glucagonomas and insulinomas, tumor processing of VIP is impaired in patients with neuroendocrine tumors and prepro-VIP levels can be detected in the circulation [128].

**Somatostatinomas**

Somatostatinomas are islet D cell tumors which usually arise in pancreas islet cells. Most somatostatinomas are malignant and accompanied by hepatic metastases [129,130]. The excessive production of somatostatin usually leads to diabetes mellitus, cholelithiasis, diarrhea, and steatorrhea. Somatostatin is a potent inhibitor of gastric acid secretion [131]. Pancreatic steatorrhea and a reduction in the intestinal absorption of fats and vitamins is common [132]. Although there is no specific provocative test for somatostatin-releasing NETs, tolbutamide and arginine can stimulate an increase in somatostatin levels in the serum [133,134].

**Ghrelin-producing neuroendocrine tumors**

Ghrelin is a 28 amino acid peptide, primarily produced by the oxyntic mucosa X/A-like neuroendocrine cells in the stomach, but also expressed by NETs in the pancreas, heart, adipose tissue, and immune system. Ghrelin production in some NETs has been demonstrated and serves to be generally predictive of disease activity [140]. In one study of 35 patients with NETs, elevated endogenous ghrelin exerted an orexigenic effect, helping to maintain body mass [141].

**Growth hormone-releasing factor tumors**

Growth hormone-releasing factor (GRF) is comprised of several different amino acid fragments (GRF-44, -40, -37, and -31) that result in acromegaly in a small percentage of patients with NETs [142]. The first patient with a GRF-releasing neuroendocrine tumor with MENI was reported in 1984 [143]. The diagnosis is established by the measurement of the serum level of GRF. Up to 30% of gastrinomas contain adrenocorticotrophic hormone (ACTH)-like immunoreactivity, suggesting that all patients with the Zollinger–Ellison syndrome or multiple endocrine neoplasia type MENI should be screened for Cushing syndrome [144]. Somatostatin receptor imaging (SRI), and In-111 octreotide and Ga-68 DOTA-TATE have been used to localize these ACTH-secreting tumors [145].

References are available at www.yamadagastro.com/textbook

**Further reading**


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Note: page numbers in italics refer to figures, those in bold refer to tables

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GERD – gastroesophageal reflux disease
IBD – inflammatory bowel disease

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