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The AFS Textbook of Foregut Disease

AMERICAN FOREGUT SOCIETY

Springer

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Preface

The American Foregut Society emerged from the recognition that improvements in patient care would require specialization that only collaboration between gastroenterologists and surgeons could provide. Cross-fertilization increases knowledge, enables new insights, and improves expertise. This textbook exemplifies that conviction; the majority of chapters are co-authored by gastroenterologist and surgical colleagues.

Since its founding in May of 2018, the society has grown membership to over 600, accomplished three national meetings (two in the time of COVID-19), launched the subscription-based journal Foregut, inspired the creation of a European Foregut Society, and through the vision and unrelenting efforts of Ninh Nguyen and John Clarke given birth to this textbook.

Medical knowledge is progressing far faster than the ability to publish and disseminate. This textbook cannot be nor is it intended to be authoritative; rather it is intended to be a reservoir of what collaborative thinking can accomplish.

The parable of the blind men and an elephant is emblematic of the historical relationship of gastroenterologists and surgeons treating foregut disease. A group of blind men who have never seen before and must rely on touch to understand what the elephant is. Each blind man feels a different part of the elephant's body, but only one part, such as the tusk, leg, tail, or ear. They then describe the elephant based on their limited experience and not surprisingly the descriptions of the elephant are different from each other.

In some versions of the parable, they even come to suspect that the other person is dishonest and they come to blows.

Physicians are not immune to the human predisposition of claiming comprehensive knowledge based on their experience. Not only is their clinical care biased; the meetings they attend and journals they read reflect their own horizons.

We believe the American Foregut Society has provided vision to individuals and foregut disease as a whole. That this textbook came to fruition within 4 years of the society's founding is a testament to the enthusiasm generated when we start to see beyond ourselves.

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Part I

Basic Considerations

History of AFS

1

Reginald C. W. Bell and Felice Schnoll-Sussman

The American Foregut Society was born out of many individuals' dreams and passions to see a specialty thrive and flourish. A hope that different disciplines could work together to accomplish lofty goals. A desire to break down silos and build bridges. Not a simple task by any stretch of the imagination. The ethos was that we would be "better together." Who is the *we*? Foregut surgeons and gastroenterologists—the main physician stakeholders in the management of patients with diseases of the foregut. Some would think that the American Foregut Society, now more commonly referred to as AFS, was an evolution—in reality it represents a revolution. A revolutionary change in the way different specialties work together, learn together, advocate together, and grow together with a single-minded purpose—collaboration and specialization to improve patient care.

The small group of foregut surgical specialists providing the initial impetus to form the AFS immediately recognized the necessity of partnering with medical foregut specialists. Without both specialties the goals and survival of such an effort would flounder. Tripp Buckley, a general surgeon, had been proctored in his first sphincter augmentation procedure (LINX™) by the world renowned and revered Dr. Tom DeMeester and found himself navigating his practice to one dedicated to the management of GERD. Dr. Reginald Bell, a private practice foregut surgeon in Colorado, developed a multicenter Registry of Outcomes in Anti-Reflux Surgery (ROARS) to prospectively collect outcomes for laparoscopic fundoplication and magnetic sphincter augmentation. Dr. John Lipham was trained by and accorded resultant recognition by Tom DeMeester as chief of upper GI surgery at the Keck School of Medicine in USC. Dr. Blair Jobe is a brilliant basic science and clinical researcher and foregut surgeon in Pittsburgh. Dr. Dan Lister, a private practice foregut surgeon in Heber Springs Arkansas, has the largest Barrett's surveillance population in the state. Kate Freeman N.P. works with Dr. Bell and would become instrumental in implementing the vision of this inchoate society. Bell, Buckley, Freeman, Jobe, Lipham, and Lister met after a LINX users meeting in Chicago on September 23, 2017, to discuss the idea of a specialty and as-yet unnamed society. Paramount to the goals were establishing collaboration between specialties and forging a path to true specialization in the disease. The surgeons were all involved in training other surgeons in a new technology, magnetic sphincter augmentation (LINX). It was obvious to the group that LINX needed to be in the hands of surgeons dedicated to the practice of foregut surgery or it could be the beginning of the end of the technique.

Blair Jobe should be credited for voicing that only a grassroots movement could create this new society in the current environment. Tripp Buckley had founded a nonprofit corporation, The Heartburn Foundation, in 2014. The Heartburn Foundation was dedicated to improving care of patients with foregut disease. (His initial board members were his mother and best friend from high school.) Tripp graciously allowed The Heartburn Foundation to be the legal and financial basis of this new society. Knowing the importance of a society name that corresponded to a URL, Dan Lister researched availability, and the American Foregut Society, www.americanforegutsociety.org, with an avatar www.foregut.org, was registered in April 2018.

Discussions continued in March 2018 during the annual Foregut Disease Foundation meeting on esophageal disorders held in Hawaii. At the time this was the only recurring locus for surgeons and gastroenterologists to meet and talk. It was (and still is) a 5-day, intensive (and often intense) in-depth series of lectures and debates, and leaves the afternoons free for socializing. Over beers and Mai Tais, gastroenterologists including Mike Smith were receptive to the concept and committed to bringing the society to fruition. Shortly thereafter the grassroots movement began with emails sent to about 100 key opinion leaders in foregut. The

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message was simple: "*A group of us (Blair Jobe, Reg Bell, Tripp Buckley, Dan Lister, John Lipham) are trying to form a Foregut Society to better position ourselves in regard to research, education/training/fellowships, and ultimately develop COEs around Foregut disease. The initial step is changing our current non-profit foundation from the Heartburn Foundation to the Foregut Foundation and recruit select Foregut Surgeons / GIs to jump on board. No real costs/dues at this point. We are just trying to get a core group together that could help steer this ultimately into a formal Foregut Society. If you are interested, let me know and we will put your name on the initial membership list that we will soon present to Ethicon and other Industry leaders in order to get some financial support to get this off the ground. Let me know. Thanks!"*

Of the 100 emails sent, 98 responses were not only positive, they were enthusiastic. Though the positive response was possibly because no fee was associated with the request, subsequent developments demonstrated both enthusiasm and need for such a collaborative society.

At SAGES in April 2018, members presented to Ethicon the concept of the society and a request for financial support. Ethicon had acquired Torax Medical, manufacturer of the LINX device, and continued Torax Medical's commitment to specialization as well as to engaging gastroenterologists as key to the best use of the LINX device. Ethicon supported the concept in principle and financially, laying the foundation for further societal interaction with industry.

An interim board initially consisting of Jobe, Lipham, Buckley, Bell, Freeman, Lister, and Mike Smith put forth their own funds to hire a consulting firm to help guide them through the formation of the society – its goals, vision, mission, size, financial plan, and organizational structure. An unsociety society, starting from scratch without preconceptions of what a society should be. Over the summer of 2018, this interim board (which now included Ken Chang, David Katzka, John Pandolfino, Joel Richter, and Rena Yadlapati) met in person monthly and more often by phone or email (this was pre-Zoom), and some found time to relax together at a Cubbies game in Chicago (Figs. 1.1 and 1.2).

Bringing early reality to this dream of a society in the form of an inaugural annual meeting would deliver the message to a broader audience, initiate the conversations between gastroenterologists and foregut surgeons, and establish industry ties. John Lipham's "go big or go home" encouraged needed contributions from board members to supplement the grant from Ethicon for the needed financial commitment to host the inaugural meeting in Las Vegas in March 2019. Dr. Felice Schnoll-Sussman, a gastroenterologist at Weill Cornell in NYC, and Reg Bell were course directors. Kate Freeman, who would become the executive director of AFS, along with the interim board and course directors hosted 550 attendees at a

Fig. 1.1 The initial interim board, Chicago June 9, 2018. From left to right: Reginald Bell, Kate Freeman, Tripp Buckley, Mike Smith, John Lipham, Dan Lister, John Pandolfino (Blair Jobe in absentia)

Fig. 1.2 Enjoying a rare moment of relaxation

3-day, state-of-the-art meeting with over 40 state-of-the-art lectures from as many leaders in their respective fields (Fig. 1.3).

On the heels of an incredibly successful meeting, the inaugural AFS board was convened to deliver on the mission of improving education, patient care, and outcomes in the diseases of the foregut (Fig. 1.4).

With that our vision became clear: "To advocate personalized treatment strategies for patients with foregut disease through a collaborative partnership across disciplines."… Our mission is "To help guide both the diagnosis and management of Foregut disease through collaboration between Gastroenterologists and Foregut Surgeons. To foster research that will culminate in the development of benchmarks for excellence while also establishing specialty specific training

Fig. 1.3 The inaugural AFS annual meeting, March 15, 2019

Fig. 1.4 The inaugural AFS board, 2019. From left to right: Mike Smith, Phil Katz, Felice Schnoll-Sussman, Christy Dunst, Kate Freeman, Santiago Horgan, John Lipham, Ken Chang, Dan Lister, Peter Kahrilas, Reg Bell, Tripp Buckley, Rena Yadlapati, Bob Ganz

Fig. 1.5 An exhausted crew, September 26, 2020

Fig. 1.6 The AFS board at the annual meeting in Opryland on September 23, 2021. From left to right: Lee Swanstrom, Ken Chang, Phil Katz, Joel Richter, Dan Lister, Mike Smith, John Lipham, Felice Schnoll-Sussman, Reg Bell, Prakash Gyawali, Peter Kahrilas, Christy Dunst, Kate Freeman (Executive Director), Kerry Dunbar

programs that will ultimately translate into the improved care, safety and value for patients with Foregut diseases."

Committees were formed, individualized sponsor relationships were developed, and a journal (later to be appropriately named *Foregut* with co-editors Philip Katz and Brian Louie) was founded. The 501(c)(3) AFS Foundation was established to provide long-term backing for the society's goals of improving patient care including patient education and research.

Then, COVID altered everyone's course in 2020; the planned in-person meeting for March was delayed until June, then September, and we all pivoted to virtual. Despite these barriers, over 400 people attended! Though Felice could not be physically present, her rousing "whoop whoop" cheered the exhausted in-person program committee! (Fig. 1.5).

A decision to keep the annual meeting in September led to an in-person 2021 meeting (fortuitously at a lull in COVID's pandemonium) at the Gaylord Opryland with over 320 in-person and 100 virtual attending (Fig. 1.6).

Very early in this course, Ninh Nguyen and John Clarke had a vision for a textbook of foregut disease with chapters co-authored by gastroenterologists and surgeons, convinced Springer of the value of this endeavor; and it is through his vision and strong encouragement that this textbook has been brought to fruition.

The American Foregut Society is still in its defining stages with the desire to forge deep collaborative ties between foregut surgeons and gastroenterologists at the epicenter. The future is bright, and the time is now—"we **are** better together."

Part II

GERD and Eosinoplhilic Esophagitis

GERD Pathophysiology: The Role of the Sphincter and Crural Diaphragm

2

Ravinder K. Mittal and John C. Lipham

A recent study that utilized National Gastrointestinal Survey using MyGiHealth determined the prevalence of GERD symptoms in the past, and persistence symptoms (heartburn or regurgitation, 2 or more days/past week) among participants taking proton pump inhibitors (PPIs). 44% of the subjects reported GERD symptoms in the past and 31% in the past week. Thirty-five percent of those who experienced GERD symptoms were currently on therapy (55% on PPIs, 24% on histamine-2 receptor blockers, and 24% on antacids). Among 3229 participants taking daily PPIs, 54% had persistent GERD symptoms. On a global level, estimates of age-standardized prevalence of GERD for various locations in 2017 ranged from 4.4 to 14% cases. Age-standardized prevalence was highest (11%) in the USA, Italy, Greece, New Zealand, several countries in Latin America, Caribbean, north Africa, the Middle East, and eastern Europe. Global prevalence peaked at 19%, between ages of 75 and 79 years, and it increased by 18% between 1990 and 2017 because of the aging and population growth. One can argue whether these epidemiological studies that utilize standardized questionnaire which equate heartburn and regurgitation symptoms with GERD truly reflect GERD, but at least they reflect the scope of "GERD" in year 2021.

Gastric acid and pepsin are the major offenders and primarily responsible for the esophageal mucosal damage in reflux diseases. Interestingly though, gastric acid secretion in majority, if not all, of patients with GERD is normal. Anatomic and functional abnormality of the sphincter mechanism at the esophagogastric junction (EGJ) and deranged esophageal peristalsis allow acid and possibly other noxious agents to reach and remain in the esophagus for extended periods of time after reflux events which induces esophageal mucosal damage and symptoms. What constitutes a normal sphincter mechanism at the EGJ and what goes wrong with it in patients with GERD is the focus of this chapter.

A person can stand upside down after eating a large hearty meal, yet no food backs up into the esophagus, and hence the presence of a sphincter/valvular mechanism at the EGJ is intuitively clear. Inglefinger wrote (1958) that the crural diaphragm, oblique entry of esophagus into the stomach which creates a flap valve, and intrinsic contraction at the gastroesophageal junction area (LES) constitute the antireflux barrier. However, he stated that the importance of each of these mechanisms can be supported or challenged on the basis of evidence, which is inconclusive. Sixty years later (2018), Pandolfino and Tach in a review article cited the same three structures, i.e., LES, crural diaphragm, and flap valve as the key components of the antireflux barrier. However, the difference between 1958 and 2018 is that the methodological improvements have provided better evidence for the anatomical and functional nature of the antireflux barrier.

Allison (1951) felt that a sliding hiatus hernia was the key player in the pathogenesis of GERD and reduction of hiatus hernia was the major element in his surgical treatment of reflux disease. On the other hand, Nissen (1956) focused on improving the LES function by gastroplication which we now call fundoplication, as the major element in his antireflux surgery. Follow-up studies revealed that approximately half of the patients following Allison repair as well as following Nissen fundoplication repair had recurrence of GERD symptoms. In both repairs, recurrence of hiatus hernia is a major predictor of the recurrent symptoms. Based on the above observations, one may argue that the lack of attention to the LES in Allison repair and lack of crural diaphragm repair in the Nissen fundoplication may be the reasons for the failure of antireflux surgery. Current thinking is that hiatal dysfunction leads to the formation of hiatus hernia and repair of esophageal hiatus (by plication, mesh, or other methods) along with fundoplication should be the key elements of antireflux surgery. However, one must keep in mind

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though that the esophageal hiatus which is formed by the right crus of diaphragm is important for two reasons: (1) separating the thoracic and abdominal cavity, i.e., physically keeping the distal esophagus/LES in the abdomen, thus preventing migration of the stomach into the chest or hiatus hernia, and (2) a sphincter-like action at the EGJ that counteracts pressure gradients between the esophagus (located in the thorax) and stomach (located in the abdomen). Along with LES and crural diaphragm, phrenoesophageal ligament that anchors the two structures is the third key player at the EGJ in the maintenance of competent antireflux barrier, which will be reviewed in this chapter.

The sphincters, in general, separate adjacent organs by circumferential closure of the junction between those organs, i.e., esophagogastric junction (EGJ). Smooth muscle LES and crural diaphragm are the two sphincter mechanisms at the EGJ. Sphincters, as per English dictionary, are donut-shaped structure. The latter implies that the LES should be a thick band of the circular muscle. However, no such distinct structure has been identified when examining the EGJ visually, neither in the autopsy specimens nor at the time of surgery, which led to the belief that the LES is a functional rather than a distinct anatomical/morphological entity. However, high-frequency ultrasound imaging using catheter probes in the live humans reveal that the muscles of the LES region is approximately two times thicker than the adjacent muscles of the esophagus. Maybe, the loss of the LES muscle tone in the autopsy specimens and surgical specimen leads to the thinning of the tissue because thickness is related to muscle tone. Lieberman-Mefferet (1976) examined the distal esophagus and proximal stomach from the live donors using a dissecting microscope and concluded that the LES region has a unique anatomy; it consists of clasp (on the lesser curvature) and sling fibers (on the greater curvature of the stomach). In Lieberman-Mefferet study, some regions, especially along the greater curvature side, did have thicker muscle as compared to the other regions. Yassi et al., for the first time, performed a computer 3D reconstruction of the microscopic images of the EGJ, 8.2 μm resolution, 652 sections, spaced 50 micron apart. Their intent was to visualize the arrangement of muscle fibers/fascicle inside the LES muscle at the microscopic level. However, the 3D data files were larger than their computer memory to build the 3D anatomy of the LES, at the resolution of the captured images. Zifan et al. used images captured by Yassi et al. to create the 3D myoarchitecture of LES at the resolution of captured images. They found that the circular muscles at the lower end of the esophagus, from the right and left side, cross at the angle of His at the greater curvature of the stomach and continue onto the anterior and posterior wall of the stomach toward the lesser curvature of stomach, as the sling fibers of the LES (Fig. 2.1). These fibers appear to be same structures which in the literature have been called by several other names, i.e., "collar of Helvetius," cardiac loop of Willis, and oblique muscle layer of the stomach. The latter is also known as the innermost of the three muscle layers of the stomach. Circular muscle fibers from the lesser curvature of the stomach which are the same as the clasp fibers of the LES are inserted into the sling fibers. Finally, the longitudinal muscles of the esophagus also terminate into the sling fibers. Based on the above morphology, the LES is not a donut-shaped muscle; instead it is like a "noose" at the EGJ. Similar to LES, the myoarchitecture of the right crus which forms the esophageal hiatus (crural diaphragm) also resembles a "noose." The right crus muscle originates from the lumbar spine (L1, L2, and L3) and divides into two muscle bundles, fibers of which decussate in a "scissorlike fashion" before surrounding the esophagus to form the esophageal hiatus (Fig. 2.2). Interestingly, muscle fascicles of the right crus also decussate one more time, in the front of the esophagus

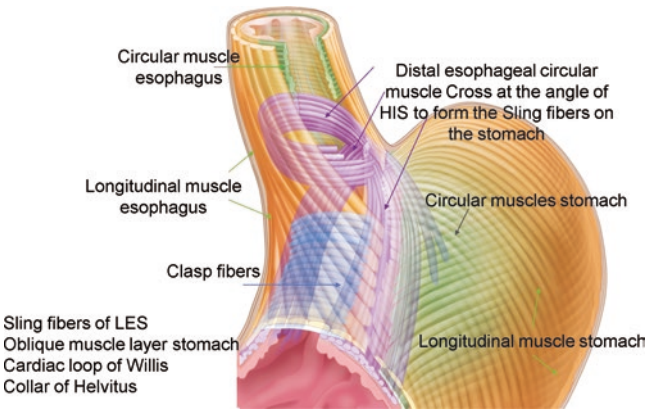

Fig. 2.1 Myoarchitecture of the lower esophageal Sphincter. Note the crossing of circular muscles of the esophagus at the angle of His and continuation as the sling fibers of the stomach. Clasp fibers of the stomach are inserted into the sling fibers of the stomach. (From Zifan A, Kumar D, Cheng LK, Mittal RK. Sci Rep. 2017 Oct 13;7 (1):13188

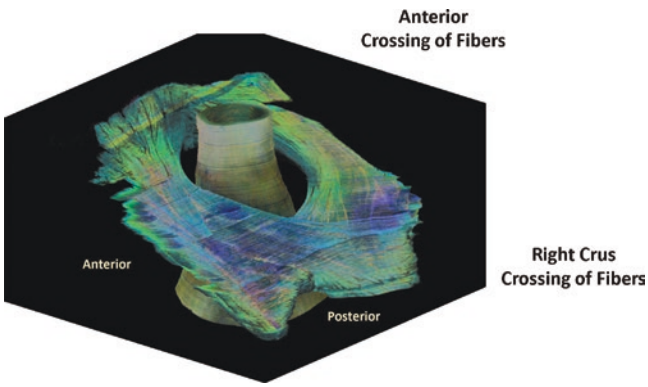

Fig. 2.2 Myoarchitecture of the esophageal hiatus is formed by the right and left crus muscles. Note that the two bundles of the right crus cross each other in a "scissorlike fashion" posterior, as well as anterior to the esophagus. From Zifan A, Kumar D, Cheng LK, Mittal RK. Sci Rep. 2017, 13;7 (1):13188

before merging into the central tendon of the diaphragm. Interestingly, the external anal sphincter also has "noose like" myoarchitecture, i.e., decussation of fibers at the anterior and posterior surfaces of anal canal. Might be, all sphincters are not donuts; instead they have "noose-like" myoarchitecture to cause circumferential closure. A longer length of muscle in the "noose-like myoarchitecture" provides mechanical advantage, i.e., it can create greater force upon contraction to cause circumferential closure.

Manometry techniques to measure the antireflux barrier function have been improving approximately every 10 years since the 1950s when Code first recorded the LES high-pressure zone using water-filled catheters. Infusion manometry using side-hole catheters by Harris, Dent sleeve sensor, electrode sleeve sensor, solid-state pressure transducers, high-resolution manometry using color topography, and 3D high-resolution LES manometry have brought us to the current state of knowledge of the function of smooth muscle LES and skeletal muscle crural diaphragm. The 3D-LES manometry catheter, the newest of all the techniques, provides all information revealed by earlier methods and much more. The 3D catheter consists of 12 rings of pressure transducers, spaced 7.5 mm apart, with each ring containing 8 separate transducers spaced 45 degrees apart. Thus, 96 high fidelity pressure transducers can record the EGJ pressure continuously in real time. Color topography of the pressure plots allows one to visualize the 3D pressure profile of the EGJ high-pressure zone as a seamless signature over time. One can determine the radial and axial location of each pressure transducer in the subject by performing a CT scan while the catheter is in place in the subject, thus making it possible to align the LES function with the anatomy of the EGJ region. These studies in normal subjects reveal a unique EGJ pressure profile that has following features (Fig. 2.3):

1. The EGJ pressure profile is longer along the lesser curvature, almost double the length, as compared to the greater curvature of the stomach.
2. The highest pressure is located in the left-posterior direction, known in the past as circumferential LES pressure asymmetry. The reason for higher pressure on the left side is because high-pressure zone is shorter in length in that direction.
3. Crural diaphragm-related squeeze is superimposed on the cranial half of the LES pressure. In other words, the LES and crural diaphragm are anatomically superimposed on each other.
4. The cranial or the proximal edge of the EGJ pressure profile is horizontal because the LES turns to the left at the level of esophageal hiatus (crural diaphragm), as it enters into the abdomen, which brings the hiatus and catheter at right angle to each other (Fig. 2.4).

The EGJ pressure profile aligned with the anatomy of the region from the CT scan images makes it is clear that the right side of the high-pressure zone related to LES aligns to that part of the stomach where clasp fibers anchor into the anterior and posterior sling muscles. There are no reports of the 3D-LES manometry in patients with hiatus hernia, which will allow one to determine the 3D pressure profile of LES and crural diaphragm separately. However, high-resolution manometry studies clearly show two separate high-pressure zones, one related to the LES and the other to the crural diaphragm in patients with sliding hiatus hernia, each one with its own characteristics. The crural diaphragm is mostly active during the inspiratory phase of respiratory cycle. When the LES and crural diaphragm are superimposed on each other, as in normal subjects, the end expiratory EGJ pressure is generally due to the smooth muscle LES. Increase in gastric pressure related to migratory motor complex of the stomach results in LES contraction with increase in the EGJ pressure. On the other hand, increase in the EGJ pressure with inspiration is generally related to crural diaphragm; the amplitude of increase is directly related to the depth of inspiration or the force of diaphragmatic contraction. Crural diaphragm can contract continuously (tonically) during abdominal compression, straight-leg raises, coughing, Valsalva, and all those physical activities that increases intra-abdominal pressure. Change in the EGJ pressure related to LES, being a smooth muscle, occurs slowly (over seconds). On the other hand, the crural diaphragm being a skeletal muscle can contract much faster (over milliseconds). The two sphincters, LES and crural diaphragm, are critical in the prevention of GER because they must respond to counter pressure gradients between the esophagus and stomach which are influenced by intrathoracic (pleural) and intra-abdominal pressures, respectively. The esophageal pressure is generally lower as compared to stomach during the entire respiratory cycle, and thus there is a pressure gradient in favor of GER; pressure gradient is 6–10 mmHg during end expiration, and it can be 50–100 mmHg during deep breathing and other physical maneuvers. Understanding of the two-sphincter concept, LES and crural diaphragm, is critical to understand the antireflux barrier function.

The esophagus enters into the stomach along its lesser curvature. It is suggested that fundus of the stomach can press on the distal most part of the esophagus or LES to make a gastric flap valve, which has a role in the prevention of GER. Based on the anatomy of the EGJ in normal subjects, as described in previous paragraphs, it is only the distal half of the LES (and not the esophagus) that is located in the abdomen, which can be influenced by gastric pressure. The LES is a tonically contracted muscle and hence it is a stiff/noncompliant muscle, which would make transmission of gastric pressure into the intraluminal LES pressure unlikely.

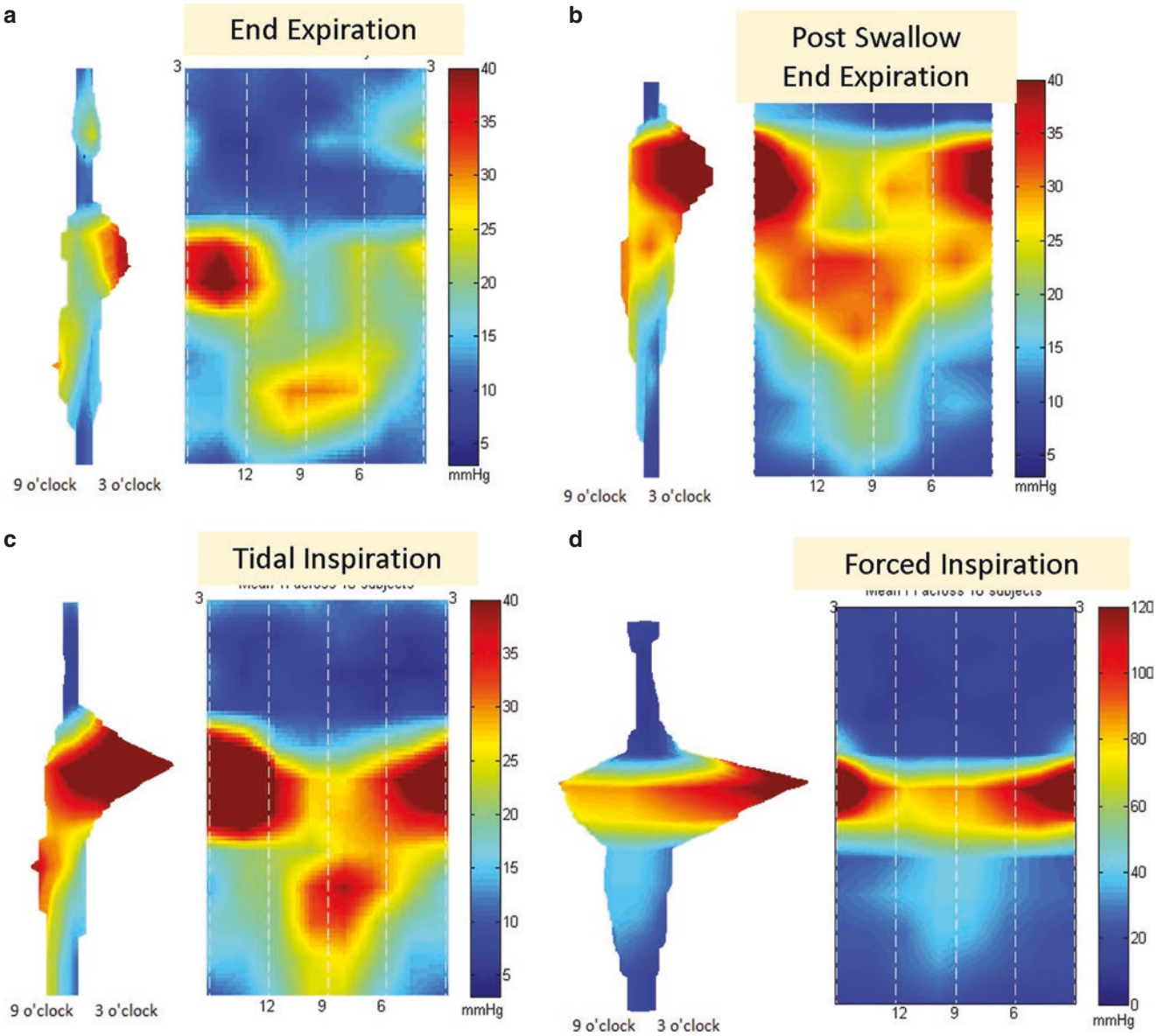

Fig. 2.3 3D-pressure topography of the esophagogastric junction (EGJ). Mean EGJ pressure profile from ten subjects. The EGJ pressure under three different end-expiration conditions: (**a**) end expiration (EE); (**b**) post-swallow end expiration (PSE) and with two different strengths of crural diaphragm contractions; (**c**) tidal inspiration (TI) and (**d**) forced inspiration (FI). The 9 and 3 o'clock positions are toward the lesser and greater curvature of the stomach, respectively, and 12 and 6 o'clock face toward the anterior and posterior direction, respectively. Mittal RK, Zifan A, et al. Am J Physiol Gastrointest Liver Physiol. 2017 Sep 1;313 (3):G212-G219

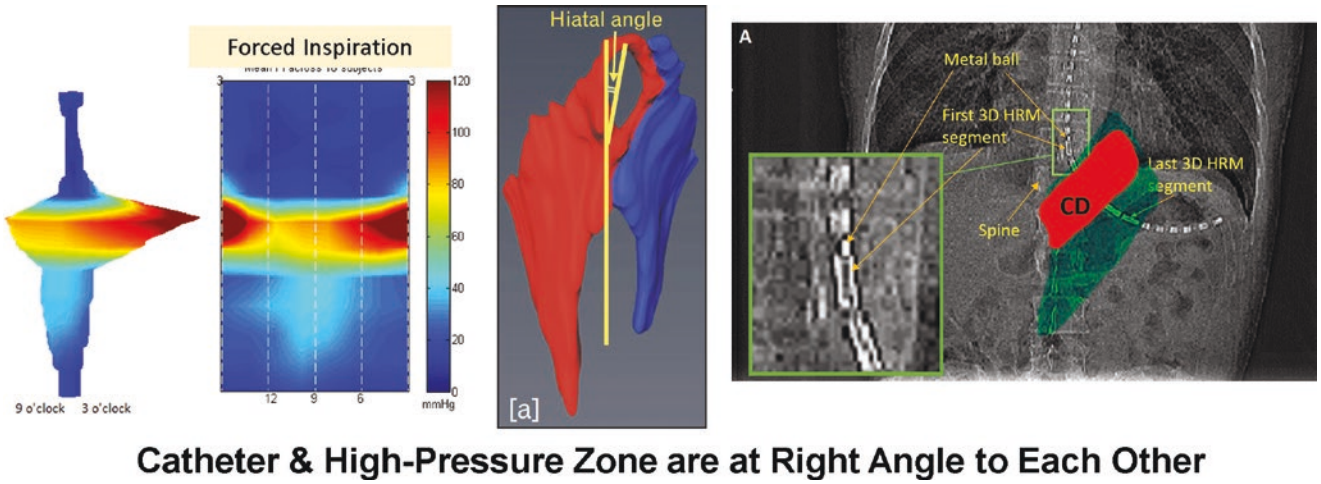

Fig. 2.4 Relationship between 3D-EGJ pressure profile and anatomy of the EGJ seen on CT images. The EGJ pressure profile was obtained at the peak of inspiration. A CT scan was obtained with the 3D-LES manometry catheter in place in the subject. Crural diaphragm was segmented from the CT scan images of the region. Superimposition of the EGJ high-pressure zone over the fluoroscopic image of the EGJ. Note that the manometry catheter bends to the left as it enters the stomach. Even though the hiatus is oriented at an angle with the spine, it is at right angle to the hiatus because of bending of the catheter at the EGJ which gives a horizontal pressure profile at the proximal end

The author's opinion is that it is unlikely that the gastric flap valve by itself can contribute to the antireflux barrier. Gastric flap valve is disturbed in the setting of sliding hiatus hernia; it is more likely that the latter, rather than the gastric flap, contributes to the GERD (as described in the following paragraphs).

Gastroesophageal Reflux Mechanisms

Reflux of gastric contents into the esophagus occurs via several mechanisms, transient LES relaxation (TLESR), low LES pressure, crural diaphragm dysfunction, and sliding hiatus hernia. TLESR is the major mechanism of belching and GER in healthy subjects (Fig. 2.5). It is also the major mechanism of GER in patients with normal LES pressure, especially in patients with no evidence of sliding hiatus hernia. The TLESR is preceded by a unique pattern of longitudinal muscle contraction of the esophagus, which starts in the distal esophagus and traverses in a reverse peristaltic fashion toward the mouth. The longitudinal muscle contraction gets stronger as the LES and crural diaphragm relaxation becomes complete. Studies show that the contraction of longitudinal muscles activates inhibitory motor neurons of the myenteric plexus through a stretch-sensitive (mechanosensitive) mechanism to induce LES relaxation and concurrent inhibition of the crural diaphragm. The inhibition of crural diaphragm is essential for the occurrence of GER during TLESR in subjects with a normal EGJ anatomy, i.e., absence of sliding hiatus hernia. Gastric distension is the predominant stimulus for the induction of TLESR. Despite the importance of TLESR in the GERD pathogenesis, drugs targeting to inhibit TLESRs have limited efficacy and significant adverse events. Crural myotomy in cats lead to an increase in the incidence of GER. Injection of botulinum toxin into the LES, used routinely in the treatment of achalasia and other spastic motor disorders, leads to partial/complete paralysis of the crural diaphragm contraction, which results in GER events during various physical maneuvers that increase gastroesophageal pressure gradients, including during the simple act of deep breath.

With each swallow-induced primary peristalsis, contraction of the longitudinal muscles of the esophagus pulls the LES in cranial direction (2–3 cm), into the thorax, resulting in what is generally known as a physiological hiatus hernia or phrenic ampulla. On the other hand, persistent herniation of the stomach into the chest resulting in anatomical separation of LES and CD is a pathologic entity. Clinicians have known for long time of strong association between sliding hiatus hernia and GERD. Separation of the LES and CD results in deformity at the EGJ, also known as the loss of flap valve of the stomach. One can grade the severity of deformity using Hill's grade classification system (Fig. 2.6). Studies show that patients with Hill's grade 3 and grade 4 flap valves have increased esophageal acid exposure, or in other words GERD. Prolonged HRM recordings show that the LES slide in and out of the hiatus (crural diaphragm) several times during the day. Interestingly, majority of GER events occurs in the setting when the LES and CD are anatomically separate, i.e., in the setting of a sliding hiatus hernia. The dynamic relationship (sliding) between LES and CD is possibly an important reason for the controversy surrounding the role of hiatus hernia in GERD. Studies show

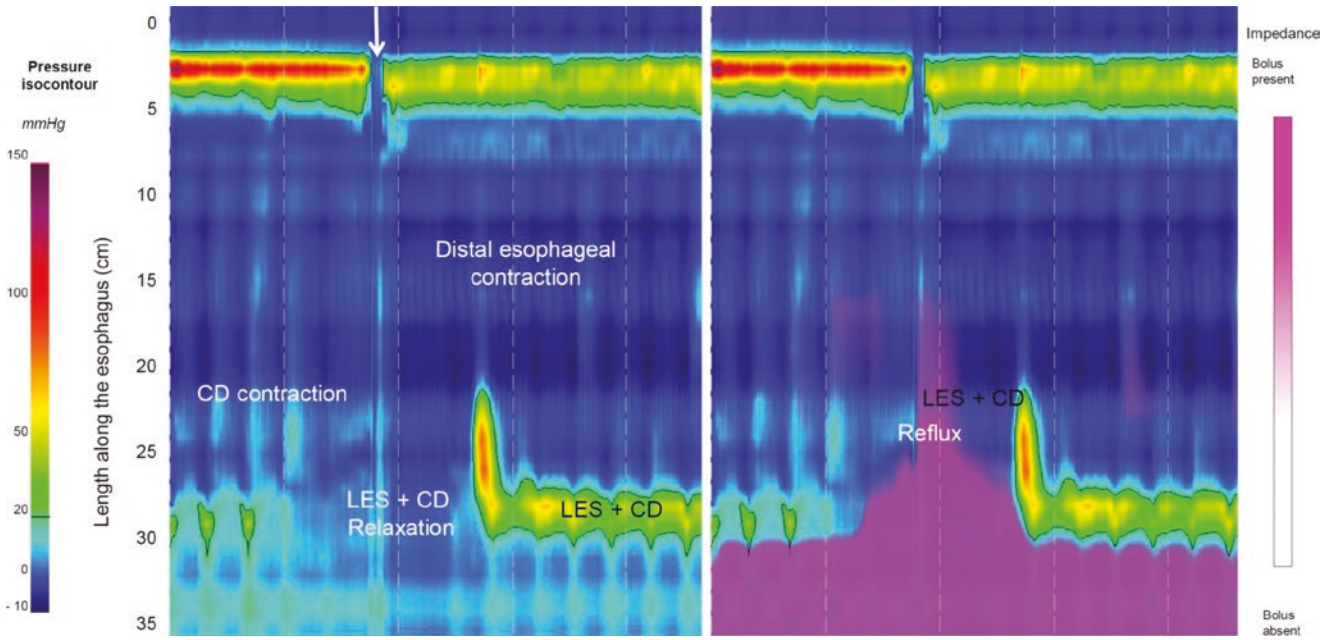

Fig. 2.5 Transient lower esophageal sphincter relaxation (TLSER) on high-resolution manometry (on the left) and impedance (on the right). Lower esophageal sphincter (LES) relaxation is >10 seconds in duration, which occurs in the absence of swallow (no pharyngeal contraction). Upper esophageal sphincter (UES) relaxation occurred during the TLESR. Also note crural diaphragm inhibition during TLESR. The TLESR is accompanied with gastroesophageal reflux (observed on impedance). Roman, S, Holloway R, Keller J, et al. Neurogastroenterol Motil 2017;29

many mechanisms by which sliding hiatus hernia may cause GER events:

1. A small amount of acid is trapped in the hernia sac (between the LES and CD) that can reflux repeatedly into the esophagus during swallow-induced LES relaxation.
2. Separation of LES and CD results in reduction of the LES pressure.
3. Widening of the esophagus hiatus by a herniated stomach impairs the sphincter function of crural diaphragm. A recent study describes respiration-induced changes in the pressure gradients between the stomach, hernia, and esophagus leads to the GER events (two-stage mechanical pump hypothesis) (Figs. 2.7 and 2.8).

In the first stage, during the expiratory phase of respiratory cycle, gastric contents flow from the stomach (positive pressure environment of the abdomen) into the herniated stomach (negative pressure environment of thorax) because crural diaphragm contraction (barrier) is generally not active during expiratory phase of the respiratory cycle. In the second stage, with inspiration phase of respiratory cycle, contraction of the CD (hiatus) causes compartmentalization of the stomach (above and below the hiatus). Furthermore, with inspiration there is a greater decrease in the esophageal than the hernia pressure, resulting in a net pressure gradient directed toward the esophagus. The LES pressure response to inspiration varies among patients; in some patients there is an increase in the LES pressure with inspiration and in others there is a decrease. In the latter setting, contents from the herniated stomach can reflux across the LES into the esophagus. Acid reflux flowing into the esophagus with each breath can be a major player in the pathogenesis of moderate to severe GERD, i.e., erosive esophagitis and Barrett's esophagus. The GER events from hiatus hernia into the esophagus, usually small in amount, may travel only to the most distal part of the esophagus, which explains why reflux-induced changes in the esophagus are greatest close to the squamocolumnar junction or the Z line.

Intrathoracic location of the LES is disadvantageous for its antireflux barrier function because a negative thoracic pressure can pull open a contracted LES muscle. It is not clear why in some hiatal hernia patients the LES pressure increases with inspiration which is advantageous for its antireflux barrier function. It is also interesting to note that all those animals that have an intra-abdominal length of the esophagus in the abdomen, such as mice, rat, rabbit, and opossum, can't vomit. On the other hand, animals with a superimposed LES and crural diaphragm, such as cats, dogs, pigs, and humans, can vomit. Surgical literature suggests that an intra-abdominal location of the LES/esophagus is important in the competency of LES. A successful Nissen fundoplication reduces hiatus hernia, restores a small length of the esophagus back into the abdomen, wraps the distal 2 cm of the esophagus with gastric fundus, and reduces the size of esophageal hiatus by either plication or placement of a mesh.

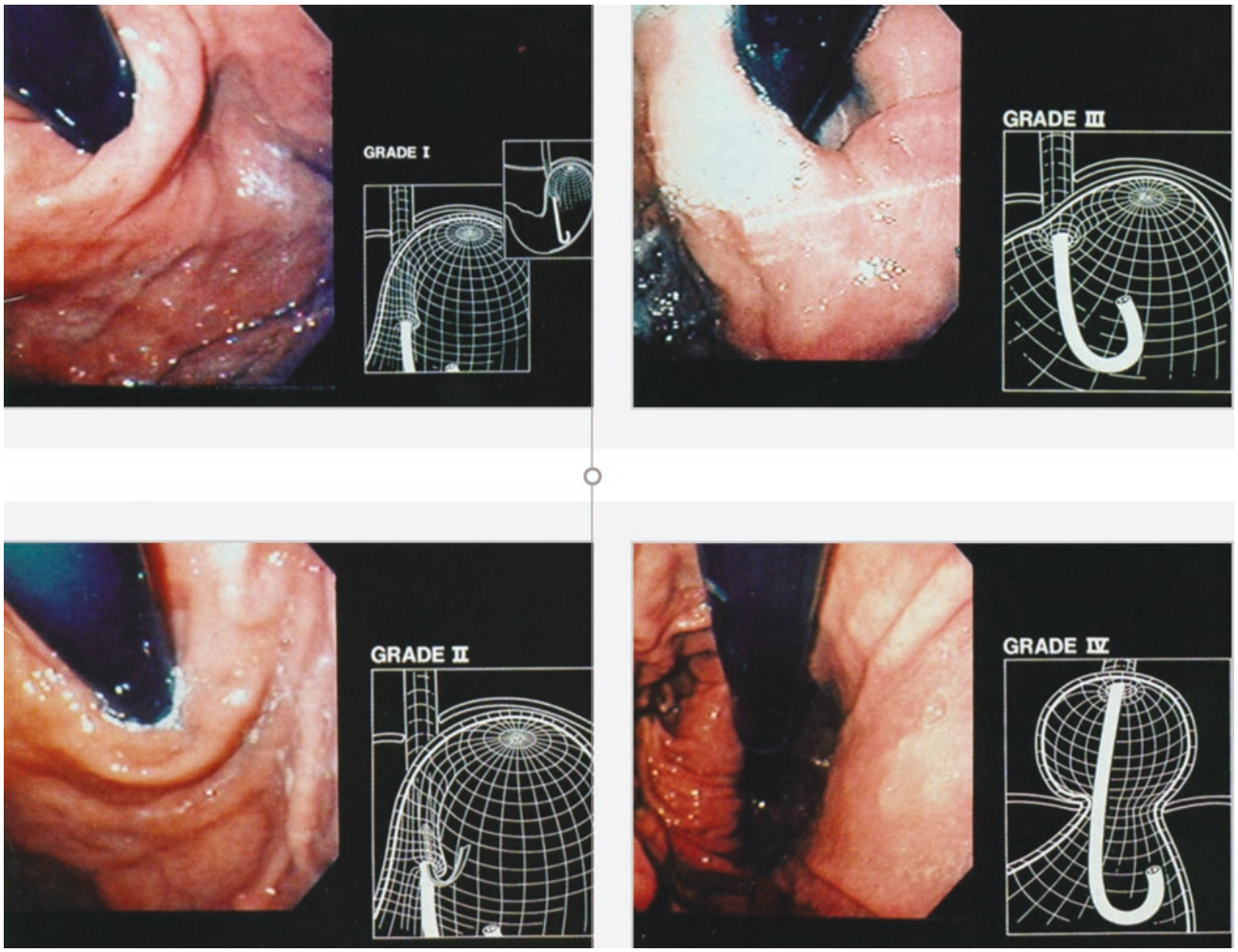

Fig. 2.6 Gastric flap valve: Hill's grades 1 through 4: Endoscopic appearance

In the setting of a large hiatal opening, a mesh is placed to reinforce the hiatal opening. Studies show several mechanisms by which Nissen fundoplication makes the reflux barrier competent: (1) reduction of hiatus hernia, (2) increase in the basal LES pressure, (3) increase in the intra-abdominal length of LES length, and (4) reduction in the frequency of TLESRs and rendering TLESRs incomplete. Since there are several things done during a fundoplication, it is not clear which component of the repair leads to which component of the antireflux barrier more effective. It is likely that plication/reinforcement of the hiatus prevents recurrence of sliding hiatus hernia; whether it leads to an improved sphincter function of crural diaphragm requires further study.

The role of phrenoesophageal ligament in the making of an effective antireflux barrier function can't be overemphasized. As described earlier, in healthy subjects, the LES and CD are physically superimposed on each other. The two structures are anchored to each other by the upper and lower leaves of the phrenoesophageal ligament, which originate from the thoracic and abdominal surfaces of diaphragm, respectively. The phrenoesophageal ligament penetrates deep into the connective tissue between the bundles of longitudinal and circular muscles of the esophagus, thus forming an extremely tight anchoring between the LES and crural diaphragm. With inspiration and expiration, the LES and crural diaphragm move in the caudal and cranial direction, respectively, without separating from each other. X-ray fluoroscopy studies show that metal clip placed endoscopically at the squamocolumnar junction (Z line) move 2–3 cm in the cranial/oral direction during primary and secondary peristalsis. They migrate from the intra-abdominal position before peristalsis into the thorax during peristalsis and return back to their baseline position at the completion of peristalsis. Z line is normally located in the middle of LES, which implies that the LES migrates into the thorax during peristalsis, or in other words, each swallow results in formation of a small sliding hiatus hernia, also referred to as physiologic sliding hiatus hernia, or phrenic ampulla. The pathological sliding

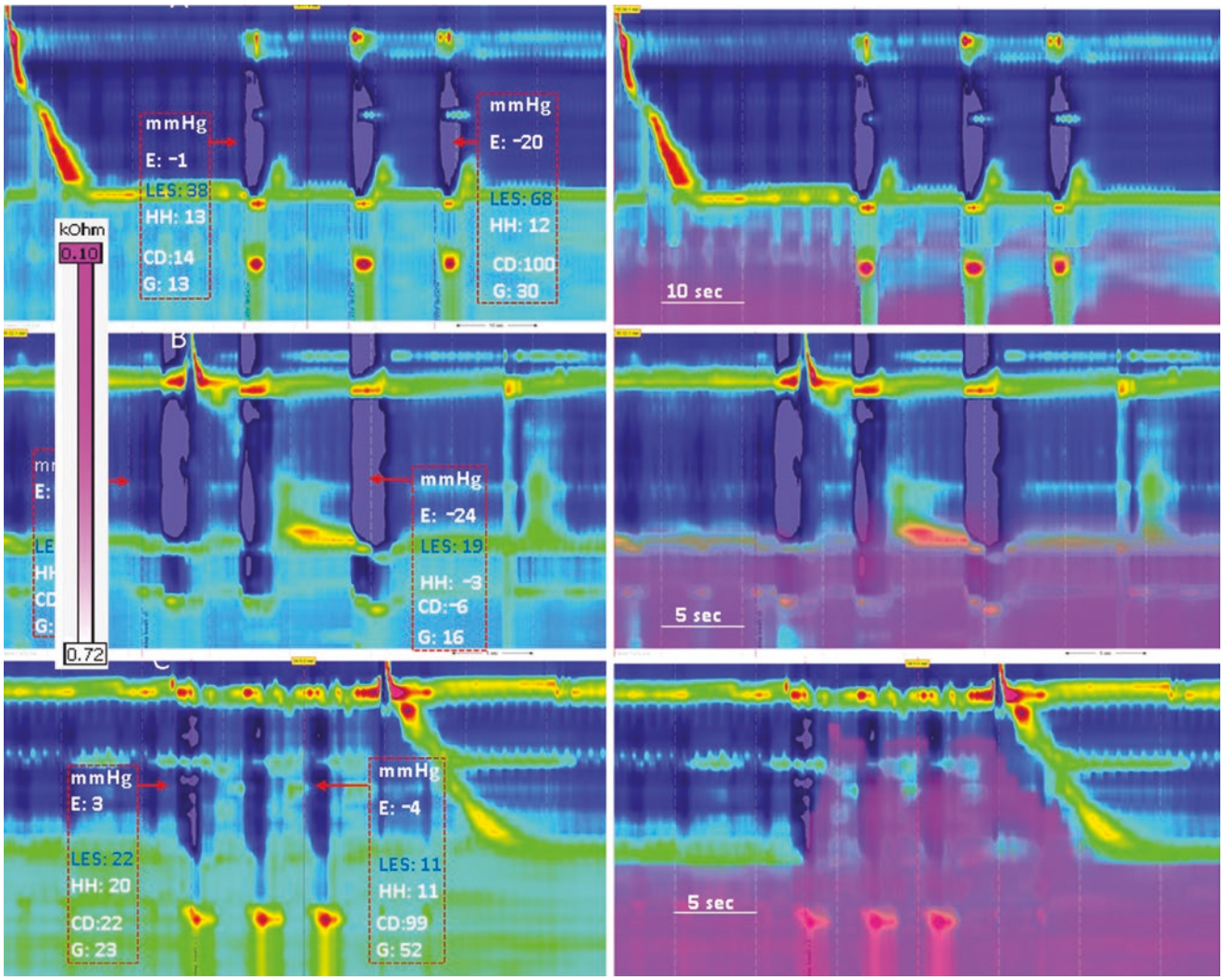

Fig. 2.7 High-resolution manometry impedance (HRMZ) recordings of three patients (A, B, and C) with sliding hiatus hernia (HH), without (left), and with impedance (right) recordings. Note pressure changes in the esophagus (E), lower esophageal sphincter (LES), hiatus hernia (HH), crural diaphragm (CD), and stomach (G) with three deep breaths. The boxes on each HRMZ recordings show pressure at the five locations, before (left) and during deep inspirations (right). In patient A, deep breaths result in an increase in the LES pressure. On the other hand, in patients B and C, deep inspirations result in the decrease in LES pressure (more significantly in patient 3). The LES pressure during deep breath in patient 3 is same as esophageal pressure. Note the changes in impedance (pink color, as a marker of fluid movement, i.e., reflux). In all patients, fluid moves from the stomach into HH in between deep inspiration (end expiration). There is no movement of fluid from HH into the esophagus in patient A, who has increase in LES pressure with deep breath. On the other hand, in patients B and C, reduction in the LES pressure with inspiration is associated with movement of fluid from HH into the esophagus

hiatus hernias are those in which LES and crural diaphragm remain separate, thus forming two high-pressure zone, which implies defective phrenoesophageal ligament. A pathological sliding hiatus hernia can be the result of either excessive pull on the esophagus (from the longitudinal muscle contraction), defective phrenoesophageal ligament, or excessive intra-abdominal pressure.

Several studies have examined for the structural defects in the crural diaphragm and phrenoesophageal ligament in GERD patients. Biopsy samples of the crura and phrenoesophageal ligament under transmission electron microscopy in GERD patients reveal abnormalities in 94% of the biopsied samples, with 75% of those having severe abnormalities. The latter were defined as extended disruption and degeneration of the crural muscle architecture. Other studies have found loss of myofibrils, inflammatory infiltrate, and neovascularization in the right and left crural diaphragm in hiatus hernia patients, but not in controls. Phrenoesophageal ligament samples obtained intraoperatively from patients with hiatal hernias found that the collagen content was 60% lower in the hiatal hernia patients (including type I and type III collagen), suggesting GERD as a genetic connective tissue disorder. Structural abnormalities of the CD have been explained on the basis of genetics studies linking altered collagen expression.

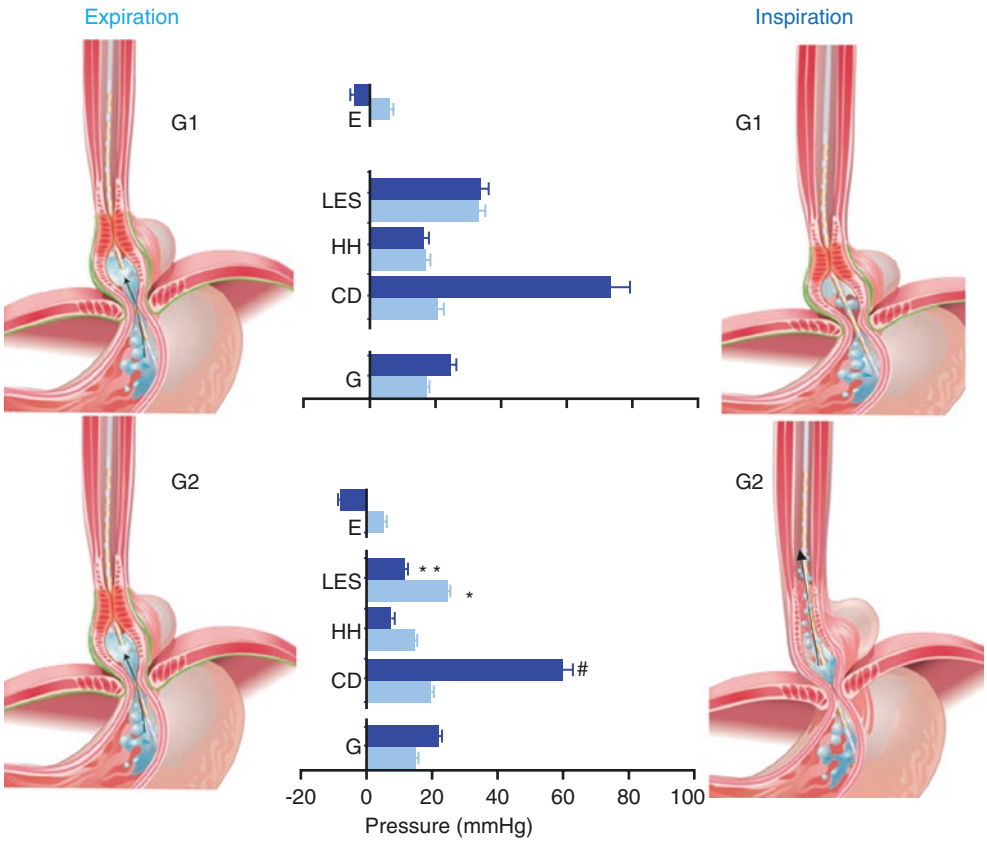

Fig. 2.8 Mean data of pressure in the esophagus (E), lower esophageal sphincter (LES), hiatus hernia (HH), crural diaphragm (CD), and stomach (G) in patients who show increase in LES pressure with inspiration (group 1) and who show decrease in the LES pressure with inspiration (group 2), before and during deep breaths. There was no difference in the G, HH, and esophageal pressure in the two groups. The LES pressure before deep breath was lower than during deep breath in group 2 (*). The LES pressure before deep breath was different between the two groups (**). The CD squeeze pressure was lower in group 2 compared to group 1 (#). The schematic shows movement of gastric fluid from the stomach into the HH during expiration

Children and adults, diagnosed with GERD and/or hiatal hernias, have been found to have higher prevalence of mutations within the collagen type III gene COL3A1. Above findings have been confirmed in a case-control cohort study in which significant association with COL3A1 mutations was found in hiatal hernia patients compared to control patients, suggesting an altered expression of collagen III, which resulted in an imbalance between collagen I and collagen III levels.

In summary, the smooth muscle LES and skeletal muscle crural diaphragm, anchored to each other by the phrenoesophageal ligament, forms a normal antireflux barrier. Both the LES and crural diaphragm have "noose"-like myoarchitecture. The 3D-LES pressure recordings and CT scan imaging done simultaneously reveal the unique EGJ high-pressure zone profile, and for the first time, it provides the relationship between EGJ pressure profile (function) and anatomy. Transient LES relaxation, a vagally mediated neurological event, which results in simultaneous relaxation of the LES and crural diaphragm is an important mechanism of GER in patients with the GERD. Disruption of phrenoesophageal ligament and crural diaphragm which results in formation of sliding hiatus hernia is also critical in the pathogenesis of GERD. Recurrence of sliding hiatus hernia following Nissen fundoplication leads to recurrence of symptoms, which suggests that repair of the crural diaphragm (hiatus) is a critical part of the antireflux surgery. Future studies need to focus on advancing our knowledge at several fronts, i.e.: (1) genesis of GERD symptoms; (2) pathogenesis of transient LES relaxation, why, and when does a physiological event such as TLESR becomes a pathological one; and (3) all those factors that are important in the genesis of hiatus hernia, and recurrence of sliding hiatus hernia following Nissen fundoplication.

Questions

1. The key elements of a competent antireflux barrier are:
   A. Smooth muscle lower esophageal sphincter
   B. Crural diaphragm
   C. Phrenoesophageal ligament
   D. All of the above
   Answer: D
2. Sliding hiatus hernia impairs antireflux barrier by the following mechanisms:
   A. It reduces LES pressure.
   B. It results in a defective gastric flap valve.
   C. It acts as a two-stage mechanical pump that drives gastric contents into the hernia during expiratory phase of respiratory cycle and pumps hernia contents into the esophagus during inspiratory pump of the respiratory cycle.
   D. All of the above.
   Answer: D

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Conflict of Interest None of the authors have any conflict of interest.

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Gastroesophageal Reflux Disorders: Diagnostic Approach

3

Subhash Chandra, Jonathan Gapp, and Kenneth Wang

Symptomatology

Empirical diagnosis of GERD based on symptomatology is common clinical practice. Based on the Montreal consensus statement, "GERD is a condition which develops when reflux of stomach contents causes troublesome symptoms or complications" [1]. Typical symptoms include burning pain starting in the upper abdomen and moving upward, behind the chest and toward the throat as well as regurgitation although only 49% of patients with GERD report typical symptoms. Extra-esophageal syndromes (reflux cough, laryngitis, asthma, dental erosion) are considered atypical symptoms. Full assessment by a physician leads to a sensitivity of approximately 65% for the diagnosis of GERD with a specificity of 70% [2]. Furthermore, the detection rate of GERD by use of symptoms seems to decrease with age, with elderly patients often remaining asymptomatic despite high rate of mucosal injury and complications [3]. Unfortunately, lack of GERD symptoms also is more common in patients with Barrett's esophagus, placing these patients at high risk for late detection of esophageal adenocarcinoma.

Clinical Questionnaires

The difficulty in ascertaining the presence of GERD accurately through physician assessment has led to the formation of questionnaires. The goal being that if specific patient-reported information is elicited, then the sensitivity and specificity for a GERD diagnosis might be improved. The Diamond study, performed in the UK, used the Reflux Disease Questionnaire (RDQ) in an attempt to improve diagnosis. However, use of the RDQ did not appear to offer substantial diagnostic improvement above physician assessment when using endoscopy and pH monitoring as the standard [2]. While questionnaires may be useful in following disease progression and response to treatment, their use for diagnostic purposes is limited.

Empiric Acid Suppression Trial

Patients with empirical diagnosis of GERD often undergo a trial of acid suppression therapy with a maximal dose proton pump inhibitor (PPI) for 2–4 weeks prior to more invasive methods of evaluation. Based upon symptoms, approximately 50% of patients will have a response to PPI therapy [4]. In those with known GERD, 69% of patients will respond to PPI trial, while 51% of those without GERD will also have response to PPI therapy [5]. Previous studies have indicated that a trial of PPI therapy for diagnosis of GERD held a sensitivity of 54% and a specificity of 65% when compared to combination of upper endoscopy and 24-hour pH monitoring. The sensitivity of a combination of empirical diagnosis with response to PPI therapy approach in 78% and specificity of 54% [2]. Such a moderate performance in testing metrics along with the questionable management of patients with a partial response to high-dose acid suppression therapy often leads to the need for further evaluation. In cases where there is symptom improvement with acid suppression and recurrence of symptoms with cessation of therapy in the absence of red flag signs, it is still considered reasonable to make a diagnosis of GERD.

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Upper Endoscopy

Upper endoscopy for the evaluation of GERD is generally indicated in patients who do not respond to acid suppression therapy or have red flag signs consisting of iron deficiency anemia, dysphagia, odynophagia, and weight loss or as part of screening for Barrett's esophagus in high-risk populations. Upper endoscopy can establish the presence of pathologic GERD based on the presence of mucosal injury (Los Angeles grade C or D esophagitis) or its complications (peptic stricture or Barrett's esophagus) occurring in 2.2%, 11%, and 3.3%, respectively, in those not already on PPI therapy [6]. However, the aforementioned findings often are not present in patients with symptomatic GERD, particularly since patients are often placed on PPI therapy prior to endoscopy. While the criteria for a definitive GERD diagnosis often are not met with upper endoscopy alone, a thorough endoscopic exam of the gastroesophageal junction and biopsies of the esophagus provide information to be used in conjunction with supplementary studies in forming a diagnosis of GERD as well as for ruling out other disease entities with a shared symptomatology. A high-quality endoscopic exam is also a prerequisite in the case that antireflux surgery is to be considered in the future.

Box 3.1 Definitive Evidence for GERD on Upper Endoscopy

LA class C or D esophagitis.

Peptic stricture.

Barrett's esophagus.

The endoscopic exam performed for an indication of GERD should include four principal components. First, thorough examination of the esophagus on forward view should be performed to determine the presence of esophagitis, Barrett's esophagus, peptic strictures, or other abnormalities that suggest tumor or achalasia. Esophagitis should be graded based upon the Los Angeles (LA) esophagitis system and if high grade (grade C or D) would require 8 weeks of therapy with follow-up endoscopy to assess healing and exclude Barrett's esophagus and long-term treatment (Fig. 3.1). Peptic strictures are most common at the squamocolumnar junction, and careful observation in this area with a high degree of distention increases detection. If salmon-colored mucosa >1 cm from the top of the gastric folds or mucosal irregularities are observed, biopsies should be performed. Examination of the esophagus for dilatation, presence of fluid in the esophagus upon initial esophageal intubation, and difficulty traversing the gastroesophageal junction with the gastroscope can indicate the presence of achalasia or pseudo-achalasia which often shares common symptomatology to patients with severe reflux disease.

Second, mucosal biopsies are not routinely performed though histologic findings of basal cell hyperplasia and papillary elongation support a diagnosis of reflux disease and are sensitive but have poor specificity for GERD. Findings of dilated intercellular spaces due to inflammatory changes are also present; however, such studies are not normally performed outside of a research setting. The one circumstance that biopsies should routinely be obtained is if the patient's symptom profile includes dysphagia in which case eosinophilic esophagitis needs to be considered. Normal histology in the distal esophagus does not exclude GERD as patients are often on PPIs at the time of endoscopy.

Third, endoscopic evaluation of the GEJ on both forward and retroflexed views can significantly alter suspicion for reflux disease when correctly performed. Upon examination of the lower esophagus, the presence of a hiatal hernia should be recorded and is considered to be part of a high-quality upper endoscopy. The presence of a hiatal hernia indicates mechanical failure of the antireflux barrier wherein the diaphragmatic crura and the intrinsic circular smooth muscle LES no longer function in tandem to form an effective barrier to refluxate. During a retroflexed exam of gastroesophageal junction, a Hill grade (I–IV) should be assigned as an assessment of the gastroesophageal flap valve (GEFV). Proper assignment of a Hill grade to the GEFV requires adequate insufflation and close inspection and is as follows. In Hill grade I, the tissue ridge is snug to the endoscope and intra-abdominal esophagus extends 3–4 cm along the lesser curvature. In Hill grade II, the tissue ridge is present and GEJ opens with respiration yet closes promptly. In Hill grade III, the tissue ridge is not present (i.e., loss of gastroesophageal flap valve). In grade IV, there is wide-open diaphragmatic hiatus (i.e., hiatal hernia) (Fig. 3.2). The loss of mechanical function of a Hill grade IV gastroesophageal flap valve is fairly evident on the retroflexed exam. However, while the changes consistent with Hill grade III GEFV are more subtle endoscopically, they also represent the presence of a failed valve, and are a precursor to formation of a hiatal hernia and correlate with the presence of esophagitis [7]. Therefore, Hill grades III and IV should increase suspicion for the presence of reflux disease. Documentation of the Hill grade for endoscopy performed for GERD as an indication can be useful in communicating likelihood of a compromised reflux barrier as cause for reflux disease.

Finally, location of the Z line should be documented to guide placement of pH sensor for reflux monitoring in the future, should it be required.

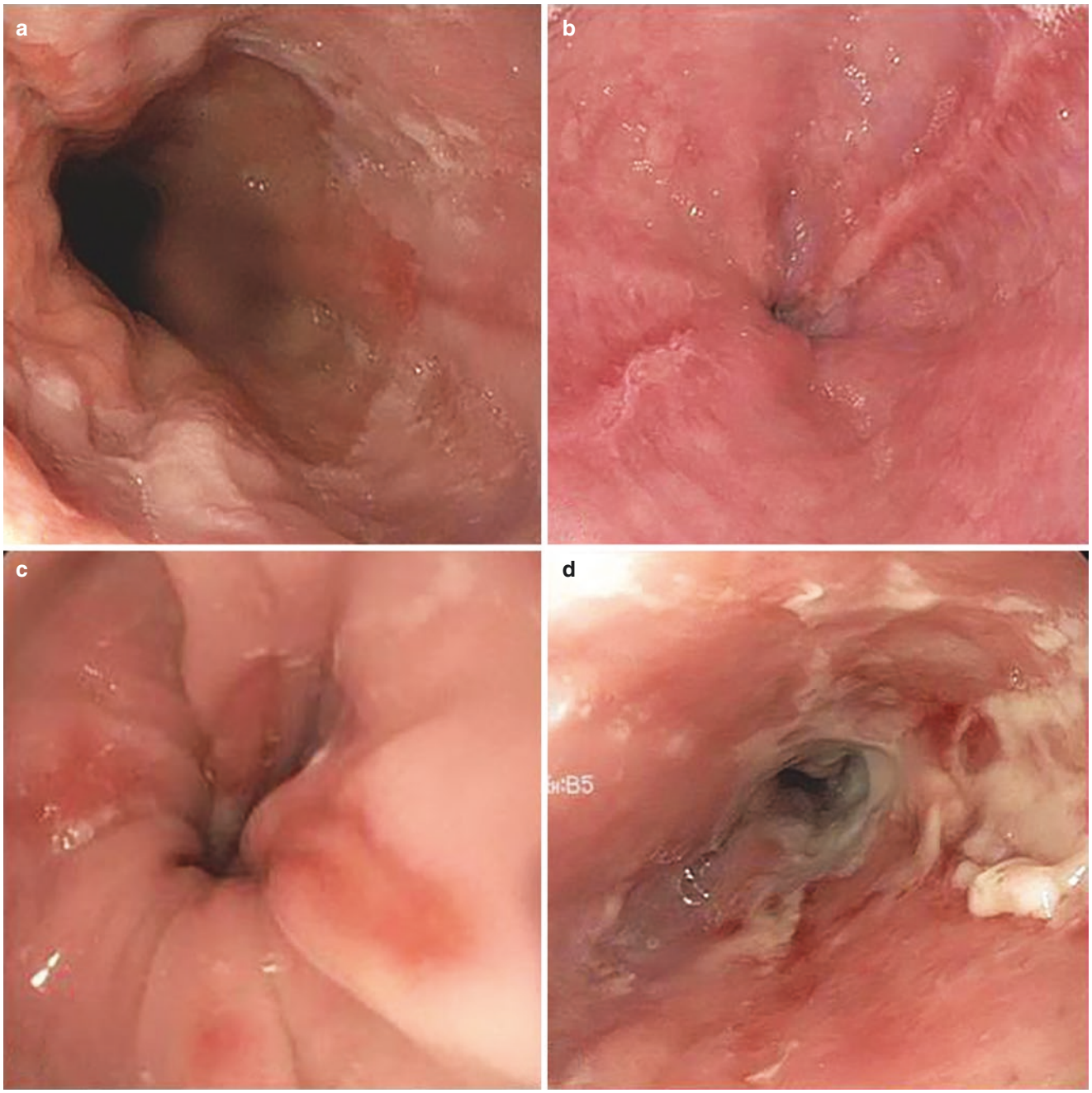

Fig. 3.1 Los Angeles grading system for esophagitis. Grade A (**a**) with one or more mucosal breaks less than 5 mm and no bridging between tops of folds. Grade B (**b**) with mucosal breaks longer than 5 mm and no bridging between tops of folds. Grade C (**c**) with mucosal breaks bridging the tops of the mucosal folds and involving <75% of the circumference. Grade D (**d**) with mucosal breaks bridging the tops of the mucosal folds and involving >75% of the circumference

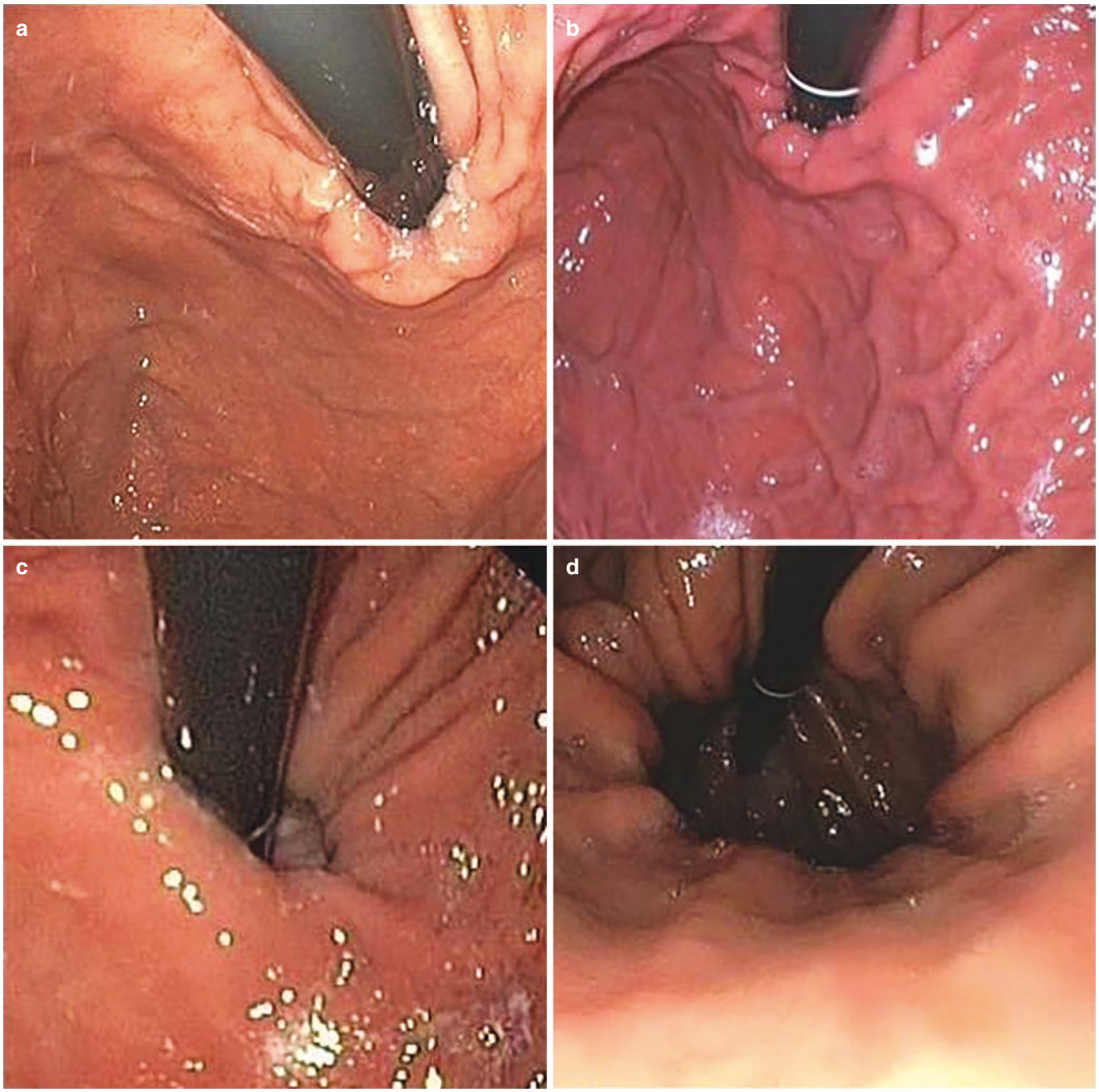

Fig. 3.2 Hill grade I (**a**): The tissue ridge is snug to the endoscope and intra-abdominal esophagus extends 3–4 cm along the lesser curvature. Hill grade II (**b**): The tissue ridge is present and GEJ opens with respiration, yet closes promptly. Hill grade III (**c**): The tissue ridge is not present, i.e., loss of gastroesophageal flap valve, Hill grade IV (**d**): Hiatal hernia

Ambulatory Reflux Monitoring

Gastroesophageal reflux disease comprises a spectrum of severity which requires both endoscopy and pH testing to fully evaluate and characterize (Fig. 3.3). Due to symptomatology that can be indistinguishable from extra-esophageal causes or functional in nature, direct monitoring of pH and of reflux episodes allows for increased sensitivity beyond that of endoscopy. This testing is most commonly indicated in cases with typical GERD symptomatology with no response or partial responsive to acid suppression without endoscopic findings to indicate pathologic reflux. In such cases, early pH monitoring has been shown to decrease cost through early discontinuation of PPIs [8]. Esophageal pH monitoring has also been used for evaluation for atypical reflux symptoms (noncardiac chest pain, chronic cough) and prior to antire-

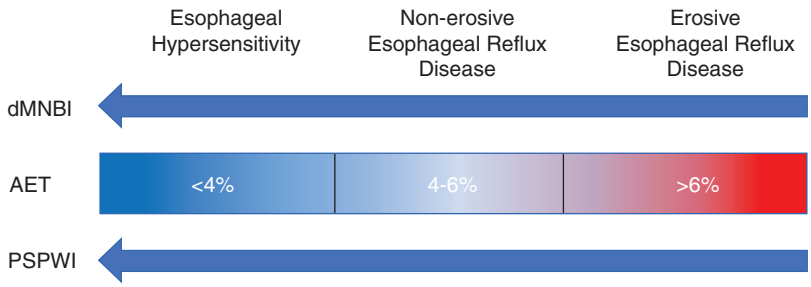

Fig. 3.3 Spectrum of reflux disease from esophageal hypersensitivity to erosive esophageal reflux disease. As acid exposure time (AET) increases, distal mean nocturnal baseline impedance (dMNBI) and post-reflux swallow-induced peristaltic wave index (PSPWI) decrease

flux surgery or following antireflux surgery if symptoms persist. There are two types of ambulatory reflux monitoring available.

Catheter-Based Impedance-pH Monitoring

Twenty-four-hour pH-impedance testing is a catheter-based test with a pH sensor located 5 cm above the manometric GEJ and impedance sensors along the length of the catheter (number of sensors depends upon manufacturer). Throughout the monitoring period, use of a patient-activated indicator allows for symptoms to be marked in order to overlie symptoms with the pH and reflux activity. Impedance monitoring allows for detection of acid and weakly acidic reflux as well as liquid and nonliquid reflux, such as belching. As such, it is considered the gold standard for reflux diagnosis. While the direct measurement of reflux and acidity is attractive for its accuracy, its use is somewhat limited due to patient tolerance.

Use of 24-h pH-impedance testing allows for assessment of multiple parameters which can, together, increase the sensitivity and specificity for a diagnosis of GERD. Acid exposure time has been the principal parameter for defining reflux with pH monitoring and has been shown to indicate response to medical and surgical therapy (Table 3.1) [9]. It is defined as the percent of total time (with meal times excluded) with pH < 4.0 at the distal pH probe. By expert consensus, an acid exposure time of <4% is considered physiologic, while acid exposure time >6% is pathologic GERD. Between 4 and 6% is regarded as indeterminant and requires assessment of other auxiliary parameters to make a diagnosis of GERD. The number of refluxes in a 24-hour period serves as an auxiliary parameter with <40 refluxes per day considered as physiologic and > 80 refluxes per day as pathologic with 40–80 regarded as indeterminant [10]. Symptom monitoring allows for correlation of pH and impedance changes from which a symptoms index (SI) and symptom-associated probability (SAP) can be determined. The symptoms index measures the (number of symptoms preceded by reflux episode within 2 minutes/total number of symptom episodes) × 100%. Expert consensus suggests an SI >50% as being a significant association. Patients with a large number of refluxes often will have very high SI simply by the fact that most symptom occurrences are likely to be temporally near a reflex episode. Symptom-associated probability makes use of Fisher's exact test to determine the probability that the reported reflux and symptom distribution did not occur by chance. As such, a SAP of 95% or greater is needed to be considered positive by statistical convention. A combination of both SI > 50% and SAP >95% indicates a high likelihood that symptoms are related to reflux and a SAP >95% has been shown to indicate response to therapy when measuring the most troublesome symptom for the patient [9]. The DeMeester score, developed in the 1970s, is a composite score including recumbent acid exposure time, total acid exposure time, number of episodes >5 min, longest reflux episode, upright acid exposure time, and total number of reflux episodes. Its performance for diagnosis of GERD has not been shown to exceed that of total acid exposure time.

Once patients with symptoms of GERD have been assessed with upper endoscopy and 24-hour pH impedance, they may be diagnosed as GERD with reflux changes on endoscopy (LA grade C or D esophagitis, peptic strictures, or Barrett's) or nonerosive esophageal reflux disease (NERD) diagnosed with pathologic reflux based on an AET >6%. However, a large fraction of patients with reflux symptoms will not meet criteria for either of these entities due to lack of endoscopic findings and an AET<4%. In such cases, consideration must be given for esophageal hypersensitivity or functional heartburn. A distinction between these entities is important as esophageal hypersensitivity can be considered as being on the spectrum of reflux disease, while functional heartburn is likely due to a different underlying pathophysiologic mechanism that does not involve reflux and requires alternative management (Fig. 3.3). A diagnosis of esophageal hypersensitivity should include a normal upper endoscopy, non-pathologic acid exposure time (<4%), and high symptom correlation. Patients with poor symptom correlation are more likely to experience symptoms from functional heartburn. Since symptom recording during testing is patient dependent, reviewing adherence to recording symptoms is important as nonadherence would lead to a false diagnosis of functional heartburn.

Novel parameters derived from 24-h pH-impedance monitoring, namely, distal mean nocturnal baseline impedance

Table 3.1 Parameters of ambulatory reflux monitoring

	Acid exposure time	Number of reflux episodes	Distal mean nocturnal basal impedance	Post-reflux swallow-induced peristaltic wave index
Normal range	≤4% (≥6% is pathologic)	≤40 (≥80 is pathologic)	>2.292 kOhm	>61%
Level of evidence	Well validated for response to treatment	Expert opinion	Not validated across multiple ethnicities	Ongoing validation
Limitation	Day-to-day variation, nonacid reflux (bile)	Clinical relevance of # of reflux not determined	Stasis and mucosal injury are not differentiated	Requires manual calculation
Potential solutions	96-h wireless pH monitoring	Use as adjunct to AET	Exclude major motility disorders	

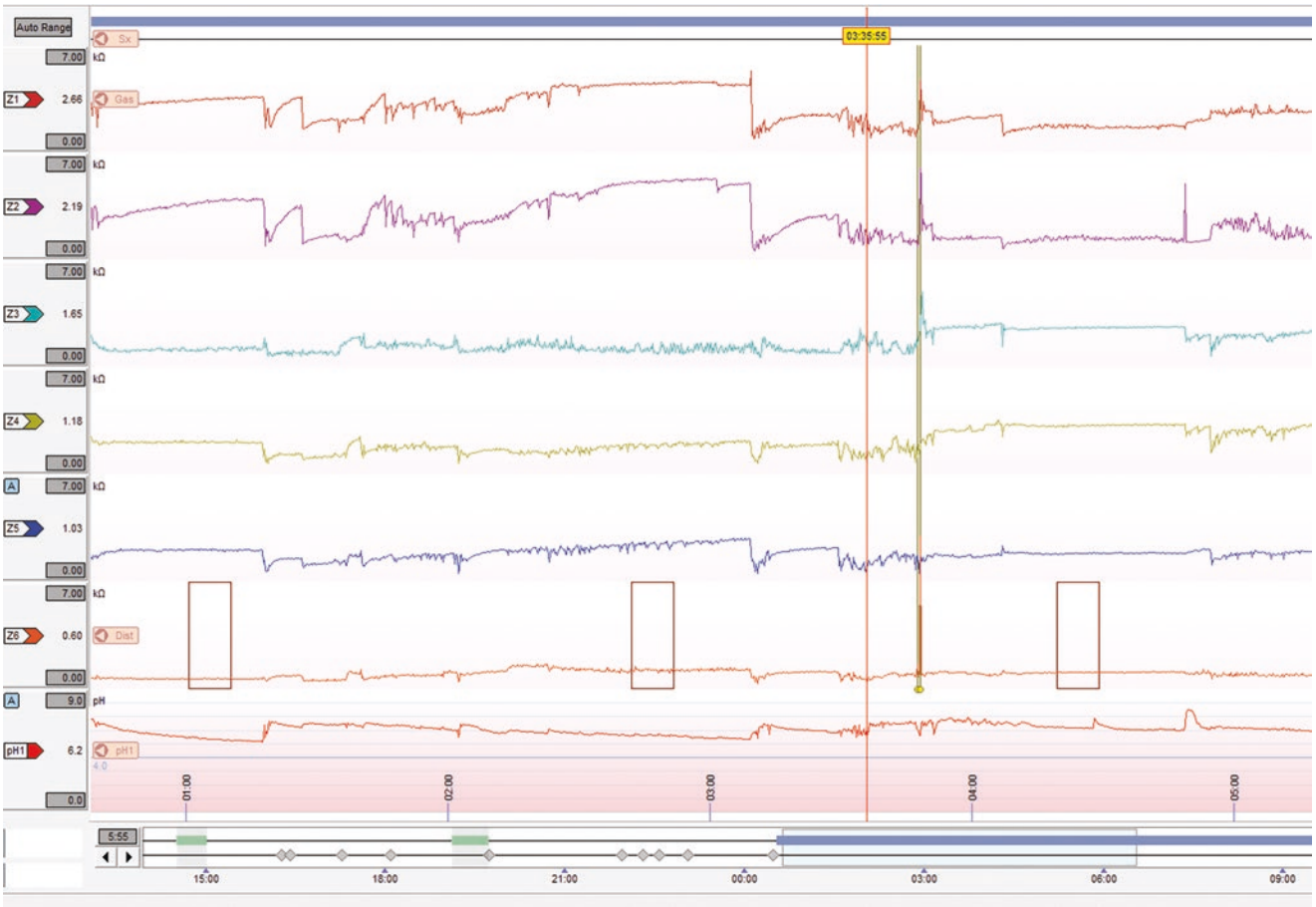

Fig. 3.4 Distal mean nocturnal baseline impedance measurements are obtained while the patient is most likely in deep sleep (postmidnight/early morning) at three discreet 10-min periods at least 1 h apart. The average is calculated from these three periods

(dMNBI) and post-reflux swallow-induced peristaltic wave index (PSPWI), can be used to evaluate esophageal mucosal integrity and acid clearance mechanisms, respectively. These parameters improve accuracy in diagnosing reflux disease as well as the distinction among the reflux spectrum entities. Distal mean nocturnal baseline impedance measures the impedance of electrical current through the esophageal mucosa as an indicator of the mucosal integrity. Because measurement of mucosal impedance must occur at times with the least amount of luminal fluid present in the esophagus (which occurs with swallowing and reflux), measurements are obtained while the patient is most likely in deep sleep (postmidnight/early morning) at three discreet 10-min periods at least 1 h apart. The average is calculated from these three periods (Fig. 3.4). An impedance <2.292 kOhms serves as an indicator of compromised esophageal mucosa due to dilated intercellular spaces that have been associated with ongoing reflux. Use of dMNBI to assess for esophageal compromise can facilitate distinction between esophageal hypersensitivity and functional heartburn [11]. In

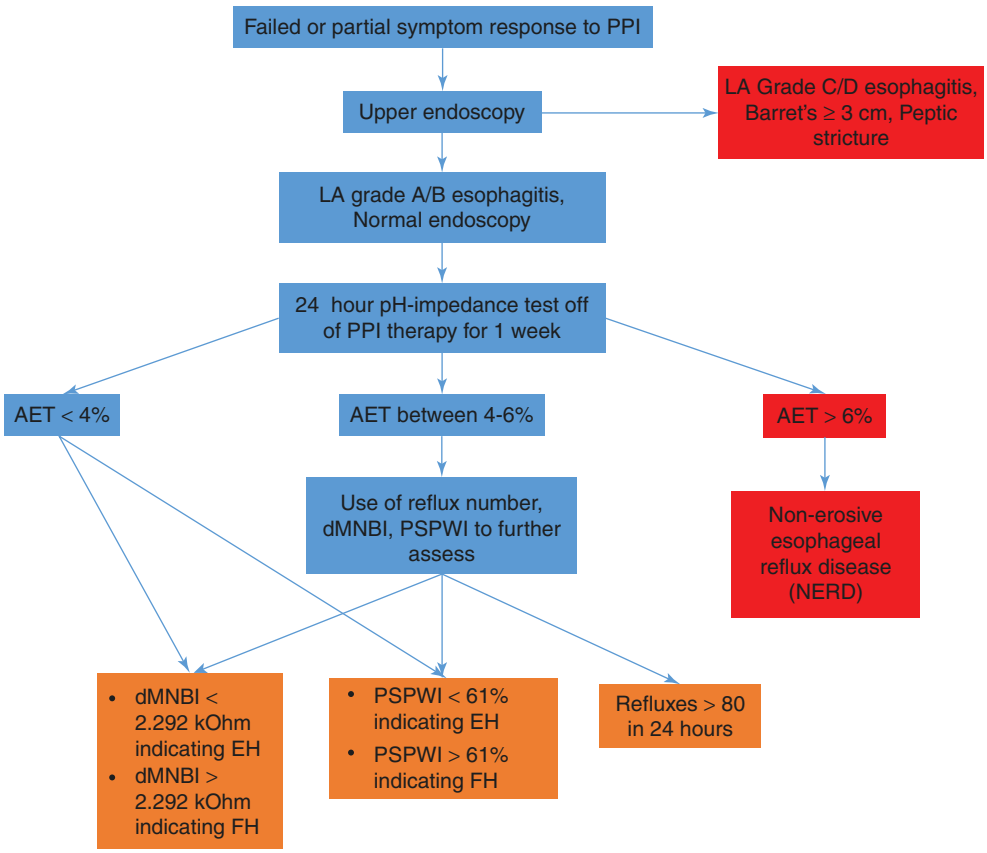

Fig. 3.5 Diagnostic algorithms for patients with reflux symptoms utilizing 24-hour pH-impedance test

the case of esophageal hypersensitivity, ongoing reflux remains the cause of symptoms, and the associated dMNBI will be low, indicating ongoing esophageal mucosal changes. On the other hand, symptoms in those with functional heartburn are likely neuropathic rather than reflux related; therefore, the associated dMNBI will typically remain >2.292 kOhms (Fig. 3.5).

PSPWI indicates the proportion of reflux events that are followed with antegrade peristalsis within 30 s of reflux. It is detected by a proximal to distal decrease in impedance indicating the occurrence of peristalsis. Post-reflux peristalsis serves as a mechanism to clear acidic or bilious refluxate as well as deliver neutralizing saliva to the esophagus to prevent mucosal damage. The index is calculated as the number of post-reflux-induced swallows divided by the total number of reflux events. Whether a decreasing PSPWI indicates poor esophageal clearance leading to esophageal damage or is related to dysmotility secondary to esophageal damage from reflux is unclear due to lack of prospective analysis. Either way, PSPWI can serve as an indirect indicator for esophageal damage particularly to allow for differentiation between functional heartburn and esophageal hypersensitivity which may be difficult to otherwise differentiate [11]. Currently available software do not provide automatic calculation and manual review is cumbersome.

On Versus Off-Therapy Testing

Whether to continue acid-reducing therapy at the time of the study is determined by the diagnostic question at hand. For patients who do not have definitive evidence of GERD, the study should be performed off of acid suppression to allow for diagnosis of GERD based upon the aforementioned parameters. For patients with proven GERD who continue to be symptomatic on antireflux therapy, testing while on acid suppression therapy can be used to verify failure of medical management prior to proceeding to procedural treatments or to reveal any further information to guide other medical therapies or lifestyle changes that may be beneficial.

Shortcomings of 24-h pH-impedance testing are related to daily variation of reflux disease and acid exposure time. Use of prolonged ambulatory pH monitoring has shown to increase sensitivity for a diagnosis of GERD. Unfortunately, patient tolerance of the catheter-based system limits monitoring times. Use of dMNBI, however, may compensate for this shortcoming since esophageal changes detected are cumulative over days. Patient-dependent symptom reporting leaves symptom association data at the mercy of patient adherence. This can make distinguishing esophageal hypersensitivity and functional heartburn difficult if adherence to symptom reporting is in question.

Wireless pH Monitoring

Wireless monitoring is performed via placement of a pH sensor 6 cm proximal to the squamocolumnar junction via direct attachment to the esophageal mucosa. Unlike 24-h pH-impedance testing, no trans-nasal catheter is required making this form of testing more tolerable to patients. Since the probe detects only changes in acidity within the esophagus and not impedance, the patient is required to discontinue acid suppression therapy at least a week prior to placement. Acid exposure time is the principal parameter obtained to determine if pathologic reflux exists. Numbers of reflux events are obtained insofar as they are acidic as weakly acidic refluxes may not be detected. Mealtimes, positional changes, and symptoms are entered by the patient in real time via push-button recorder. Given the improved tolerance, the wireless capsule allows for 96 hours of recording. This increased time of monitoring increases the chance of detecting pathologic reflux despite daily variations in reflux [12]. Patients with 2 or more days of elevated acid exposure time are considered to have pathologic GERD. For patients with a high suspicion for reflux disease but a normal 24-h impedance test, prolonged wireless monitoring could help exclude daily variation (Fig. 3.6). Otherwise, this form of testing may be used if patients are intolerant to catheter-based testing.

High-Resolution Esophageal Manometry

High-resolution esophageal manometry (HRM) is most often obtained in the course of GERD testing to localize the GEJ prior to placement of the pH and impedance probe for 24-h pH-impedance testing. While HRM does not provide direct evidence to diagnose or rule out GERD, information gleaned from testing can provide evidence for underlying conditions that may be allowing reflux to occur as well as rule out motility disorders which may share common symptomatology with GERD. HRM is also normally prerequisite for determining which patients are candidates for antireflux surgery, making it helpful to have on hand when deciding the direction and goals of treatment of GERD patients without adequate response to acid suppression therapy. Full interpretation of HRM should be conducted as per the Chicago Classification 4.0 criteria [13] and will be addressed here only insofar as it pertains to reflux disease.

HRM provides assessment of the morphology and contractility of the esophagogastric junction. As the pressure catheter passes through the EGJ, the circular muscles of the LES and the diaphragmatic crura, which comprise the antireflux barrier along with the GEFV, apply pressure to the esophageal wall and the in situ catheter. When these two mechanisms overlie each other, the LES pressure appears as

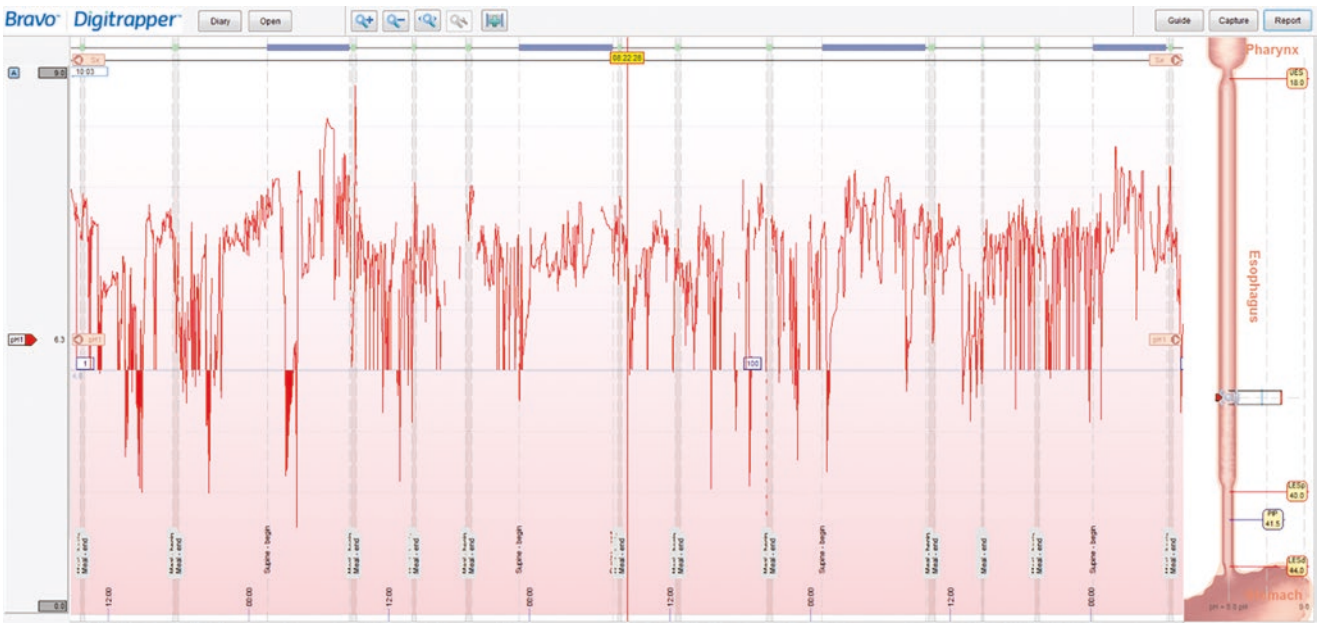

Fig. 3.6 Prolonged (96-h) wireless pH monitoring using Bravo showing daily variation

a homogenous, high-pressure segment across time (type I EGJ). A continuous but undulating high-pressure segment indicates mild separation (<3 cm) of the diaphragmatic crura and the intrinsic circular muscles of the LES (type II EGJ) and indicates the early stages of EGJ dysfunction leading to hiatal hernia formation. Complete separation (>3 cm) of the high-pressure area of the diaphragmatic crura and the LES (type III EGJ) indicates an incompetent EGJ. Esophagogastric junction-contractile integral (EGJ-CI) is another metric to assess reflux barrier function. It is a measure of EGJ pressure, and it takes into account the changes in EGJ tone with breathing. It is shown to improve with antireflux surgery and predicts response to antireflux therapy. Therefore, EGJ-CI can be used as an important supplementary metrics in EGJ barrier function assessment.

HRM also allows for assessment of the peristaltic function of the esophagus, both propagation and vigor. In cases where antireflux surgery may be considered, presence of adequate peristaltic function is required to avoid postoperative dysphagia. Peristaltic function can be quantified by the mean distal contractile interval (DCI) with the associated number of failed or absent swallows as well as with provocative testing. Multiple rapid swallows, wherein five 2 mL swallows are taken 3–5 s apart, can be used to assess the esophageal contractile reserve. This is demonstrated wherein the repeated swallows lead to inhibition of full propagation of the prior swallow; however, the final swallow shows a higher amplitude DCI when compared with the mean DCI of the previous normal swallows. This elevated ratio of provoked DCI to that of a normal swallow predicts an intact neural and muscular function that is important prior to progressing to antireflux surgery to minimize risk of dysphagia after the surgery. Often times, as reflux changes increase from nonerosive to erosive esophagitis, absent and failed swallows as well as fragmented swallows become more common from reflux injury. Another provocative test, the rapid drinking challenge, requires the patient to drink 200 mL of water within 30 s. The pressure tracing is evaluated for proper LES relaxation, presence of esophageal pressurization, and initiation of full peristalsis at the last swallow of the rapid drinking test. Failure of peristalsis following the RDC has been associated with erosive esophagitis. These provocative tests are now part of HRM protocol as per Chicago Classification v.4.0.

Barium Esophagram

The barium esophagram continues to play a role in the evaluation for reflux. It is particularly useful in evaluating for the presence and type of hiatal hernia as well as for patients with prior bariatric and antireflux surgery, and to exclude motility disorders. Some recommend that a normal video esophagram, as part of the preoperative assessment for fundoplication, rules out the need for manometry to further assess for dysmotility that might predispose patients to postsurgical dysphagia [14].

While evaluation of the mucosa is best performed with EGD, esophageal foreshortening is more likely to be identified with an esophagram and is important to identify prior to antireflux surgery. The esophagram has traditionally been used for the detection of reflux with sensitivity increased with provocative maneuvers such as cough, Valsalva, and water siphon testing; however, this has mostly been replaced with 24-h pH-impedance testing. However, the esophagram can still provide information as to the volume of refluxate which cannot be evaluated by impedance and may portend more severe reflux disease. The esophagram plays a substantial role for patient's post-antireflux surgery and most often is the initial test performed as it provides information regarding the postsurgical anatomy as well as a degree of functional evaluation and can be followed up with more specific testing depending those results [15].

Box 3.2 Role of High-Resolution Manometry in Diagnostic Assessment of GERD

Rule out major motility disorder as cause for reflux symptoms.

Assessment of esophagogastric junction competency by measuring contractile integral and lower esophageal sphincter to diaphragmatic crura separation, i.e., hiatal hernia.

Assess for contractile reserve in esophageal peristalsis to assess for post-fundoplication risk of dysphagia, via multiple rapid swallow.

Endoscopic Functional Luminal Imaging Probe

Gastroesophageal reflux disease is due, in part, to the failure of the reflux barrier at the EGJ. Endoscopic functional luminal imaging probe (or EndoFLIP) uses a saline-filled infinitely compliant bag with impedance sensors that allow for the measurement of EGJ cross-sectional area as well as distensibility. The initial prevailing thought was that patients with GERD should have an increased distensibility and increased cross-sectional area at the GEJ, allowing for refluxate to more easily traverse from the stomach into the esophagus. However, presence of reflux strictures can decrease distensibility and would abrogate this relationship. Multiple studies have had a mixed outcome in correlating distensibility to occurrence of GERD, though the largest and

most recent trial to date with 791 patients has shown increased distensibility to be related to erosive esophagitis. Due to the current limited access to EndoFLIP and lack of validation of its clinical utility, its role in assessment of GERD has not been established [16–18].

Gastric Emptying Study

In many respects, it stands to reason that decreased gastric emptying would lead to an increase in esophageal reflux, and initial studies regarding gastric emptying in GERD patients did show an increased proportion of patients with impaired gastric emptying when compared to non-GERD patients [19–21]. However, this finding had not been reproducible across all studies, and furthermore, other studies failed to show a correlation between delayed gastric emptying and increased esophageal acid exposure on ambulatory reflux monitoring [22, 23]. Similarly, there has not been a clear correlation between reduced gastric emptying and high-grade esophagitis to suggest pathologic reflux [24]. One study which performed 24-h pH-impedance simultaneous to gastric emptying study did find that prolonged gastric emptying leads to high pH of gastric contents and therefore refluxate is mild/non-acidic [25]. As such, it is unlikely to cause erosive esophagitis or elevated acid exposure time but may cause symptoms of regurgitation. In short, while a portion of patients with GERD do also have abnormal gastric emptying, risk factors for both conditions are similar and a clear correlation is not established. At the very least, impaired gastric emptying is not a prerequisite for the development of GERD, and obtaining further testing for evaluation of gastroparesis should be based upon the presence of other classic symptoms of gastroparesis (postprandial bloating, early satiety, postprandial nausea) and is not a routine study in the workup for GERD.

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Medical Therapy for GERD

4

Philip O. Katz, Gaurav Ghosh, and Katharine Rooney

Objectives

1. To learn the goals and endpoints for medical treatment of patients with GERD.
2. To know the frequently recommended diet and lifestyle options for treatment of GERD, their proposed pathophysiology, and if there is supporting data.
3. To review the menu of pharmacologic GERD therapies, their mechanistic targets, and the situations for which there is supporting evidence.
4. To become familiar with the reported side effects that have been associated with proton pump inhibitors.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common conditions encountered by healthcare providers. As GERD affects 15–20% of the global adult population, there is no one therapy or algorithm that will be effective for all patients, so it is important that the clinician is comfortable with the different options for medical therapy. A prevalent strategy is to empirically prescribe a proton pump inhibitor (PPI) trial, but this approach alone cannot guarantee optimal results and may contribute to the overuse of PPIs.

In this chapter, we first examine the goals of treating GERD. We will then review the medical toolbox for GERD treatment, including diet and lifestyle modifications, antacids, mucosal coating agents, promotility agents, GABA agonists, H2 receptor antagonists (H2RAs), and PPIs (Fig. 4.1). We will also present a brief discussion of potassium-competitive acid blockers (P-CABs), a new class of agents not yet approved for use in the USA. These interventions target different contributing mechanisms of GERD, including decreased esophageal mucosal integrity, delayed esophageal bolus clearance, reduced lower esophageal sphincter (LES) pressure, number of transient LES relaxations (TLESRs), increased gastric acid exposure time, and delayed gastric emptying. We will discuss short- and long-term optimization of treatment, including medically refractory disease, and review reported adverse events associated with PPIs to aid in expected discussions with patients.

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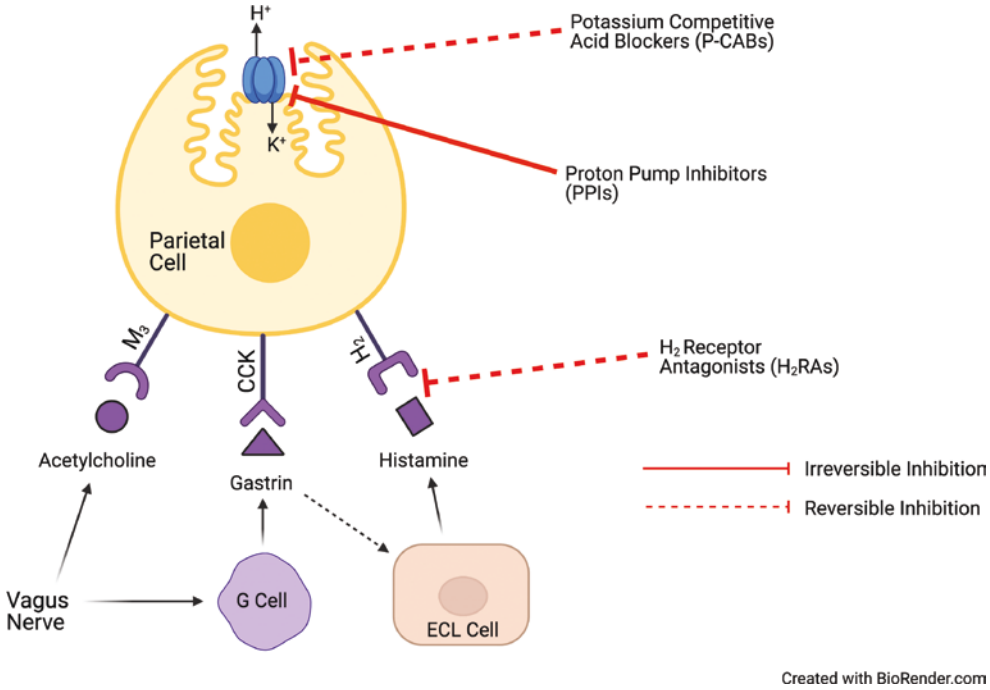

Fig. 4.1 Medications and mechanisms

Goals of Treatment

Understanding the goals of medical treatment is crucial to individualize and optimize therapy. A patient with a normal endoscopy and only monthly heartburn can be managed differently from someone with severe erosive esophagitis. Although both may benefit from gastric acid reduction, they can be offered different medical agents or varying emphasis on lifestyle interventions. It is important to identify a patient's predominant symptoms, as some respond more effectively to therapy than others. Heartburn is the best studied symptom of GERD, and empiric treatment with PPIs or H2RAs generally leads to a ~70% and 54% improvement in heartburn, respectively, compared to placebo. Regurgitation does not respond as well as heartburn. A systematic review of PPI trials found the response for regurgitation was only 17% greater than for placebo, with H2RA response even lower than PPIs in head-to-head trials, suggesting it is not as amenable to medical treatment as the symptom of heartburn.

Patients may present with "atypical" or extraesophageal symptoms which may be attributed to reflux, including chronic cough, asthma, and multiple throat symptoms including laryngitis. These symptoms are more difficult to treat and causality difficult to establish. Randomized controlled trials (RCTs) of GERD therapies for these conditions have been inconsistent, with positive results only in non-placebo-controlled trials or highly specific subpopulations, such as GERD with nocturnal respiratory symptoms. Overall, PPIs are rarely superior to placebo in controlled trials for extraesophageal symptoms. Aggressive acid suppression can be trialed for atypical symptoms, with a low threshold for using pH testing off of therapy to exclude GERD as the cause of symptoms if there is little or no response to an initial trial.

Though attention to patient-centered outcomes such as GERD symptoms and diminished quality of life is important, treatment ideally will prevent complications from the disease. Erosive esophagitis is the most common complication of GERD, and duration of esophagitis correlates with other complications such as peptic stricture formation, which can occur in an important minority of patients with untreated or partially treated erosive esophagitis. Esophagitis is an important measure of therapeutic efficacy, as adequate acid suppression promotes rapid healing of the esophageal mucosa. Objective measures of acid suppression, such as intragastric pH and healing of esophagitis, are important for understanding risk of complications. However, acid suppression does not always correlate with symptom relief.

Lifestyle and Diet Changes

Most physicians recommend a combination of lifestyle and diet modifications as part of symptom management. These suggestions are based largely on physiologic data on the effect of certain foods, tobacco, alcohol, elevated BMI and particular body positions and sleep habits on esophageal mucosa, LES tone, gastric motility, intra-abdominal pressure gradient, and gastric acid production. Unfortunately, many of these interventions lack sufficient outcomes data to objectively support their utility (Table 4.1: Lifestyle modifica-

Table 4.1 Lifestyle modifications

Lifestyle element	Proposed mechanism	Pathophysiologically conclusive	Strength of evidence	Modification suggested?
Sleeping flat	C	Equivocal	Moderate	Yes, elevate HOB 6 inches
Sleeping on right side	B, C, D	Yes	Moderate	Yes, attempt sleep on left side
Late meals	C, G	Yes	Equivocal	Yes, for nocturnal symptoms
Large meals	C, F, G	Yes	Weak	Yes, avoid
Tobacco	A, B, C	Yes	Weak	Yes, avoid
Alcohol	A, B, C, D, F, G	No, different effects in different alcoholic beverages	Equivocal	No
Fatty foods	B, C, F	Equivocal	Equivocal	No
Chocolate	B, C	Equivocal	Weak	No
Acidic foods (including tomato, citrus)	A, C	Yes	Weak	No
Caffeine/coffee	A, B, C, G	Equivocal	Equivocal	No
Carbonation	B, C, F	No	Equivocal	No
Spicy food	A, G	No	Weak	No
Onion	B	Equivocal	Weak	No
Mint	B	No	Weak	No
Obesity	E	Equivocal	Moderate	Yes, attempt weight loss

A Direct irritant, *B* Decreases LES pressure, *C* Increases esophageal acid exposure, *D* Increases frequency of transient LES relaxations (TLESRs), *E* Increases intra-abdominal pressure, *F* Changes motility, *G* Increased gastric acid production

tions). Despite limited outcomes data, these lifestyle changes are of low cost and easily discontinued. As such, it makes sense for patients to consider including them.

Diet and Weight

Outcomes data showing improvement in GERD symptoms with avoidance of specific food and drink (carbonated beverages, fatty foods, acidic foods, caffeine, alcohol) is limited. However, it is reasonable to advise patients to avoid dietary triggers which they have noticed worsen symptoms and to recommend consuming smaller meals. Large meals increase gastric acid production, slow gastric emptying, and cause gastric distension, which in turn increases the frequency of TLESRs, all of which can lead to increased symptom burden. Similarly, patients should avoid eating meals within 2–3 h of sleep if they struggle with nocturnal symptoms, as proximal acid migration is greatest during sleep and sleep delays esophageal acid clearance. There is an association between increasing BMI and symptomatic GERD, and some studies have suggested a correlation between increasing BMI and esophageal acid exposure time. Other studies have shown a correlation between weight loss and improved symptom burden, supporting the recommendation of weight loss in patients who are obese. Weight loss in obese patients carries additional health benefits, including reduction of their risk of developing Barrett's esophagus and esophageal adenocarcinoma, and improvement in their cardiovascular well-being overall.

Sleep

There is more data to support modification of sleep habits for the treatment of GERD symptoms as compared to dietary habits. Sleeping in the left lateral position compared to the supine, prone, and right lateral positions has been shown to decrease both total esophageal acid exposure time and reflux frequency, and there is evidence that patients who sleep on their right side experience increased reflux. These findings have been attributed to an increase in TLESRs in the right lateral position and the orientation of the LES with respect to the acid pocket in left lateral versus right lateral position. It is reasonable to routinely recommend that patients endeavor to sleep on their left side. Some studies have shown that raising the head of the bed by six to eight inches or using a bed wedge that flexes them at the waist is associated with fewer and shorter reflux episodes and faster acid clearance, but this intervention is often inconvenient for patients and does not always correlate with improvement in symptoms.

Antacids and Alginates

Antacids and alginates continue to be widely used by patients who have intermittent symptoms or as additions to prescription therapy for breakthrough symptoms. Antacids, such as sodium bicarbonate, magnesium hydroxide, and calcium carbonate, are basic compounds which neutralize acid in the esophagus and stomach. They act quickly and can deliver short-term relief in patients with intermittent, episodic symp-

toms, and have been shown to be superior to placebo in this scenario. However, they have not been shown to be superior to placebo for frequent GERD symptoms. When used on a regular basis, side effects include diarrhea, constipation, and, in rare cases, renal dysfunction from excess mineral intake.

While ingested food neutralizes acid in the stomach, meals also prompt the stomach to produce additional acid, forming an "acid pocket" on top of existing stomach contents. This acid pocket is a possible source of postprandial reflux symptoms. Alginates, or formulas containing alginic acid derivatives, act by displacing the postprandial acid pocket away from the LES. In the presence of gastric acid, alginates precipitate into a gel raft which acts as a barrier between the acid pocket and the LES. Alginates have been shown to be superior to antacids and placebo for the relief of mild GERD symptoms. Gaviscon is an alginate-antacid combination that is commonly used globally, but unfortunately the formulations of Gaviscon available in the USA (in which alginic acid is often listed as an inactive ingredient) do not appear to be as effective as those available in the rest of the world.

H2 Receptor Antagonists (H2RAs)

H2RAs and other medications which inhibit gastric acid production do not reduce overall reflux events, but instead increase the pH of the refluxate. The histamine H2 receptor of the gastric parietal cell promotes acid secretion, and H2RAs act by reversibly binding to and inhibiting this receptor. H2RAs achieve peak plasma concentrations 1–3 h after ingestion, and acid secretion is reduced by 60–70% before relatively rapid elimination of the medication. H2RAs have better efficacy in alleviating reflux symptoms and healing esophagitis than antacids. A meta-analysis found that heartburn resolved in up to 48% of patients with 4–12 weeks of treatment. Healing of esophagitis varies between studies depending on the severity of baseline esophagitis. Early studies reported esophageal healing at 70–80%, but the majority of these patients had mild (grade 2 Savary-Miller) esophagitis or less at baseline. In more recent placebo-controlled trials, healing rates are 41–50% in patients without severe esophagitis compared to 18–20% in the placebo group. In general, symptoms and mucosal healing are most improved with twice-daily dosing (equivalent to famotidine 20 mg twice a day).

The use of H2RAs has declined given the well-documented superior efficacy of PPIs. However, H2RAs can still be used effectively in the patient with mild GERD symptoms; H2RAs are often offered as on-demand therapy or as a "step-up" approach prior to a trial of PPI. However, this latter approach has been shown to be less cost-effective than starting with PPI therapy in patients with heartburn symptoms. After a PPI-induced remission, patients without erosive esophagitis or Barrett's esophagus can attempt to use H2RAs as a method of weaning from PPIs or acid-suppressing medications altogether. In one prospective study, 34% of patients on PPIs were successfully transitioned to an H2RA and 16% off of any medication at 1-year follow-up. The patient who pursues this approach should be counseled that they may need to resume PPI therapy during the first year.

Another popular use of H2RAs is for nocturnal GERD symptoms. Studies have found that patients on twice-daily PPIs will still have overnight periods of intragastric pH measurements <4. In patients on PPI therapy (whether once or twice daily) who report nocturnal breakthrough symptoms, adding an H2RA at nighttime has been shown to significantly reduce the amount of time that intragastric pH is <4 and improve symptoms. There is controversy regarding when tachyphylaxis develops after repeated H2RA administration, with conflicting evidence. In patients with nocturnal symptoms, adding bedtime H2RA therapy (for instance, famotidine 20–40 mg) can be considered, but if tachyphylaxis occurs on-demand dosing can be tried.

Overall, H2RAs are well tolerated with few side effects. Reported minor adverse effects include headache, dizziness, and mild gastrointestinal symptoms, though in a pooled analysis these side effects were no greater than placebo. Theoretical concerns about interactions with other medications via the cytochrome P450 system have not been borne out in clinical practice. Though acid suppression is invoked as a mechanism for reported PPI-related side effects, possible side effects of H2RAs have not been pursued with the same vigor. The studies which have evaluated potential adverse events did not find any relationship between H2RAs and bone mineral density, pneumonia, or *C. difficile* infections though systematic reviews with significant heterogeneity among studies have reported a slightly increased risk of other enteric infections.

Proton Pump Inhibitors

PPIs are the most effective widely available medications for GERD at this time (Fig. 4.2). PPIs are prodrugs and weak bases which preferentially diffuse to the acidic spaces of the secretory canaliculi of activated parietal cells, where they build to concentrations 1000-fold of that in the blood. The prodrug is then protonated to its active form in the acidic environment of actively secreting H+/K+ ATPase proton

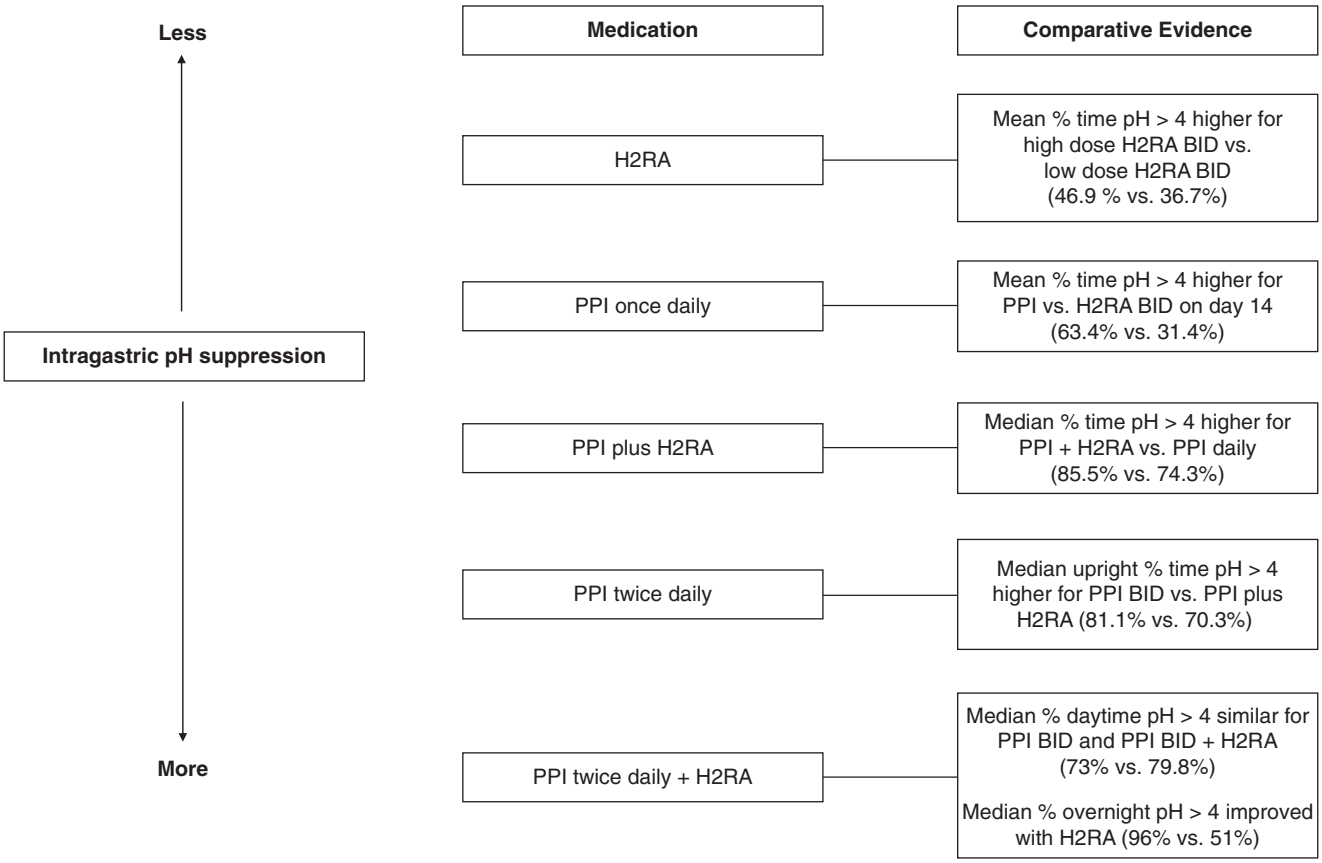

Fig. 4.2 Hierarchy of increasing acid suppression potency

pumps prior to irreversibly blocking the pump. Since only a fraction of pumps are active when patients are fasting, PPIs should be administered so that peak concentrations coincide with the highest number of active pumps for efficient prodrug activation. To achieve this, these medications should be administered 30 min to an hour before the first meal of the day. If a second dose of PPI is needed, it should be given before the last meal of the day rather than at bedtime. Not all proton pumps are active at the time of PPI ingestion, and new pumps are continuously being created. Therefore, acid secretion is never completely suppressed, and it can take approximately 5–7 days to reach steady-state gastric pH. Thus, patients should be counseled not to expect immediate symptom relief.

There are currently seven PPIs on the market. While studies have found some small differences between them, there does not appear to be a clinically significant distinction in symptom relief or healing of esophagitis. When compared head-to-head, symptom relief is consistently superior with PPIs compared to H2RAs. One meta-analysis found that by week 2 of therapy, PPI-treated patients were heartburn-free at faster rates (31.8%/week) compared to H2RAs (17.9%/week), while another found that heartburn remission was approximately 34% higher for PPIs compared to H2RAs at the end of trial periods ranging from 4 to 12 weeks in length. In RCTs, once-a-day PPI therapy has shown heartburn remission in 57–76% of patients. Furthermore, most studies of PPIs show 80–93% of patients have successful healing of erosive esophagitis after an 8-week course of therapy. This discrepancy in rate of heartburn remission and healing of esophagitis reflects that healing does not always correlate with patient symptom relief; refractory symptoms may be an indication for further testing (Fig. 4.3).

Short-term side effects of PPIs, including headache and diarrhea, are rare and resolve with medication cessation or switching to another PPI. However, physician and patient concerns about long-term side effects of PPI therapies continue to grow with the number of observational studies reporting associated adverse effects, which will be discussed later in this chapter.

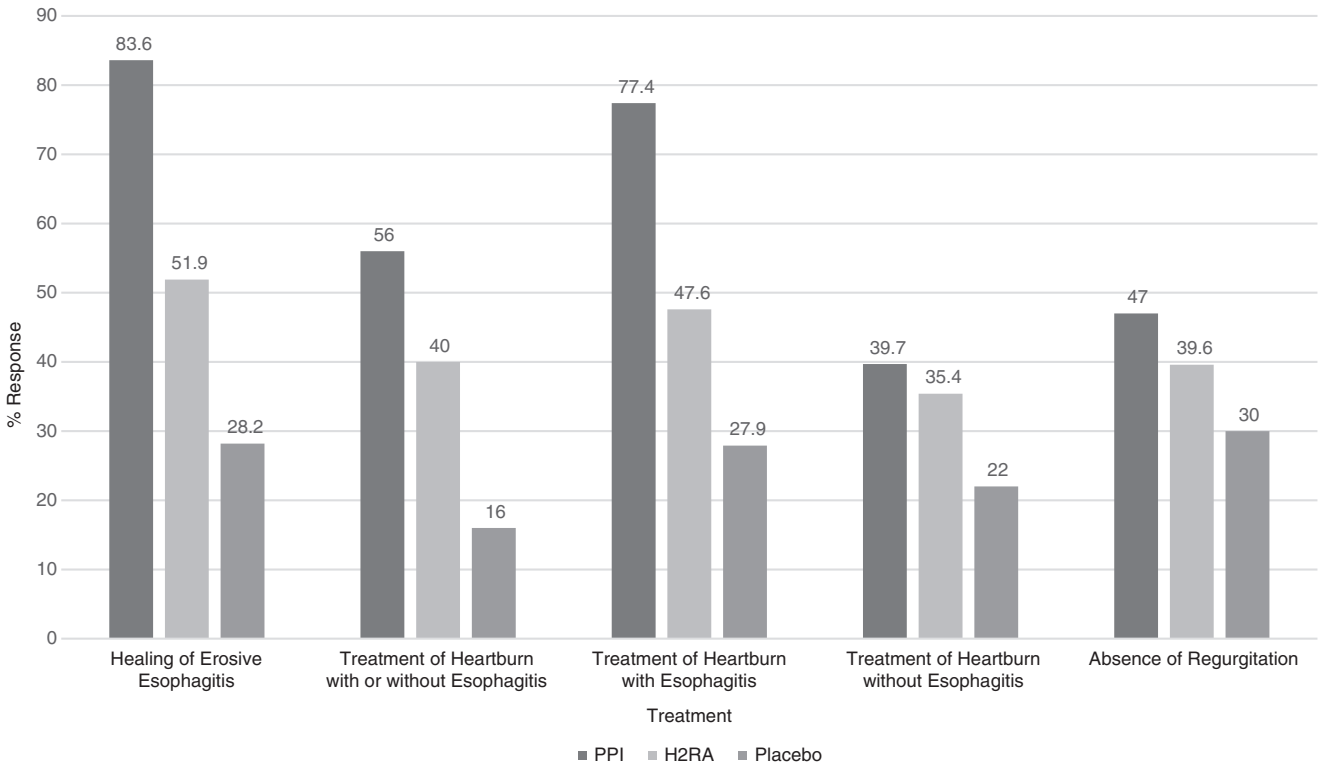

Fig. 4.3 Efficacy of PPIs and H2RAs on esophagitis and symptoms in systematic reviews. Sources: Chiba, et al.; Kahrilas, et al.; Sigterman, et al.

Other Pharmacologic Options

Sucralfate (a combination of sucrose octasulfate and aluminum hydroxide) is a mucosal protective agent that dissociates in the stomach and binds to ulcerated tissue. It likely binds to any inflamed tissue and may protect the esophageal mucosa by blocking the diffusion of gastrin and pepsin across the mucosal barrier. It also promotes bicarbonate production and encourages ulcer healing. It has been shown to be equally effective in controlling GERD symptoms when compared with H2RAs. However, dosing is cumbersome, and there is concern that sucralfate may block the absorption of other medications. For these reasons it is rarely used in general GERD management, though it is utilized in pregnant patients for symptom relief.

Baclofen is a GABA(b) agonist which has been shown to reduce TLESRs, increase LES tone, and decrease the rate of postprandial acid and nonacid reflux events, nocturnal reflux, and belching. It can be used in patients with objective documentation of symptomatic reflux despite PPI therapy. One recent meta-analysis of nine RCTs comparing baclofen to placebo suggests that baclofen is superior to placebo for the short-term treatment of GERD. However, its significant side effect profile (dizziness, somnolence, constipation) and lack of long-term safety data preclude more general use, and it is not approved by the FDA for this indication. We use baclofen only with objective evidence of reflux, usually in patients with regurgitation who decline surgery or endoscopic therapy.

Metoclopramide is a dopamine antagonist which acts as a prokinetic agent; its precise mechanism of action is unclear, though it is thought to sensitize tissues to the action of acetylcholine. Metoclopramide has been shown to increase LES tone, enhance esophageal peristalsis, and accelerate gastric emptying and for these reasons has been proposed as a possible therapy for GERD symptoms. As a single agent, it has not been compared to PPIs and is equivalent to H2RA. It has not been shown to provide additional benefit when combined with H2RA, or when added to a PPI. It is an option in patients with documented delayed gastric emptying, though has not been systematically studied. Additionally, its use is limited by a side effect profile stemming from its antidopaminergic effects on the central nervous system, including tardive dyskinesia, drowsiness, motor restlessness, anxiety, and hallucinations, among other undesirable symptoms. We do not use prokinetics unless gastric emptying delay is documented. We suggest documenting a discussion of these side effects if the drug is used.

Future Medications

Potassium-competitive acid blockers (P-CABs), approved in Japan, are an emerging therapy for both erosive and nonerosive GERD, particularly in cases refractory to other available treatments. These agents reversibly inhibit the gastric proton pumps (H^+/K^+ ATPases) in a potassium-competitive manner. Unlike PPIs, these agents do not require acid catalyzation to assume their active form and compared to PPIs have quicker onset of action and a longer half-life, which allows for daily dosing and the control of nocturnal acid breakthrough resistant to BID PPI. Additionally, in head-to-head comparisons, P-CABs have been shown to provide a more profound degree of acid suppression than PPIs; P-CABs have been associated with decreased esophageal acid exposure time, decreased duration of acid reflux events, and gastric pH sustained at >4 for a longer period of time. One such agent, vonoprazan, is currently on the market in Asia, and efforts are underway to introduce it to the US and Canadian markets.

Long-Term Management

The long-term goals of GERD management are symptom control and healing of erosive disease; patients are often on PPI for a prolonged period of time in pursuit of these goals. While the overwhelming data around PPIs are in support of their safety, observational studies have raised concerns about long-term harms which have prompted more patient interest in discontinuing these medications. In an effort to provide perspective on this topic, Table 4.2 summarizes the most common potential associations, their proposed biologic mechanisms, and some of the notable studies. The majority of long-term consequences are suggested to be the result of continued and significant acid suppression.

However, observational studies cannot establish a cause-effect relationship, and are prone to bias, such as confounding by indication and protopathic bias. A recent large, prospective, placebo-controlled trial followed 17,598 patients given pantoprazole or placebo (with rivaroxaban and/or placebo) for 3 years. The only side effects that were statistically significant different between the PPI and placebo groups were for non-*C. difficile* enteric infections (1.4% vs 1.0% for placebo; OR 1.33; 95% CI 1.01–1.75). The number needed to harm for this small increase does not justify major change in practice. The rate of *C. difficile* trended toward being more common with PPI, the PPI and placebo groups were similar for kidney disease, dementia, pneumonia, fracture, heart attack, stroke, cardiovascular death, and all-cause mortality. A 2010 RCT which followed 3761 patients given either PPI or placebo for a median of 110 days found an increased risk of (non-*C. difficile* mediated) diarrhea in the PPI group but otherwise no difference in adverse events. After considering this evidence, a reasonable conclusion is to assess each patient's true need for PPI therapy and their ability to be tapered off the medication.

Although PPIs are generally safe and effective, it is good practice to minimize medication use when possible. Currently an 8-week trial of PPI therapy is recommended for patients with typical GERD symptoms. If this trial period is successful in improving symptoms, it should be followed by de-escalation to lowest possible effective dose, or on-demand or intermittent treatment. Studies have shown that a proportion of patients will remain asymptomatic for a year or more after the withdrawal of PPI, and others with recurrent symptoms can be managed with as-needed H2RAs. Additionally, a recent systematic review and meta-analysis comparing on-demand PPI vs continuous PPI vs placebo found that on-demand PPI was superior to placebo and continuous PPI in patients with nonerosive GERD. If a patient has been on PPI for a prolonged period of time and an attempt is made to de-escalate or stop therapy, many choose tapering the medication gradually to help mitigate potential rebound symptoms. However, if rebound does occur, it is usually short-lived so discontinuing medication without weaning is acceptable. Patients who do not have acceptable symptom relief should have further workup to objectively document the presence or absence of GERD.

Patients with severe erosive disease usually need and are recommended to continue daily PPI long term given high rates of recurrence when PPI is discontinued and evidence that on-demand therapy is inferior to continuous therapy. Those with Barrett's esophagus are often encouraged to continue daily PPI, as PPIs have been suggested to decrease progression to dysplasia. Management of Barrett's esophagus is addressed in other chapters.

Refractory Disease

A significant percentage (up to 40%) of patients will have symptoms refractory to standard PPI therapy. The first step in the management of these patients is to ensure that they are compliant with their PPI and are taking them optimally (i.e., 30 minutes prior to meals). If symptoms persist despite PPI taken consistently and in an appropriate manner, some consider a switch to a different PPI or to increase dosing to twice daily. While not routinely done in practice, trialing a CYP2C19-independent PPI (i.e., rabeprazole) may improve

Table 4.2 Summary of potential adverse events associated with long-term PPI use

Potential adverse event	Proposed mechanisms	Source; study design	OR (95% CI)	Strength of evidence[a]; comments
Chronic kidney disease	Recurrent acute interstitial nephritis	Moayyedi et al., Gastroenterology 2019; RCT	1.17 (0.94–1.45)	1b
		Nochaiwong et al. Nephrol Dial Transplant 2018; Meta-analysis	1.36 (1.07–1.72)	2a −; 4 cohort studies, I^2 = 99.4%
Dementia	1. Limits dietary B12 absorption 2. Decreased clearance of beta-amyloid peptides	Moayyedi et al., Gastroenterology 2019; RCT	1.20 (0.81–1.78)	1b
		Song et al., PLoS One 2019; Meta-analysis	1.04 (0.92–1.15)	3a −; 10 cohort or case-control studies, I^2 = 95.6%
Myocardial infarction	1. Reduction of endothelial NO leading to thrombosis 2. Competition with clopidogrel at CYP2C19	Bhatt et al., NEJM 2010; RCT	0.92 (0.44–1.90)	1b
		Moayyedi et al., Gastroenterology 2019; RCT	0.94 (0.79–1.12)	1b
		Batchelor et al., Aliment Pharmacol Therap 2018; Meta-analysis	1.19 (0.25, 5.73)	1a −; 4 RCTs, I^2 = 56%
Infection				
Clostridium difficile	Vegetative *C. diff* survival increased	Moayyedi et al., Gastroenterology 2019; RCT	2.26 (0.70–7.34)	1b −
		Cao et al., J Hosp Infect 2018; Meta-analysis	1.26 (1.12–1.39)	3a −; 50 cohort or case-control studies, I^2 = 80.6%
Non-*C. diff* enteric infection	Changes in gut microflora encourage pathogenesis of enteric infections	Moayyedi et al., Gastroenterology 2019; RCT	1.33 (1.01–1.75)	1b −; only statistically significant finding in an RCT
		Hafiz et al., Ann Pharmacother 2018; Meta-analysis	4.28 (3.01, 6.08)	3a −; 9 cohort or case-control studies, I^2 = 94.3%; Egger's test with moderate Asymmetry suggestive of publication bias
Pneumonia	Increased colonization of gastric bacteria which are then micro-aspirated	Moayyedi et al., Gastroenterology 2019; RCT	1.02 (0.87–1.19)	1b
		Lambert et al., PLoS One 2015; Meta-analysis	1.49 (1.16–1.92)	3a −; I^2 = 99.2%; subgroup analysis shows only PPI duration of <1 month significant, suggestive of protopathic bias
Bone				
Osteoporosis	1. Reduced calcium absorption 2. Hypergastrinemia causing parathyroid hyperplasia	Liu et al., Life Sci 2019; Meta-analysis	1.23 (1.06–1.42)	3a −; 6 cohort or case-control studies, I^2 = 90.6%
Hip fracture		Moayyedi et al., Gastroenterology 2019; RCT	0.96 (0.79–1.17)	1b

For most adverse events, all relevant RCTs and one meta-analysis are included (largest, most recent, most cited, or highest quality)

[a]Evidence level according to the Oxford Centre for Evidence-Based Medicine. Evidence level 1a: systematic review of RCTs (with homogeneity). Evidence level 1b: individual RCT (with narrow confidence interval). Evidence level 2a: systematic review of cohort studies (with homogeneity). Evidence level 2b: individual cohort study or low-quality RCT. Evidence level 3a: systematic review of case-control studies (with homogeneity). Evidence level 3b: individual case-control study. Evidence level 4: case series (and poor-quality cohort and case-control studies). Evidence level 5: expert opinion. A minus-sign "−" denotes a lower level because of either a result with a wide confidence interval or a systematic review with troublesome heterogeneity

control in patients who are rapid metabolizers. If nighttime symptoms predominate and GERD has been documented, a nighttime H2RA may be added to once- or twice-daily PPI.

If symptoms persist after 8 weeks of these modifications, it is prudent to obtain objective evidence of GERD as the cause of symptoms. Those with predominantly extraesophageal symptoms should be referred to the appropriate specialist (pulmonary, allergy, ENT) for workup of non-GERD etiologies for their symptoms. The patient with typical symptoms should undergo endoscopy if they have not already done so; the patient's first endoscopy should ideally be performed off PPI for 2–4 weeks. If EGD is unrevealing, then ambulatory reflux monitoring should be pursued to assess reflux burden and association with symptoms. Reflux monitoring through pH or pH-impedance modalities should be performed off treatment. Patients with a negative workup and no previous documentation of GERD should stop PPI therapy. Patients with objective evidence of GERD and a positive workup for uncontrolled GERD despite twice-daily PPI should be considered for anti-reflux surgical referral.

Those with objective evidence of GERD without documented reflux on PPI should also be assessed for other causes or surgical/endoscopic treatment for their GERD.

Conclusions/Summary Points

1. Symptom relief may occur with weight loss, sleeping in the left lateral position, and not eating for at least 2 h before sleep.
2. PPIs are the most effective medications for symptom relief and healing of esophagitis. Once-daily PPI should be taken 30–60 min prior to the first meal of the day. If a second dose of PPI is required, it should be taken before the last meal of the day.
3. If a patient's symptoms persist despite appropriate medication use, esophageal testing (endoscopy and/or pH testing) should be considered to determine source of symptom generation.
4. If PPIs are required long term, it is best clinical practice to administer at the lowest effective dose and consider intermittent therapy.
5. H2RAs may be an appropriate therapy for nocturnal GERD symptoms and used as a tool for weaning from PPI therapy.
6. Adjunctive therapies can be helpful in certain situations. However, given the side effect profiles of prokinetic therapies and baclofen, these medications should be used sparingly.

Questions

1. A 50-year-old woman with GERD has been on once-daily PPI for 3 years with complete relief of symptoms. She had an endoscopy at the time of starting medication with Los Angeles grade A esophagitis. She saw on the evening news that there are many risks associated with taking PPIs for a long period of time, so she stopped taking her PPI the next day. A few days later, she began to have severe heartburn again. The patient comes to your office for counseling and is still motivated to try PPI cessation.

   What is the best next step in management?

   A. Increase the PPI to twice daily to treat current symptoms, then step down to once daily, and then trial discontinuation of PPI
   B. Restart the PPI to treat current symptoms, then step down to H2RA, and then trial discontinuation of H2RA
   C. Restart the PPI to treat current symptoms, then step down to TCA, and then trial discontinuation of TCA
   D. Treat current symptoms with baclofen, and then trial discontinuation of baclofen
   E. Counsel the patient that PPI discontinuation is unlikely and indefinite therapy is necessary

Answer: B.

This patient has abruptly stopped PPI therapy and may be suffering from symptoms due to "rebound" acid hypersecretion. Intragastric pH studies suggest this phenomenon is uncommon and short-lived, but a return of severe heartburn symptoms suggests a patient will be unsuccessful in immediate PPI cessation. Instead, this patient may benefit from a step-down approach to intermittent PPI therapy or a H2RA (Answer B). The patient has no indication for twice-daily PPI, and this approach is similar to what was already attempted (Answer A). TCAs would be considered if there was concern for esophageal hypersensitivity (Answer C), and baclofen has not been studied for step-down therapy in GERD (Answer D). This patient may not need long-term therapy, as she does not have severe erosive esophagitis or Barrett's esophagus (Answer E).

2. A 50-year-old man with metastatic lung cancer presents to your office after recent hospitalization for GI bleeding. He recently had systemic chemotherapy associated with nausea/vomiting and presenting with hematemesis. His endoscopy showed no esophagitis or peptic ulcer disease, and the culprit lesion was thought to be a Mallory-Weiss tear. He was treated with IV PPI therapy and discharged on once-daily oral PPI.

   What is the best next step in management?

   A. Repeat endoscopy to check for esophageal healing.
   B. Send *H. pylori* stool antigen.
   C. Double the dose of PPI.
   D. Step down PPI therapy to H2RA.
   E. Discontinue the PPI.

Answer: E

This patient likely developed a Mallory-Weiss tear in the setting of vomiting after recent chemotherapy. It is important to review the indication for PPI therapy and discontinue if the patient will no longer derive benefit (Answer E). There is no role for repeat endoscopy in the absence of severe esophagitis or gastric ulcer (Answer A). A patient with a Mallory-Weiss tear does not need further workup or continuation of gastric acid suppression (Answers B, C, D).

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Phenotypes of Gastroesophageal Reflux Disease and Personalized Management

5

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Objectives

1. Define and describe gastroesophageal reflux disease (GERD) in general practice including the complexities in diagnosis and management based on historical paradigms.
2. Identify the various specific phenotypes of GERD and the underlying pathophysiologic mechanisms that characterize each subtype.
3. Illustrate targeted management of GERD for various phenotypes based on differences in pathophysiology and symptom burden.
4. Identify future directions in the personalized management of GERD based on phenotypic identification.

Introduction

Gastroesophageal reflux disease (GERD) is a condition that affects 18.1–27.8% of Americans. It is characterized by symptoms that develop as a result of the backflow of gastric contents and fluid into the esophagus and is further defined by the Montreal consensus to include the presence of troublesome symptoms and/or complications. GERD symptoms are variable and include heartburn, belching, hiccups, dysphagia, globus sensation, and chest pain. Extra-esophageal manifestations include throat clearing, pharyngeal pain, cough, and hoarseness. Symptoms of GERD are neither sensitive nor specific to the condition with significant overlap with symptoms of gastroparesis, eosinophilic esophagitis, and functional dyspepsia. Though GERD is more common in men, the prevalence of symptoms is actually higher in women (16.7% vs. 15.4%). Established risk factors for GERD include obesity, pregnancy, presence of hiatal hernia, tobacco use, connective tissue diseases (i.e., scleroderma), and gastrointestinal dysmotility. GERD represents a significant burden to the healthcare system in the United States; the direct annual costs of over $12 billion further balloons to over $50 billion when including expenditures for patients with extra-esophageal reflux symptoms. Despite the high prevalence of this condition and significant costs associated with GERD, the paradigm of management has up until recently been oversimplified and ineffective for many patients.

Concept of Personalization in GERD Management

Historically, patients diagnosed with GERD have been approached in a linear algorithm that often starts with empiric acid suppression using proton pump inhibitor (PPI) therapy. This tactic fails to account for the various physiologic mechanisms that can lead to GERD, as well as individual variations in response to medical therapy. This is evidenced by the fact that 40% of patients diagnosed with GERD will have no response or partial response to PPI therapy. Therefore, a personalized approach to the diagnostic evaluation and management of GERD is paramount to successful therapy and symptom relief. Rather than a "one-size-fits-all" methodology, management should account for the patient's symptoms and address the underlying pathophysiology leading to their GERD. To aid in this personalized approach, gastroenterologists have identified many permutations of GERD that result in specific phenotypes with unique symptomology and pathophysiology. Therefore, identifying specific GERD phenotypes is a crucial step in the personalized approach to GERD.

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GERD Phenotypes (Table 5.1)

Erosive Esophagitis

A recent shift in the model for management of GERD has been the recognition that the condition reflects multiple syndromes stemming from an array of pathophysiologic mechanisms. The more traditional syndrome of GERD known to gastroenterologists is that of erosive esophagitis, which is graded by the degree of mucosal disruption using the Los Angeles (LA) scale with increasing degree of severity from A through D (Table 5.2). This syndrome can further be subdivided into patients with low-grade erosive esophagitis (LA esophagitis grades A and B) and high-grade esophagitis (LA esophagitis grades C and D). High-grade erosive esophagitis is most often seen in obese men and results from severely impaired function of lower esophageal sphincter (LES) and is often associated with the presence of a hiatal hernia. These patients typically have significant supine reflux and poor esophageal clearance of gastric contents leading to extremely prolonged esophageal acid exposure, which results in severe mucosal inflammation and damage in the esophagus. Mucosal damage does not always correlate with symptoms; in fact, 11%–47% of this group report being asymptomatic despite their significant endoscopic findings. In contrast, low-grade erosive esophagitis results from less severe dysfunction of the esophagogastric junction (EGJ). Though patients may have either LA grade A or grade B esophagitis, grade A esophagitis alone is not felt to be diagnostic of GERD following the Lyon consensus. This change was made based on evidence of poor interobserver agreement on this grade of esophagitis and the lower sensitivity for GERD from studies examining esophagitis and reflux physiologic testing.

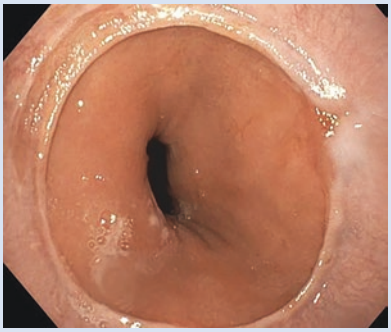
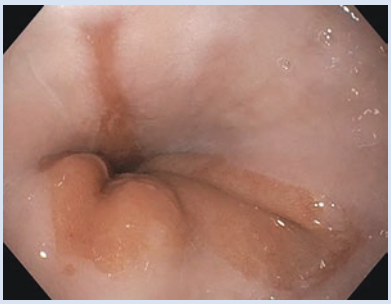
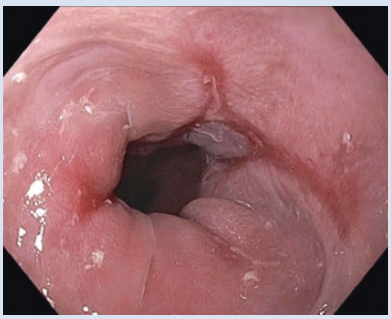
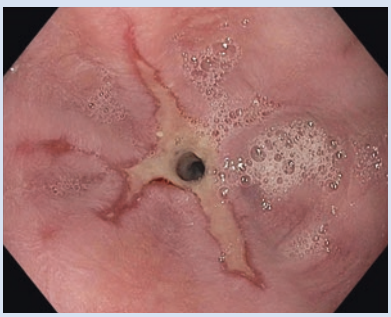
Nonerosive Reflux Disease

Historically, nonerosive reflux disease (NERD) has been considered a complex GERD syndrome defined on patient-reported symptoms or physiologic testing. The definition of the NERD phenotype stems from the Rome IV consensus and is defined as GERD based on documented abnormal ambulatory reflux testing (either pH alone or with imped-

Table 5.1 Gastroesophageal reflux disease (GERD) phenotypes, characteristics, symptoms, and diagnostic findings

GERD phenotype	Description	Pathophysiology	Diagnostic criteria
Erosive esophagitis	Acid reflux causing esophageal mucosal injury, significant supine reflux	Incompetent EGJ causing gastric reflux, delayed clearance of esophageal refluxate causing mucosal inflammation. High-grade disease often associated with hiatal hernia	Diagnosed on endoscopy with typical symptoms
	Prolonged esophageal acid exposure time causes worse esophagitis		LA C and D esophagitis
Barrett's esophagus (BE)	More often in obese, Caucasian, older men. Often silent reflux given low esophageal acid sensitivity	Prolonged acid exposure from low esophageal sphincter motility leads to intestinal metaplasia (IM)	Irregular Z-line on endoscopy with salmon-colored mucosa at EGJ. Biopsies confirm intestinal metaplasia
Proven nonerosive reflux	Typical reflux symptoms present. No specific gender or age predominance	Likely decreased esophageal mucosal integrity leads to acid irritation of underlying esophageal enteric nerves	Documented abnormal ambulatory reflux testing with the absence of esophagitis on endoscopy
Functional heartburn	Retrosternal chest pain or discomfort without physiologic evidence of GERD	Peripheral and/or central sensitization that leads patients to perceive reflux stimuli with greater intensity and pain	Normal physiologic ambulatory reflux testing. No correlation of symptoms to any acid exposure on reflux testing
Chest pain-dominant syndrome	Noncardiac chest pain is predominant symptom, with or without typical GERD symptoms. Response based on level of acid exposure on pH testing	Possible element of nerve sensitization	Pain correlates with abnormal physiologic reflux events. May or may not have abnormal endoscopy findings
Reflux hypersensitivity	Typical reflux symptoms occur with physiologic reflux exposure. Form of nonerosive reflux disease	Peripheral and/or central sensitization that leads patients to perceive reflux stimuli with greater intensity and pain	Typical reflux symptoms coinciding with normal esophageal acid exposure on pH testing and normal esophageal endoscopic findings
Regurgitation-predominant syndrome	Predominant symptom is regurgitation of refluxate into the esophagus and hypopharynx	Frank failure of the barrier at the EGJ which allows for the free flow of gastric refluxate into the esophagus	Symptoms classic on history. Manometry can confirm low sphincter tone
Extra-esophageal syndromes	Symptoms are typically chronic cough, hoarseness, and throat clearing. With or without esophageal symptoms	Sensitivity of the hypopharynx to any acid exposure can precipitate symptoms	No gold-standard testing. Laryngoscopy is nonspecific. No physiologic standards for upper esophageal sphincter

Table 5.2 Los Angeles (LA) classification of esophagitis

LA grade	Description	Image
A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds	
B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds	
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involve less than 75% of the circumference	
D	One (or more) mucosal break which involves at least 75% of the esophageal circumference	

ance) with the absence of esophagitis on endoscopy. The underlying pathophysiology of NERD is heterogeneous, but poor esophageal mucosal cellular integrity is thought to be the main driver of this phenotype. This is evidenced by studies demonstrating that NERD patients have increased intercellular spacing in esophageal mucosa on microscopic evaluation. This increased spacing results in increased mucosal permeability, allowing refluxed gastric contents to irritate the submucosal sensory nervous system. This leads to symptoms of GERD while leaving no evidence of mucosal inflammation on endoscopy due to the shorter esophageal acid exposure duration. However, given the widespread use of PPIs, the emerging expert consensus is that NERD and erosive esophagitis likely exist on a spectrum where the pathophysiology may be more similar than previously believed.

Functional Reflux Syndromes

Reflux hypersensitivity and functional heartburn are two phenotypes that are thought to account for up to 90% of all patients who fail maximum dosage PPI therapy for GERD. Reflux hypersensitivity is a phenotype defined by the Rome IV consensus as patients having typical reflux symptoms coinciding with physiologic esophageal acid exposure on ambulatory reflux testing and normal esophageal endoscopic findings (as well as the absence of other esophageal disorders to explain symptoms). Furthermore, symptoms must be present for at least 6 months and occur at least twice weekly for 3 months. In this phenotype, hypersensitivity to reflux requires peripheral and/or central sensitization that leads patients to perceive reflux stimuli with greater intensity and pain. Studies have demonstrated that there is an increased chemoreceptor sensitivity to acid exposure and increased mechanoreceptor sensitivity to balloon distension in these patients. Therefore, perception of symptoms by these patients seems out of proportion to physiologic testing.

In contrast, functional heartburn is defined by Rome IV criteria as specifically retrosternal chest pain or discomfort without physiologic evidence of GERD and no correlation of symptoms to any acid exposure on pH/impedance testing. Similarly, this must be at least 6 months in duration with symptoms occurring at least two times weekly for 3 months. Similar mechanisms with respect to central and peripheral sensitization occur with functional heartburn as well as reflux hypersensitivity. However, these mechanisms appear to be more pronounced in functional heartburn, and overall patients with this phenotype have been shown to have a lower threshold for painful stimuli regardless of location (including non-esophageal locations).

In both reflux hypersensitivity and functional heartburn, cognitive factors and psychological stressors have a significant role in the perception and progression of symptoms. The underlying central and peripheral sensitization that leads to hypersensitivity can also lead to visceral anxiety, whereby patients dwell on symptoms and catastrophize symptoms. Further selective focus and specific awareness of esophageal symptoms result in hypervigilance, which is a key driver of poor coping mechanisms and reduced quality of life.

Barrett's Esophagus

A unique subset of GERD patients with marked similarity to high-grade erosive esophagitis patients is Barrett's esophagus (BE). This phenotype has a strong predisposition for Caucasian males over the age of 50 with central adiposity. This condition affects 1–2% of all Americans and results from chronic gastroesophageal reflux. Prolonged acid exposure leads to intestinal metaplasia (IM) from esophageal squamous cells. This can progress in a stepwise fashion from IM to dysplasia and can ultimately lead to esophageal adenocarcinoma (EAC), though the annual risk of progression to EAC is low at 0.1–0.4% per year. Studies have shown that patients with BE are more likely to have elevated acid exposure on ambulatory reflux testing, a history of chronic GERD symptoms, a concurrent hiatal hernia, and a history of erosive esophagitis. Patients with BE have been shown to have low LES tonicity and a higher likelihood of ineffective esophageal motility. Similar to patients with high-grade erosive esophagitis, patients with BE are less sensitive to esophageal acid exposure, and 40% of patients diagnosed with BE do not report preceding heartburn or typical reflux symptoms.

Reflux Chest Pain Syndrome

This particular phenotype of GERD presents with retrosternal pain with or without typical reflux symptoms. Reflux-related chest pain can be difficult to separate from cardiac chest pain, and all cardiac causes must be excluded. The gold standard for diagnosis of reflux chest pain syndrome is when symptoms coincide with periods of abnormal acid exposure on ambulatory pH testing. Patients with reflux-related chest pain and abnormal esophageal pH acid exposure are also more likely to have typical GERD symptoms including heartburn and regurgitation.

Regurgitation-Dominant Reflux Disease

Certain patients experience significant regurgitation of gastric refluxate as the primary symptom. In the regurgitation-dominant reflux disease phenotype, there is frank failure of the barrier at the EGJ which allows for the free flow of gastric refluxate into the esophagus. The large volume of refluxate into the esophagus is appreciated by the patient as the esophagus distends and will often travel into the hypopharynx. This can lead to a sour sensation in the patient's mouth as they taste the refluxate. Symptoms are exacerbated in the supine position when the effect of gravity cannot aid the malfunctioning EGJ. Unlike other GERD phenotypes, the presence of acidic pH has a milder effect on the nature of symptoms. Regurgitation is often postprandial, acidic, and prompted by positional changes. For patients with GERD, 13% report regurgitation, which typically occurs at night when the patient is asleep and recumbent often leading patients to prefer sleeping with the head of the bed elevated. When regurgitation in GERD is present, it must be differentiated from rumination syndrome which may present similarly. However, as opposed to regurgitation, rumination is typically bland, occurs during eating, and is prompted by

abdominal muscle tension increasing intragastric pressure above that of the esophageal pressure. The diagnosis of rumination syndrome is made on postprandial high-resolution esophageal manometry.

Extra-Esophageal Syndromes

A complex and difficult patient population to treat in gastroenterology involves patients with laryngopharyngeal reflux (LPR) and chronic cough. A significant number of patients with laryngeal symptoms are diagnosed with LPR based on nonspecific laryngoscopic findings. The hypopharynx has a much higher sensitivity than even the esophagus to acid exposure with many hypothesizing that even small, infrequent penetrations of acid into the hypopharynx can cause significant inflammation. Unfortunately, there is no simple means to determine reflux events at the upper esophageal sphincter since most diagnostic tools are tailored to evaluation of the LES. For instance, the role of 24-hour dual-sensor pH probe in the diagnosis of LPR is controversial. To start, it is not well established if the probes are able to accurately detect the small amounts of acid that can lead to symptoms of LPR. There is debate about raising the pH cutoff for acid exposure at the upper esophageal sphincter to five from four, as the larynx has a lower tolerance for acid exposure compared to the esophagus. There is also no consensus on the number reflux events at the upper esophageal sphincter considered physiologic compared to the lower esophageal sphincter, which further makes pH probe results difficult to interpret for LPR. An additional diagnostic difficulty with this phenotype is that a majority of patients have isolated extra-esophageal symptoms and no concurrent esophageal symptoms of GERD suggesting a significant component of neuronal hypersensitivity driving this phenotype.

Assessing GERD Phenotype (Fig. 5.1)

The concept of personalization begins with a stepwise approach in the assessment and management of suspected GERD patients in order to identify their phenotype. By identifying the phenotypes outlined above, personalized therapy can be considered to optimize the probability of successful symptom management while minimizing cost and risk.

Clinical Presentation

The stepwise approach first starts with an assessment of the patient's clinical presentation through detailed history of predominant symptoms, response to PPI therapy if previously trialed, and assessment of risk factors. This assessment can be aided with addition of more objective symptom quantification using validated questionnaires including the GERDQ and Carlsson-Dent questionnaire. Additionally, at this early stage in evaluation, it is also important to identify features of psychosocial stress, anxiety, and symptom hypervigilance. This can be done with the Esophageal Hypervigilance and Anxiety Scale (EHAS) which is a validated tool to assess for symptom-specific anxiety and hypervigilance. These psychosocial factors can exacerbate symptoms as well as decrease the probability of PPI success in the management of GERD symptoms. The last crucial aspect of this step is the identification of red flag symptoms or risk factors including dysphagia, weight loss, melena, and iron-deficiency anemia that would prompt early endoscopic evaluation regardless of GERD phenotype. At this step in the evaluation process, it can often be determined if patients have regurgitation-predominant symptoms, extra-esophageal symptoms, heartburn, and/or chest pain-predominant symptoms, which is crucial in phenotypic determination.

Endoscopic Evaluation

If the phenotypic determination of GERD is still unclear after clinical presentation assessment or initial PPI management is unsuccessful, the next step in the personalized assessment of GERD is evaluation with upper endoscopy. With respect to GERD, endoscopy allows for assessment of erosive esophagitis where LA B esophagitis is highly suggestive for reflux disease and, based on the Lyon consensus, LA C esophagitis or greater is definitive for GERD. This can be used to rule out alternative diagnoses such as eosinophilic esophagitis. Endoscopy also allows for evaluation of BE, which requires tissue acquisition to assess for presence of dysplasia. Furthermore, assessment of the integrity of the anatomical antireflux barrier can be made. First, antireflux anatomy can be assessed by inspecting for axial separation of the crural diaphragm from the LES by measuring the distance from the top of the gastric folds to the diaphragmatic impression to assess for hiatal hernia. Second, grading gastroesophageal flap valve can help in determining GERD phenotype and guide management. Third, evaluation of transient lower esophageal sphincter relaxation (TLESR) can further be used to assess antireflux anatomy and guide therapy decision-making. By this step, endoscopy can reveal whether a patient's phenotype is either erosive esophagitis (low grade or high grade), NERD, BE, or an entirely different diagnosis.

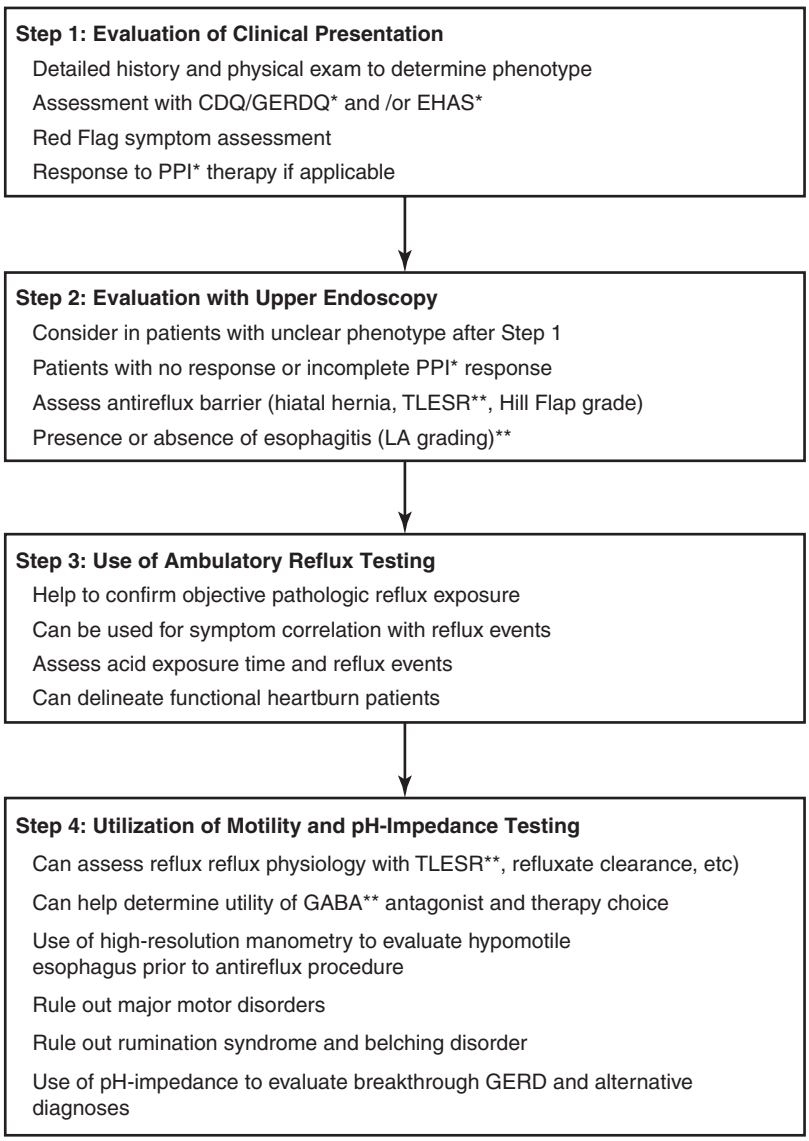


Fig. 5.1 Stepwise approach to GERD evaluation
**PPI* Proton Pump Inhibitor, *CDQ* Carlsson-Dent Questionnaire, *GERDQ* Gastroesophageal Reflux Disease Questionnaire, *EHAS* Esophageal Hypervigilance and Anxiety Scale
***TLESR* Transient Lower Esophageal Sphincter Relaxation, *LA* Los Angeles, *GABA* Gamma aminobutyric acid

Ambulatory Reflux Monitoring

An important tool in personalized GERD diagnosis and phenotypic assessment is the use of ambulatory reflux monitoring. This is particularly useful as the next diagnostic step if there is no evidence of erosive esophagitis on upper endoscopy. The Lyon consensus argues that in patients with a low pretest probability of GERD, ambulatory reflux testing should be performed when the patient is not on any acid-suppressing medications. In patients with a high pretest probability of GERD or with established GERD who are not responding to therapy, ambulatory reflux testing can be performed on acid suppression to assess for efficacy of therapy. There are several options for ambulatory pH testing including both catheter-based and wireless options. Transnasal pH catheter testing can be performed with or without impedance monitoring and is 24 h in duration. The Bravo pH capsule system (Medtronic, Minneapolis, Minn) allows for wireless pH probe monitoring that can record several days of data. The Lyon consensus established diagnostic cutoffs for pathologic and physiologic esophageal acid exposure. On wireless pH monitoring, an acid exposure time (AET) less than 4% is physiologic, 4–6% is indeterminate, and greater than 6% is consistent with GERD. In terms of actual reflux events, less than 40 events is considered physiologic, 40–80 is indeterminate, and greater than 80 events may be consistent with GERD. In patients without erosive esophagitis, abnormal acid exposure data can establish GERD or what has previ-

ously been referred to as "true" NERD. Additionally, ambulatory reflux monitoring also allows for symptom correlation. In patients with symptoms correlating with physiologic reflux events, an identification of reflux hypersensitivity can be made. Other phenotypes can be established if abnormal acid exposure correlates with symptoms of chest pain or regurgitation. Beyond the significant diagnostic utility of wireless pH monitoring, Bravo testing can also help guide GERD management. A recent study by *Yadlapati* et al. demonstrated that four consecutive days of AET less than 4% correlated with a tenfold odds increase in the ability to stop PPI therapy. Patients with four consecutive days of AET greater than 4% more often had symptoms upon PPI cessation, resulting in unsuccessful weaning of PPIs.

Esophageal Motility and Esophageal Function Evaluation

The final step in the diagnostic assessment of GERD is evaluation of esophageal function, esophageal content movement, and motility with the use of high-resolution manometry (HRM) and pH impedance. HRM can be used as a more sensitive evaluation of the antireflux anatomy and overall EGJ function. HRM allows for assessment of the resting LES tone and can also assess for the presence of a sliding hiatal hernia that can be missed on endoscopy. This data can further elucidate the mechanism of GERD and efficacy of the esophagus to clear esophageal refluxate, which can help guide management. For instance, patients with evidence of poor esophageal refluxate clearance and/or extremely low LES tone on HRM may respond best to endoscopic or surgical antireflux interventions rather than medical therapy. Furthermore, HRM can be used to quantify duration and frequency of TLESRs which are difficult to assess on endoscopy. An additional finding on HRM that can help predict therapy response involves assessing esophageal peristaltic function. Specifically, patients with an aperistaltic esophagus have a higher risk of developing post-fundoplication dysphagia if the antireflux barrier is restored through antireflux surgery. Both HRM and pH impedance have utility in the personalized management of GERD as well. The American Gastroenterological Association (AGA) recommends both studies in patients who fail standard PPI therapy. In particular, pH impedance is more sensitive than wireless pH testing while patients are on PPI therapy and can help quantify acid burden. This data can be used to see if GERD therapy needs to be escalated or if there is an overlapping functional component to symptomology that would better respond to alternative therapies.

The last arena of utility for HRM and pH impedance in the phenotypic assessment of GERD is identifying the etiology of certain symptoms that are not specific to GERD such as belching, rumination, and hiccupping. For example, by measuring pressures in the stomach and esophagus on HRM, regurgitation can be delineated from rumination, as well as determining whether belching or hiccupping is reflux-mediated or functional. The use of pH impedance can also help in the delineation of symptoms by allowing for localization of esophageal contents to see if symptoms correlate to GERD (belching, regurgitation) or alternative diagnoses such as rumination and supragastric belching.

Personalized Approach to GERD Therapy (Table 5.3)

By following a personalized stepwise approach to the evaluation of GERD, identification of GERD phenotypes can be established, which allows for targeted management through a variety of therapeutic tools ranging from medications and lifestyle modifications to surgical interventions.

Role of Acid Suppression in GERD Therapy

Though PPI response is often considered part of the stepwise approach to GERD evaluation, it is a crucial aspect of GERD therapy. In patients with erosive esophagitis, acid suppression is appropriate and reduces the acidity of the refluxate that causes esophageal mucosal injury and GERD symptoms. PPI therapy is very effective in low-grade erosive esophagitis with more than 90% of patients responding to acid suppression. Moreover, a significant portion of low-grade esophagitis patients will have spontaneous resolution of GERD symptoms without any therapy. In high-grade erosive esophagitis, initiation of PPI therapy can be effective; however, given the increased esophageal acid exposure time, many patients will require dose titration. Some high-grade patients may still only be partial responders despite maximum dosage and high potency PPI therapy. In those patients, ambulatory reflux monitoring on PPI or HRM may be helpful to determine if they are PPI refractory and may benefit from alternative therapies.

Similar to erosive esophagitis, PPI is crucial in BE patients. Despite the fact that the BE patient phenotype includes low esophageal acid sensitivity and a significant proportion of asymptomatic patients, PPI is necessary for acid suppression to minimize risk of BE progression to dysplasia and EAC. Additionally, PPIs have been shown to

Table 5.3 GERD phenotype treatment strategies

GERD phenotype	Goal of therapy	Proton pump inhibitor (PPI) responsiveness	Targeted therapy
Erosive esophagitis	Acid suppression to reduce acid exposure time. Improve esophageal clearance	Very responsive	PPI, lifestyle modifications, sometimes antireflux procedures
Barrett's esophagus (BE)	Promote healing and BE regression with acid suppression to reduce acid exposure time. Improve esophageal clearance	Very responsive	PPI or antireflux procedure
True nonerosive reflux	Acid suppression to reduce acid exposure time	Very responsive	PPI, lifestyle modifications, antireflux procedure
Functional heartburn	Modulate sensitivity to esophageal stimuli	Poorly responsive	Lifestyle modifications, neuromodulatory medications, cognitive-behavioral therapy
Chest pain-dominant syndrome	Acid suppression to reduce acid exposure time	Variably responsive (improved response if positive pH testing)	PPI, lifestyle modifications
Reflux hypersensitivity	Modulate sensitivity to esophageal stimuli	Poorly responsive	Lifestyle modifications, neuromodulatory medications, cognitive-behavioral therapy
Regurgitation-predominant syndrome	Decrease volume of refluxate by restoring antireflux barrier	Poorly responsive	Antireflux procedure
Extra-esophageal syndromes	Reduction in hypopharyngeal acid exposure	Poorly responsive	Lifestyle modifications, neuromodulatory medications, cognitive-behavioral therapy

increase the probability of BE regression. PPI is also appropriate for patients with proven GERD, but no evidence of erosive esophagitis. Confirmation with both ambulatory pH monitoring and endoscopy is important because patients with proven GERD without esophagitis have similar PPI response rates to erosive esophagitis patients. In contrast, patients with functional heartburn and reflux sensitivity patients are unlikely to respond to PPI therapy. Additionally, acid suppression is unlikely to be effective in patients with regurgitation-predominant reflux disease as symptoms are driven more by volume of refluxate rather than refluxate acidity. Finally, patients with extra-esophageal reflux symptoms (LPR and chronic cough) are unlikely to respond to PPI in the absence of esophageal symptoms.

Role of Endoscopic and Surgical Therapy

In certain phenotypes, antireflux surgery with fundoplication or magnetic sphincter augmentation (MSA), as well as endoscopic therapy with transoral incisionless fundoplication (TIF), can be effective management options. In patients with high-grade erosive esophagitis or BE, antireflux surgery is an effective therapy for reducing esophageal acid exposure. Patients with large hiatal hernias or incompetent EGJs may respond better to restoration of antireflux barrier with surgery than acid suppression. A specific subset of patients with the regurgitation-predominant reflux phenotype in the absence of large hiatal hernia (less than 2 cm) can be treated effectively with TIF. In patients with both morbid obesity and GERD, gastric bypass is an effective therapy to treat both obesity and reflux disease.

As mentioned previously, prior to consideration of TIF, surgical fundoplication, or MSA, HRM is crucial as patients with hypomotile esophagus may develop dysphagia post-intervention. There are specific phenotypes who are unlikely to respond well to antireflux surgery or procedures. Specifically, surgery should be avoided in patients with chest pain reflux syndrome without ambulatory correlation between reflux and pain, patients with functional heartburn, and patients with isolated extra-esophageal symptoms. Interestingly, in patients with reflux hypersensitivity, there are conflicting data regarding utility of antireflux surgery; however, pure acid sensitivity has been shown to be a negative predictor for improvement following antireflux surgery, and those patients are unlikely to benefit from surgery.

Lifestyle Modifications

Weight loss and avoidance of food triggers can be effective strategies in certain GERD phenotypes. In patients with BE and erosive esophagitis, weight loss can be effective in improving acid reflux by improving the natural antireflux anatomy and ultimately facilitate mucosal healing. Randomized controlled trials have shown significant decreases in AET on ambulatory reflux monitoring with effective weight loss. Postprandial upright positioning and avoidance of eating within short intervals of sleep can be effective short-term strategies in regurgitation-predominant

GERD phenotype as well as high-grade erosive esophagitis. Studies have shown that positional changes as well as a longer gap between mealtime and bedtime are associated with reduced AET on ambulatory reflux monitoring. In patients who use tobacco with a normal BMI, tobacco cessation has been associated with reduced reflux symptoms.

Alternative Therapies

In specific GERD phenotypes, alternative medical therapies can also be of benefit for symptom control. In patients with functional heartburn and reflux hypersensitivity, pain modulation can improve symptoms with use of tricyclic antidepressants (TCAs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Cognitive-behavioral therapy has also been shown to be an effective therapy for these patients, and management can be guided by following changes in patients' EHAS scores. In patients with proven GERD without esophagitis or chest pain-predominant reflux who are partial PPI responders and have significant TLESR burden on manometry, use of gamma aminobutyric acid (GABA) agonists, such as baclofen, can be used. GABA agonists have been shown to reduce TLESR frequency by 25% and improve symptoms in partial PPI responders with GERD.

Conclusions

Despite the fact that GERD is incredibly common in the western hemisphere, management has traditionally relied on empiric acid suppression or antireflux surgery with mixed results. The concept of personalized GERD evaluation and management has emerged with recognition of multiple GERD phenotypes with a developing appreciation of the underlying mechanisms that lead to each phenotype. By using a stepwise approach to evaluate clinical presentation with a detailed history and targeted use of upper endoscopy, HRM, and ambulatory reflux testing, we can identify GERD phenotypes. Using these data and knowledge of specific phenotypes, we can predict response to various treatments and personalize management to increase the probability of successful GERD therapy.

Questions

1. All of the following GERD phenotypes can be considered for antireflux surgery except:
   A. Erosive esophagitis
   B. Chronic cough
   C. Regurgitation-predominant reflux
   D. Barrett's esophagus

Answer: B. Patients with isolated extra-esophageal symptoms have not been shown to benefit from antireflux surgery.

2. A patient reports heartburn with eating spicy foods 3 days per week and is started on once-daily PPI. He reports minimal improvement in his symptoms after 4 weeks and undergoes upper endoscopy that was normal. Which of the following would you do next for this patient?
   A. Ambulatory reflux testing off PPI
   B. Ambulatory reflux testing on PPI
   C. High-resolution manometry
   D. Start amitriptyline 10 mg nightly

Answer: A. Given the lack of erosive esophagitis and minimal response to PPI, confirmation that heartburn is reflux-mediated would be the next step. The best answer is to pursue ambulatory reflux testing off PPI therapy to assess baseline reflux physiology.

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Laryngopharyngeal Reflux and Pulmonary Manifestations

6

Shahin Ayazi and Blair Jobe

Introduction

Gastroesophageal reflux disease (GERD) is the most common foregut disease in the world and accounts for approximately 75% of all esophageal pathologies. This disease was recognized as a clinical entity in the mid-1930s when Jackson in 1929 and later Winkelstein in 1935 used the newly developed esophagoscope to describe for the first time clinical peptic esophagitis. Gastroesophageal reflux disease can present with either typical symptoms such as heartburn, regurgitation, and dysphagia or atypical symptoms such as cough, hoarseness, globus sensation, and throat clearing. Additionally, gastroesophageal reflux may contribute to the development of pulmonary diseases such as adult-onset asthma and idiopathic pulmonary fibrosis. The link between upper gastrointestinal pathology and airway symptoms was first suggested by Bray in 1934. The magnitude of this association is now thought to account for 10% of patients presenting to an ear, nose, and throat (ENT) specialist, and up to 75% of patients with refractory ear, nose, and throat symptoms.

The laryngopharyngeal and pulmonary symptoms that appear to be due to reflux of gastric content to the upper aerodigestive tract have been commonly referred to as laryngopharyngeal reflux (LPR) or extraesophageal reflux disease. This clinical entity represents a significant economic healthcare burden in the United States, with a mean direct cost for diagnosis and treatment of a patient with typical GERD $971 and of atypical GERD $5438 per patient in the first year. Delay in diagnosis, absence of a testing modality with sufficient sensitivity, and limited response to medical and surgical treatments contribute to the higher healthcare burden of LPR and pulmonary manifestations of reflux disease. The focus of this chapter is on the pathogenesis of the LPR symptoms, the difficulty in determining the cause of the symptoms, and an appreciation for how effective both medical and surgical therapies are in providing symptom relief.

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Pathophysiology

A majority of investigators believe that the retrograde flow of gastric contents or microaspiration of acid, bile acids, pepsin, and other gastrointestinal proteins results in exposure of the upper aerodigestive tract to the acidic gastric content. This exposure then causes direct injury which manifests as variety of ear, nose, throat, and pulmonary symptoms commonly referred to as laryngopharyngeal reflux (LPR). Other investigators believe in reflex theory. In this less popular hypothesis, acidification of the distal esophagus induces a vagally mediated reflex that present with laryngopharyngeal symptoms.

Laryngopharyngeal and Pulmonary Symptoms

A variety of extraesophageal reflux symptoms can occur when refluxed gastric juice contacts the mucosa of the upper aerodigestive tract (Table 6.1). The challenge is that reflux is only one of many etiologies that cause these symptoms. In patients with primary atypical symptoms of GERD, less than 50% complain of significant heartburn, and in these patients, it is difficult to determine the etiology of their laryngopharyngeal symptoms. In a study on patients with LPR symptoms, acid suppression therapy was beneficial in 83% of the patients even though heartburn was present in only 16%. This suggests that increased esophageal and pharyngeal acid exposure was responsible for LPR symptoms even in patients without heartburn. Consequently, diagnosing GERD as the cause for LPR symptoms requires a high index of suspicion. A careful history with detailed questions about the character and timing of the respiratory and esophageal symptoms is

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Table 6.1 Laryngopharyngeal and respiratory symptoms and associated conditions of extraesophageal reflux

Laryngopharyngeal	Respiratory	Other symptoms and associated conditions
Hoarseness	Chronic cough	Postnasal drip
Sore throat	Wheezing	Halitosis
Globus sensation	Nocturnal aspiration	Water brash
Stridor	Chronic obstructive pulmonary disease	Dental caries
Choking	Apnea	Sinusitis
Throat clearing	Recurrent pneumonia	Laryngeal carcinoma
Pharyngitis		Vocal cord polyps
Laryngitis		
Spastic cough		

crucial to establish a relationship between the two conditions. The key to establish this relationship is to determine if the laryngopharyngeal or pulmonary symptoms worsen when the patient is in the supine position, if respiratory medications are more commonly required after meals, and if a time relationship exists between the symptoms of heartburn or regurgitation and the LPR symptom.

The Challenge of Establishing the Diagnosis

The diagnosis of laryngopharyngeal reflux has proven to be more challenging than typical GERD. A 2-month trial of empiric PPI therapy has been proposed as an initial step in the diagnosis and treatment of patients with LPR. If symptoms are relieved with a trial of acid suppression therapy, GERD is considered the cause of the LPR symptoms. However, meta-analysis of several studies has demonstrated no therapeutic benefit of PPIs in this setting with only about 50% of patients with LPR respond to empiric trials of acid-suppressive therapy. This leaves the other 50% in a conundrum.

Laryngoscopic evidence of laryngeal erythema, edema, granulomas, and interarytenoid hypertrophy in patients with LPR symptoms has been used to indicate that GERD is the cause of their LPR symptoms. These same laryngoscopic findings have been reported in a majority of asymptomatic subjects and imply the low specificity of laryngoscopy in evaluating LPR symptoms.

Upper gastrointestinal endoscopy is the most sensitive test to identify reflux-induced esophageal injuries such as esophagitis, stricture, Barrett's metaplasia, and adenocarcinoma. Endoscopy is usually not helpful in identifying a relationship between GERD and laryngopharyngeal symptoms because these symptoms commonly occur in the absence of esophagitis. A barium esophagram can be used to identify patients with poor esophageal clearance, a large paraesophageal hiatal hernia, or an intrathoracic stomach. These findings are very nonspecific to establish the diagnosis of LPR but increase the probability that the patient's extraesophageal reflux symptoms are from aspiration of gastric acid or residual esophageal content. Similarly, gastric emptying studies can identify patients with gastric stasis which can also contribute to gastroesophageal reflux and laryngopharyngeal symptoms.

In patients with normal chest X-ray, bronchoscopy offers a low diagnostic yield (4%) in identifying a cause for laryngopharyngeal or respiratory symptoms. Taking a detailed history including tobacco use or taking various drugs known to cause cough such as angiotensin-converting enzyme inhibitors or β-blockers provides valuable information about the etiology of extraesophageal reflux symptoms.

Ambulatory pH Monitoring

Distal esophageal pH monitoring has been used to establish GERD as the cause of the extraesophageal symptoms, but its diagnostic accuracy varies from a low of 18 to a high of 80 percent. Monitoring of esophageal acid exposure in both the distal and proximal esophagus appears to improve the accuracy of the test, but clinical experience with this approach has been mixed with only a minority of patients with increased proximal esophageal acid exposure responding well to treatment. Pharyngeal pH monitoring (Restech, Respiratory Technology Corporation, San Diego, CA) and hypopharyngeal multichannel intraluminal impedance monitoring (MII-pH) (Sandhill Scientific Inc., Highlands Ranch, CO) are the other available tests. Both techniques are thought to be an improvement and have provided additional benefit in the establishing GERD as the cause of extraesophageal reflux symptoms. The oropharyngeal pH catheter (Restech) is a device used to measure oropharyngeal acid reflux (Fig. 6.1). The device has an ion flow sensor that is designed to accurately measure the pH in both liquid and aerosolized droplets in the oropharynx. This approach has introduced a number of additional problems. Technical artifacts are common due to the sensor drying, causing disruption of the electrical circuit between the references and sensing electrodes. Food and mucous accumulation on the sensor can interfere with its ability to detect acid in the pharynx.

MII-pH is a specialized impedance catheter that directly measures reflux events in the hypopharynx and proximal esophagus. The potential benefit of MII-pH in detecting LPR events has been reported in the management of certain pulmonary and laryngeal conditions such as end-stage lung disease, adult-onset asthma, and chronic cough. However, there is a paucity of data supporting that the addition of MII-pH has a role in improving patient selection or predicting the outcomes of antireflux surgery.

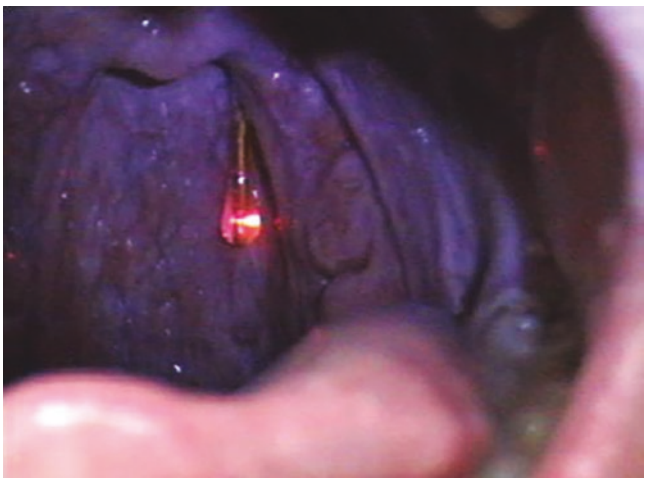

Fig. 6.1 Restech pharyngeal pH probe positioned 5–10 mm below the level of the uvula. The flashing LED light is used to guide appropriate position of the probe

Novel Biomarkers

The role of several biomarkers, such as pepsin, interleukin-6, carbonic anhydrase, E-cadherin, and mucins, and depletion of squamous epithelium stress protein (Sep70) as a diagnostic marker for LPR have been investigated. However, none of them have been routinely used as a definitive diagnostic marker for LPR. Pepsin and Sep70 have gain more popularity than other markers. The novel pepsin test (Peptest, Biomed) is a simple, noninvasive test that detects salivary pepsin at a concentration ≥16 ng/mL, but its role in diagnosis has yet to be clearly established. The Sep 70/pepsin ratio has also been used as a marker, but its role is limited by a low specificity of 36% and the lack of correlation with symptom response after therapy.

Medical Therapy of Patients with LPR

Acid suppression therapy with proton pump inhibitors (PPIs) is shown to be effective in healing esophagitis and relieving typical symptoms of reflux. This is demonstrated by the ability of PPI(s) to decrease gastric acid secretion and reduce the volume of gastric juice. In contrast, less than 50% of the patients with extraesophageal reflux symptoms respond to PPI(s). The difference in symptom relief suggests that extraesophageal reflux symptoms require more aggressive and longer PPI treatment to be effective. This has prompted some clinical investigators to suggest that a double dose of PPI(s) for 8–12 weeks is necessary to achieve adequate relief of LPR symptoms. Randomized clinical trials have not supported this aggressive approach as being effective. Table 6.2 shows the result of three randomized controlled trials (RCTs) that have compared use of PPI(s) to placebo for the therapy of LPR symptoms. None of the studies showed a benefit of PPI treatment over placebo. A recent systematic review on this topic included two systematic reviews and seven meta-analyses. Six of these studies showed that PPI is not superior to placebo; the remaining three reported that PPI significantly improved LPR symptoms but did not result in significant change in laryngoscopic findings suggestive for LPR. The high placebo response rate and the ineffectiveness of PPI therapy have led some experts to conclude that patients with extraesophageal reflux symptoms may have an irritable larynx and that the role of refluxed acid is of lesser significance. They have suggested the term "irritable larynx syndrome" to describe this condition.

Explanations for Limited Effect of Medical Treatment

Several explanations have been proposed for why acid suppression therapy is less effective in the treatment of LPR symptoms:

- Although medical therapy effectively decreases gastric acid secretion and reduces the volume of gastric juice, other components in the gastric juice such as bile are minimally affected by acid suppression therapy. It has been shown that reflux of the nonacid gastric juice can still lead to microaspiration and cause laryngeal and respiratory symptoms.
- Smooth muscle relaxants used for some patients with airway symptoms, such as those suffering from asthma, may lower the distal esophageal sphincter pressure and cause delayed gastric emptying. Both effects lead to a greater tendency for gastroesophageal reflux and aspiration.
- An episode of coughing or an asthmatic attack can significantly increase intra-abdominal pressure, and if the LES is incompetent lead to gastroesophageal reflux and aspiration.
- Cough and bronchitis have been associated with hiatal herniation, and Sontag has shown that 58% of patients with asthma have a hiatal hernia. A hiatal hernia places the lower esophageal sphincter at a mechanical disadvantage and encourages gastroesophageal reflux. While medical therapy can improve the symptoms of heartburn, it is not able to stop reflux due to an anatomic defect such as a hiatal hernia.
- During sleep, there is minimal esophageal motor activity, decreased salivary flow, and loss of the gravitational component of esophageal clearance. For these reasons, if an episode of acid reflux occurs during sleep, it is likely to be of prolonged duration. It is possible that extraesophageal reflux symptoms may depend partially on nocturnal reflux, which is poorly controlled by medications.

Table 6.2 Randomized clinical trials comparing PPI(s) to placebo in treatment of LPR

Author/study setting	Number (PPI/placebo)	≥50% reduction in LPR symptoms		PPI and dosage	Therapy duration (week)	Risk ratio[a]
		PPI (%)	Placebo (%)			
Vaezi et al./multicenter	146 (95/51)	42%	46%	Esomeprazole (40 mg BID)	16	0.93
Wo et al./single center	39 (20/19)	40%	42%	Pantoprazole (40 mg OD)	12	0.95
Steward et al./single center	42 (21/21)	38%	43%	Rabeprazole (20 mg BID)	8	0.89
Pooled	227 (136/91)	41%	44%	–	–	–

[a]Risk ratio more than 1 favors PPIs

Surgical Therapy for LPR

In 1956 Rudolf Nissen introduced a 360° fundoplication placed around the area of the lower esophageal sphincter as an effective antireflux procedure; this procedure is still the most commonly performed antireflux surgery today. In contrast to medical therapy, surgery can correct the antireflux barrier by restoring the lower esophageal sphincter and repairing a hiatal hernia preventing both acid and nonacid refluxes. The best surgical results are obtained in patients whose symptoms respond well to medical therapy. A failure to respond to medical therapy, however, should not eliminate consideration of surgical therapy. Multiple studies have shown that antireflux surgery is greater than 90% successful in controlling typical reflux symptoms over 10 years. In contrast, the majority of studies report that the outcomes of antireflux surgery when performed for LPR symptoms are less favorable compared to those achieved in patients with typical GERD symptoms. This highlights the multifactorial nature of LPR symptoms (i.e., non-GERD etiologies) and absence of a testing modality with sufficient sensitivity to directly measure LPR events, to establish GERD as the underlying cause. The majority of publications on the outcome of antireflux surgery for laryngopharyngeal and pulmonary symptoms are retrospective and uncontrolled, the populations studied are small and include a variety of different antireflux procedures, the entry criteria for the study and selection criteria for surgery are inconsistent, the outcome evaluations are mainly symptomatic, and in most studies the effectiveness of the antireflux procedure was not tested with pH monitoring.

Results of Surgery for LPR and Pulmonary Symptoms

Table 6.3 shows the improvement following surgery in patients who had combinations of different LPR symptoms. The improvement rate varied from 76 to 95%. These studies did not report the results for each symptom, and no objective assessment was made of the effect of surgery on esophageal acid exposure.

The most common laryngopharyngeal and pulmonary symptoms evaluated are wheezing as a manifestation of asthma, chronic cough, hoarseness, and chest pain. These symptoms are commonly associated with increased esophageal acid exposure. For example, 80% of unselected patients with asthma have increased esophageal acid exposure, 55% with chronic cough, 60% with laryngitis, and 50% with noncardiac chest pain. Many of these patients are referred for surgical therapy.

Several studies have shown that 49–85% of patients with reflux-related asthma benefit by an antireflux procedure. The improvement is commonly evident immediately after surgery, and those who do not show a benefit are unlikely to improve over time. In a randomized controlled trial of medical and surgical therapy versus placebo therapy for asthma, Larrain and colleagues found a statistically significant improvement in the pulmonary symptoms score at 6 months with either therapy compared to placebo alone, with asthma symptoms improving in 80% of therapy group vs 33% in placebo group. Further, there was a mild improvement in the pulmonary function test of those who received medical and surgical therapy. At a 5-year follow-up, the same authors showed that only the surgical patients maintained their clinical and functional improvement. Patients who received medical or placebo therapy regressed to baseline symptom levels.

A cough that persists for more than 3–8 weeks is a common complaint seen by ENT and pulmonary physicians. The likelihood that reflux is the initiating factor is estimated to be from 11 to 43%. Like other extraesophageal reflux symptoms, the outcome of surgery for chronic cough is not as good as that reported for typical reflux symptoms. The success rate varies between 60 and 100%. The nonspecific nature of "chronic cough" requires a detailed preoperative

Table 6.3 The outcome of surgery in patients with LPR symptoms

Institution	Number of patients	Type of surgery	Mean follow-up (months)	Improved (%)	Cured (%)
Chen et al.	63	NF ± Collis	36	–	76
Gadenstatter et al.	80	LNF TTF	6	86	66
Farrel et al.	151	LARP	28	95	44
Brouwer et al.	29	LNF	14	80	50

NF Nissen fundoplication, *LNF* Laparoscopic Nissen fundoplication, *LTF* Laparoscopic Toupet fundoplication, *LNF* Laparoscopic Nissen fundoplication, *LARP* Laparoscopic antireflux procedure(unspecified)

investigation to rule out other etiologies. Allen and Anvari reported that 68% of GERD patients complained of cough during either long- or short-term omeprazole therapy.

Factor Influencing the Outcome of Surgery in Patients with LPR

There is a paucity of publications on predicting surgical outcome for LPR symptoms. In general, a favorable outcome for the surgical therapy is likely to occur if the laryngopharyngeal or pulmonary symptom is nocturnal in occurrence, if there is increased esophageal acid exposure on 24-h pH monitoring, if there is an association between the LPR symptoms and a reflux episode, and if there is a good response of the LPR symptoms to medical therapy. Rattner showed that a good response to acid suppression therapy and abnormal esophageal acid exposure on dual-probe pH monitoring were two preoperative factors that predicted relief of LPR symptoms with antireflux surgery. Pellegrini further showed that abnormal pharyngeal acid exposure was a factor that predicted a good response to medical or surgical therapy. Patti and colleagues reported that chronic cough resolved after antireflux surgery in 83% of patients in whom there was a correlation between a coughing episode and proximal esophageal acid exposure on pH monitoring.

In contrast, impaired esophageal body motility has been reported to be associated with a poor outcome after antireflux surgery for LPR symptoms. Esophageal motility is known to deteriorate as a consequence of mucosal injury, and the altered motility persists after surgical therapy. Studies have shown a direct correlation between prevalence of a motility abnormality of the esophageal body and the number of respiratory symptoms (Fig. 6.2). It is likely that the altered motility allows the escape of esophageal contents in an oral direction, predisposing the patient to aspiration. These observations encourage earlier surgical intervention in the likelihood that less altered esophageal body function would reduce the prevalence of respiratory symptoms after surgical intervention. Despite this encouragement, surgery is commonly the last therapy suggested to a patient with repeated aspiration or worsening respiratory symptoms. The delay in referring patients with extraesophageal reflux symptoms for surgical intervention is a main factor in suboptimal outcomes.

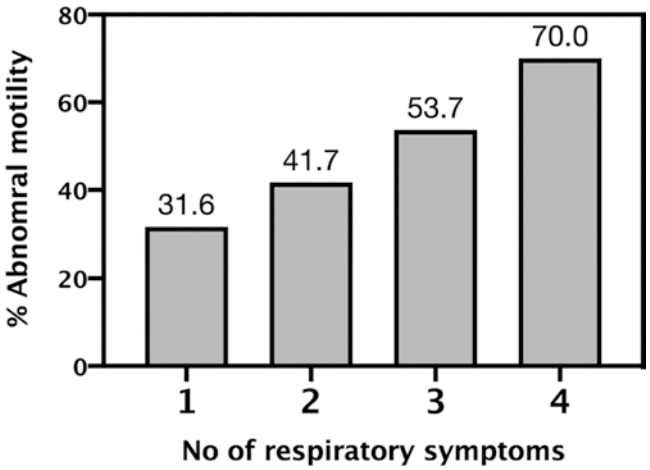

Fig. 6.2 Prevalence (%) of abnormal esophageal contractions (failed or weak) in the manometry of 54 patients with LPR and abnormal esophageal acid exposure, stratified by the number of reported laryngopharyngeal or respiratory symptoms

Explanations for Suboptimal Outcome of Surgery

Antireflux surgery is extremely effective in normalizing distal esophageal acid exposure and relieving the typical reflux symptoms of heartburn and regurgitation. In contrast, its ability to relieve LPR symptoms is less satisfactory. Several factors can explain these suboptimal results:

- There is no gold standard to confirm gastroesophageal reflux as a cause of extraesophageal reflux symptoms. This leads to a tendency to overdiagnose reflux as the etiology of these symptoms. Consequently, the studied populations are diluted with patients in whom reflux of gastric contents is not the cause of their respiratory or laryngeal symptoms. Surgical therapy in such a patient population is less effective.

- Multivariable analysis has identified three factors that significantly predict a successful outcome of laparoscopic antireflux surgery for typical reflux symptoms. These are (1) an abnormal composite pH score on distal esophageal pH monitoring, (2) typical reflux symptoms, and (3) a >50% symptomatic improvement with PPI acid suppression therapy. None of these factors are common findings in patients with only extraesophageal reflux symptoms. Consequently, the selection of patients for surgery leaves room for error.

Other Surgical Options

Magnetic sphincter augmentation (MSA) using LINX device is a promising surgical treatment and has been applied with increasing frequency in the treatment of patients with GERD. The device was developed to address the need for an alternative treatment option in the management of patients with GERD through an outpatient laparoscopic procedure that does not alter gastric anatomy, augments the physiologic barrier to reflux, and can be reversed if necessary. The use of this device in patients with LPR has been encouraging with favorable outcome in 84% of patients. Those with a favorable outcome were found to have a higher preoperative reflux symptom index (RSI) score, higher distal esophageal acid exposure, and a larger hiatal hernia compared to those with an unfavorable outcome.

Conclusion

Patients with LPR symptoms are difficult group of patients to diagnose and manage. Several studies have emphasized the importance of measuring proximal esophageal or ideally pharyngeal acid exposure to confirm the presence of reflux. Once reflux is confirmed, the workup should focus on demonstrating an association between the reflux episodes and the LPR symptoms. The combination of pH and impedance monitoring has improved our ability to make this association between LPR symptoms and an acid, weakly acidic reflux episode. If an association is confirmed, antireflux surgery can be offered, preferably in the early phase of the disease. Ideally, it is also encouraging to have the patient's symptoms respond to medical therapy. However, this is not an absolute requirement to proceed with surgery. Although excellent surgical outcomes have been reported in patients with typical reflux symptoms, this is not the case for LPR symptoms. Consequently, careful patient selection, early surgical intervention, and realistic expectations are important in optimizing the outcome of surgical therapy.

Questions

1. Which of the following statements is incorrect regarding diagnosis of laryngopharyngeal reflux (LPR)?
   A. The diagnosis of laryngopharyngeal reflux is more challenging than typical GERD.
   B. A 2-month trial of empiric PPI therapy has been utilized as an initial step in the diagnosis and treatment of patients with LPR.
   C. Laryngoscopic evidence of laryngeal erythema, edema, granulomas, and interarytenoid hypertrophy are specific signs to establish LPR diagnosis.
   D. Studies report wide range for diagnostic accuracy of esophageal pH monitoring in patients with LPR.

   Answer C. The diagnosis of laryngopharyngeal reflux has proven to be more challenging than typical GERD. Existing diagnostic tests lack sufficient sensitivity and specificity to confirm the presence of laryngopharyngeal reflux (LPR). A 2-month trial of empiric PPI therapy has been utilized as an initial step in the diagnosis and treatment of patients with LPR. The laryngoscopic findings suggestive for LPR have been reported in a majority of asymptomatic subjects and imply the low specificity of laryngoscopy in evaluating LPR symptoms. Distal esophageal pH monitoring has been used to establish GERD as the cause of the extraesophageal symptoms, but its diagnostic accuracy varies from a low of 18 to a high of 80.5%.
2. Which of the following statements is incorrect regarding surgical management of laryngopharyngeal reflux (LPR)?
   A. The outcomes of antireflux surgery for LPR symptoms are less favorable than typical GERD symptoms.
   B. A failure to respond to medical therapy, should not eliminate consideration of surgical therapy.
   C. Impaired esophageal body motility is associated with a poor outcome after antireflux surgery for LPR symptoms.
   D. Antireflux surgery is greater than 90% successful in controlling LPR symptoms over 10 years.

   Answer D. The majority of studies report that the outcomes of antireflux surgery when performed for LPR symptoms are less favorable compared to those achieved in patients with typical GERD symptoms. Ideally, it is encouraging to have the patient's symptoms respond to medical therapy. However, this is not an absolute requirement to proceed with surgery. Impaired esophageal body motility has been reported to be associated with a poor outcome after antireflux surgery for LPR symptoms. Multiple studies have shown that antireflux surgery is greater than 90% suc-

cessful in controlling typical reflux symptoms over 10 years. In contrast, the majority of studies report that the outcomes of antireflux surgery when performed for LPR symptoms are less favorable compared to those achieved in patients with typical GERD symptoms.

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The Spectrum of Eosinophilic Esophagitis

7

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Abbreviations

EGD	Esophagogastroduodenoscopy
EndoFLIP	Functional luminal imaging probe
EoE	Eosinophilic esophagitis
EOE-HSS	Eosinophilic esophagitis-specific histological score system
EREFS	Eosinophilic Esophagitis Endoscopic Reference Score
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
PPI	Proton pump inhibitor
QoL	Quality of life
TGF-β1	Transcription growth factor-β1
TH2 T cells	Type 2 helper T cells

Objectives

1. Review the epidemiology and pathophysiology of eosinophilic esophagitis
2. Assess how a diagnosis of eosinophilic esophagitis is made
3. Differentiate treatment options for the disease
4. Identify emerging directions for eosinophilic esophagitis

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Definition, Epidemiology, and Incidence/Prevalence

Eosinophilic esophagitis (EoE) was recognized in the early 1990s when several case series reported an esophageal disease of atopic individuals that lacked response to reflux management and had higher association with stricture formation than gastroesophageal reflux disease (GERD). It is a disorder in which the esophageal mucosa is characterized by marked eosinophilia leading to inflammatory type symptoms in children and inflammation as well as fibrosis-induced esophageal symptoms, mainly dysphagia, in adults.

It has since been termed an allergic esophagitis as it is associated with a unique esophageal transcriptome—thought to be induced by food and possibly environmental triggers.

Since discovery, interest and research in EoE have evolved. The first international consensus guidelines were published in 2007 and have since been updated multiple times. The first ICD-9 classification came in 2008. Overall, this disease has a history spanning 25 years and shows continual advancement in knowledge of pathogenesis and treatment of the disorder still today.

EoE is a growing health problem causing a significant burden for healthcare systems. The disease is now a leading cause of esophageal morbidity with estimated annual healthcare cost up to $1.4 billion in the USA. This appears to be a biologic increase in addition to enhanced diagnosis through awareness and endoscopy. EoE has become the most frequent cause of esophageal food bolus impaction (46–63%), and estimates of up to 25% of patients undergoing esophagogastroduodenoscopy (EGD) for symptoms of dysphagia will have EoE. As EoE is an allergic and esophageal disease of both children and adults, it is managed by gastroenterologists, allergists, pediatricians, and internal medicine providers. As a result, these specialties should be aware of the disease to optimize timely and accurate diagnosis. A protracted diagnostic delay following symptom onset correlates with advanced esophageal stricture formation.

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The incidence of EoE is increasing with some studies showing up to 10/100,000 in adults. Prevalence can vary widely in population studies with estimates of the US population ranging from 26 to 90/100,000 individuals depending on recognition and coding. The disease is more common in Caucasians, but can affect all races. A 2016 study assessing over 7000 US patients with EoE found 89.3% were Caucasian, 5.6% were Asian, and 6.1% were African American. Interestingly, there may be some differences in EoE based on race as racial minorities are less likely to have typical endoscopic findings or strictures. This disease also affects men 2–3 times more often than women, which may be explained by a protective effect from estrogen. EoE can occur in all ages, but the majority of patients are under 50 and it has a peak prevalence in 35–39-year-old men. EoE is considered a chronic disease that relapses with treatment cessation. There is no evidence to suggest spontaneous remission or lack of progression. Natural history studies suggest the longer the disease is left untreated, the greater the likelihood that a patient will develop esophageal strictures. Additional evidence for this comes from therapy withdrawal, leading to histologic and symptomatic recurrence. There is evidence that those with longer duration of symptoms preceding diagnosis have increased psychiatric comorbidities of anxiety and depression, and risk of food impaction increases.

Pathophysiology/Mechanism

EoE is an aberrant antigenic or immune response where allergens trigger a type 2 helper T cell delayed hypersensitivity reaction to food allergens. While type 2 helper T cells (TH2 T cells) hold a critical role in disease development, there are multiple other cytokines, mediators, and cells involved in the disease development and ultimate sequela of fibrotic remodeling. TH2 T cells are likely induced by thymic stromal lymphopoietin (TSLP) which is released by epithelial cells. This promotion of TH2 T cells leads to stimulation of certain cytokines such as IL-13, IL-4, and IL-5 which induce and upregulate genes. These genes then alter esophageal epithelial barrier function. Lack of invariant natural killer T cells and increase in mucosal mast cells occur. Overall a milieu of cells and mediators create the environment that perpetuates inflammation, with eosinophils releasing granule proteins causing cytotoxic damage, disrupting the mucosal barrier, and leading to profibrotic mediations. Mast cells produce transcription growth factor-β1 (TGF-β1) leading to collagen deposition and increase in smooth muscle mass. Ultimately remodeling of the esophagus occurs leading to narrowing, decreased compliance, and risk of food bolus impaction.

Patients with EoE express a unique esophageal transcriptome, and this with interplay of environmental factors leads to development of the disease. Altered germ line genetic loci have been identified leading to disease susceptibility including TSLP, calpain-14 (CAPN14), EMSY, LRRC32, STAT6, and ANKRD27. The strongly associated EoE gene, CCL26, has also been identified, which encodes eotaxin-3 which is induced via IL-13. Together these genes support a cellular environment that leads to squamous epithelial cell dysfunction and barrier breakdown. However, this alone does not cause the disease, as epigenetic factors are likely involved as demonstrated in family studies.

There is a strong link between atopic disorders and EoE. EoE patients have higher rates of extraesophageal atopic diseases including asthma, airway hyperresponsiveness, allergic rhinoconjunctivitis, eczema, and IgE-mediated food allergies. Sensitization to ingested allergens is necessary to develop the disease, and there may be some cross-reactivity to aeroallergens. Human data demonstrates that this disease is principally mediated by food antigens as complete withdrawal of inciting food antigens leads to complete normalization of esophageal mucosa and clinical response in most patients. It is still unclear how much antigen exposure is required to initiate eosinophilic inflammation and how long that exposure needs to be.

Environmental exposures have been implied in disease development and are suggested to drive the changing epidemiology, but the exact role is not known. In animal models, priming of the esophagus with subdermal ovalbumin injection or intratracheal instillation of aspergillus is effective in producing EoE. In humans, EoE tends to be of later onset than other atopic diseases such as atopic dermatitis and rhinitis. Some data supports the existence of an allergic march in which patients evolve through various common atopic diseases to eventually develop EoE. Early life exposures including antibiotic use, and cesarian section, have been implicated, while geographic factors such as arid climate, cold climate, and rural setting have been linked to increased risk of disease development. In addition, childhood exposure to microbes, presence of *Helicobacter pylori* infection, and interplay with commensal bacteria may limit food sensitization and provide a protective role in disease development. Overall, however, no proven causality of any one environment exposure has been identified. Nevertheless, these associations suggest a role for abnormal microbiome development in the esophagus and/or gut as an important predisposing factor to

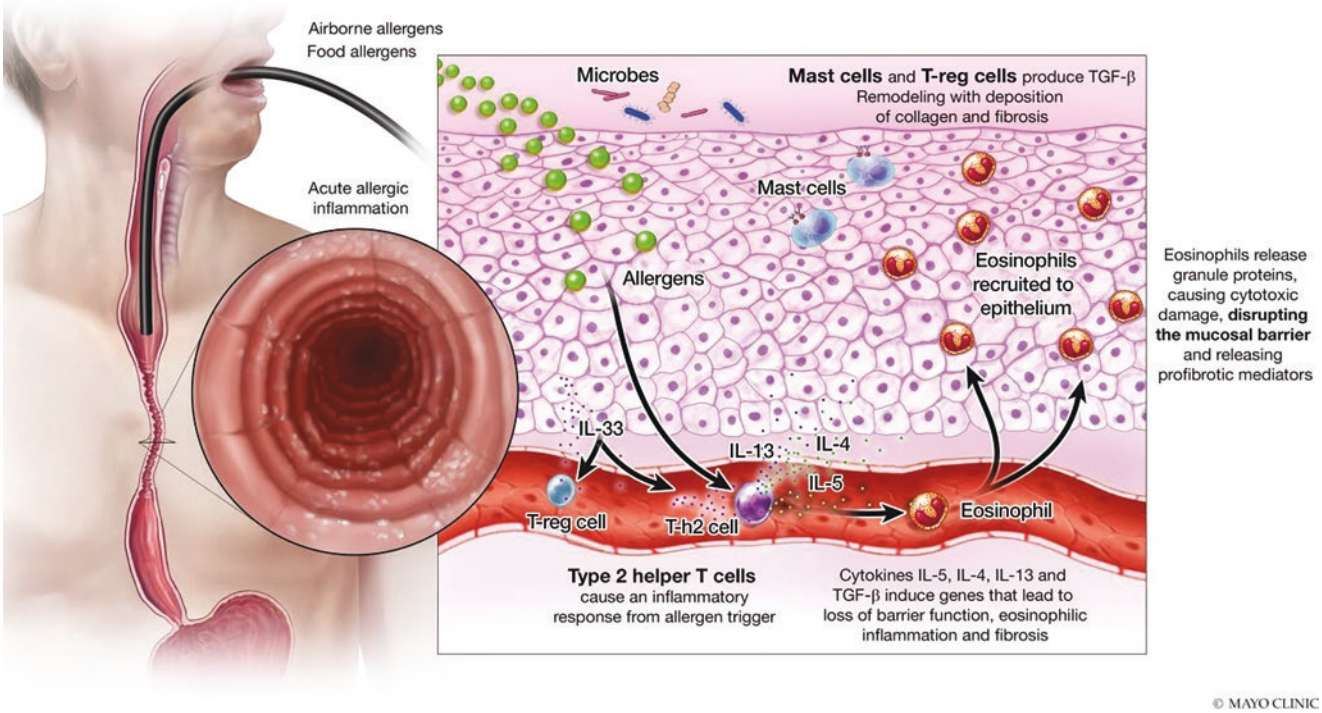

Image 7.1 Pathogenesis of EoE

EoE. This is consistent with other atopic diseases such as asthma and atopic dermatitis which have been associated with abnormal bacterial colonies and altered diversity in the intestine (Image 7.1).

Diagnosis

EoE is a clinicopathologic disorder characterized by symptoms of esophageal dysfunction and eosinophil predominant inflammation with exclusion of secondary causes that could contribute to the esophageal eosinophilia. There is no single test at present that definitively diagnoses EoE. Other diseases that can lead to esophageal eosinophilia need to be considered before a diagnosis of EoE is made. These can include achalasia, connective tissue diseases, graft-versus-host disease, infection, pill esophagitis, Crohn's disease, drug hypersensitivity, and, most frequently, gastroesophageal reflux disease. Furthermore, with both GERD and EoE now being common, these may coexist in some patients.

- A critical aspect of diagnosis in EoE is symptoms. These can sometimes be blatant, and other times subtle given that the disease can be insidious in onset and patients frequently develop compensatory eating behaviors to minimize symptoms. In children, symptoms most commonly include abdominal or epigastric pain, nausea, difficulty feeding, food avoidance, vomiting, and failure to thrive. These symptoms reflect the inflammatory changes of EoE. Adults often present with dysphagia, which is the predominant symptom and reflects the fibrotic nature of the disease. This can transpire with or without food bolus impaction. Heartburn and chest pain are also frequent symptoms of esophageal dysfunction in adults and children. As the type, severity, and compensation for symptoms can be varied in EoE, validated questionnaires such as the dietary screener questionnaire (DSQ) and eosinophilic esophagitis activity index (EEsAI) have been developed to better define and quantitate symptoms. These questionnaires are routinely used in clinical trials but are now being used or adopted for use in clinical practice. Some specific questions eosinophilic esophagitis (EoE) diagnosis that can easily be incorporated into office visits and can help determine if a patient is symptomatic include:
  - Do you excessively chew your food?
  - Do you have to repetitively swallow to get food to pass?
  - Are you the last person at the table to finish during a meal?
  - Do you avoid foods with a certain food texture?
  - Do you modify your foods? Examples would include cutting to extra small pieces or pureeing.

  - Do you lubricate your foods with sauces or condiments?
  - Do you need liquids present to complete a meal?
  - Do you avoid pills?
- Do you completely avoid social situations where eating will take place? Do you go to social events but avoid eating during the social setting?

Upper endoscopy with esophageal biopsies is required to confirm the diagnosis of EoE. Gross endoscopic inspection of an esophagus with EoE can display numerous traits suggestive of the diagnosis. Endoscopy findings include white plaques or exudates on the surface of the esophagus; decreased vascularity or pallor to the tissue; fragile mucosa that tears with endoscope passage termed "crepe-paper" mucosa; rings, strictures, or narrowing of the esophageal lumen; linear tracts or furrows; and firmness sensed during biopsy, which has been called "tug sign." To create a universal language, allow for consistency in description, and standardize reporting of what an endoscopist sees during the procedure, the EoE Endoscopic Reference Score (EREFS) was devised. This scoring system has been validated, and an elevated score is highly predictive of active disease, while it decreases with histologic remission. EREFS is an acronym for Edema, Rings, Exudates, Furrows, and Stricture(s) (Table 7.1, Image 7.2a,b).

Unlike the rest of the GI tract, the esophageal mucosa is normally devoid of eosinophils. Histopathologic studies have shown that equal or greater to 15 eosinophils per high-powered field approaches 100% sensitivity and 96% specificity for the disease. This number is still used in clinical guidelines for diagnosis to date, and peak eosinophil count remains the most widely used histologic assessment tool used to assess the disorder. An eosinophil count below 15 is also used to define remission. Eosinophilic inflammation is patchy and variable in location in EoE. Usually, 2–4 biopsies obtained from at least 2 different locations in the esophagus are recommended for diagnosis and assessment of activity. Five biopsies have been shown to have 100% sensitivity. The distal esophagus is considered around 3–5 cm from the gastroesophageal junction, and mid proximal esophagus is considered 10–15 cm from the gastroesophageal junction. The role of routinely obtaining gastric and/or duodenal biopsies in adult EoE patients to rule out coexisting eosinophilic gastroenteritis is controversial. Biopsies should be obtained if patients have other gastrointestinal-related symptoms or other endoscopic abnormalities seen during upper endoscopy. In addition to eosinophilia, there are multiple other characteristics that are found on esophageal biopsy in patients with EoE. These can include basal cell hyperplasia, dilated intercellular spaces (spongiosis), elongation of the vascular papilla, basal zone hyperplasia, superficial eosinophils, eosinophilic microabscesses, and eosinophil degranulation. The formal eosinophilic esophagitis-specific histological score system (EOE-HSS) is utilized frequently during research studies and may be adapted for routine use in practice.

Table 7.1 EoE Endoscopic Reference Score (EREFS). Scoring system used during endoscopy to report EoE findings

Edema (loss vascular markings)	
Grade 0	Distinct vascularity
Grade 1	Decreased
Grade 2	Absent
Rings (trachealization)	
Grade 0	None
Grade 1	Mild
Grade 2	Moderate (distinct rings)
Grade 3	Severe (not pass scope)
Exudate (white plaques)	
Grade 0	None
Grade 1	Mild (≤10% surface area)
Grade 2	Severe (>10% surface area)
Furrows (vertical lines)	
Grade 0	None
Grade 1	Mild
Grade 2	Severe (depth)
Stricture	
Grade 0	Absent
Grade 1	Present

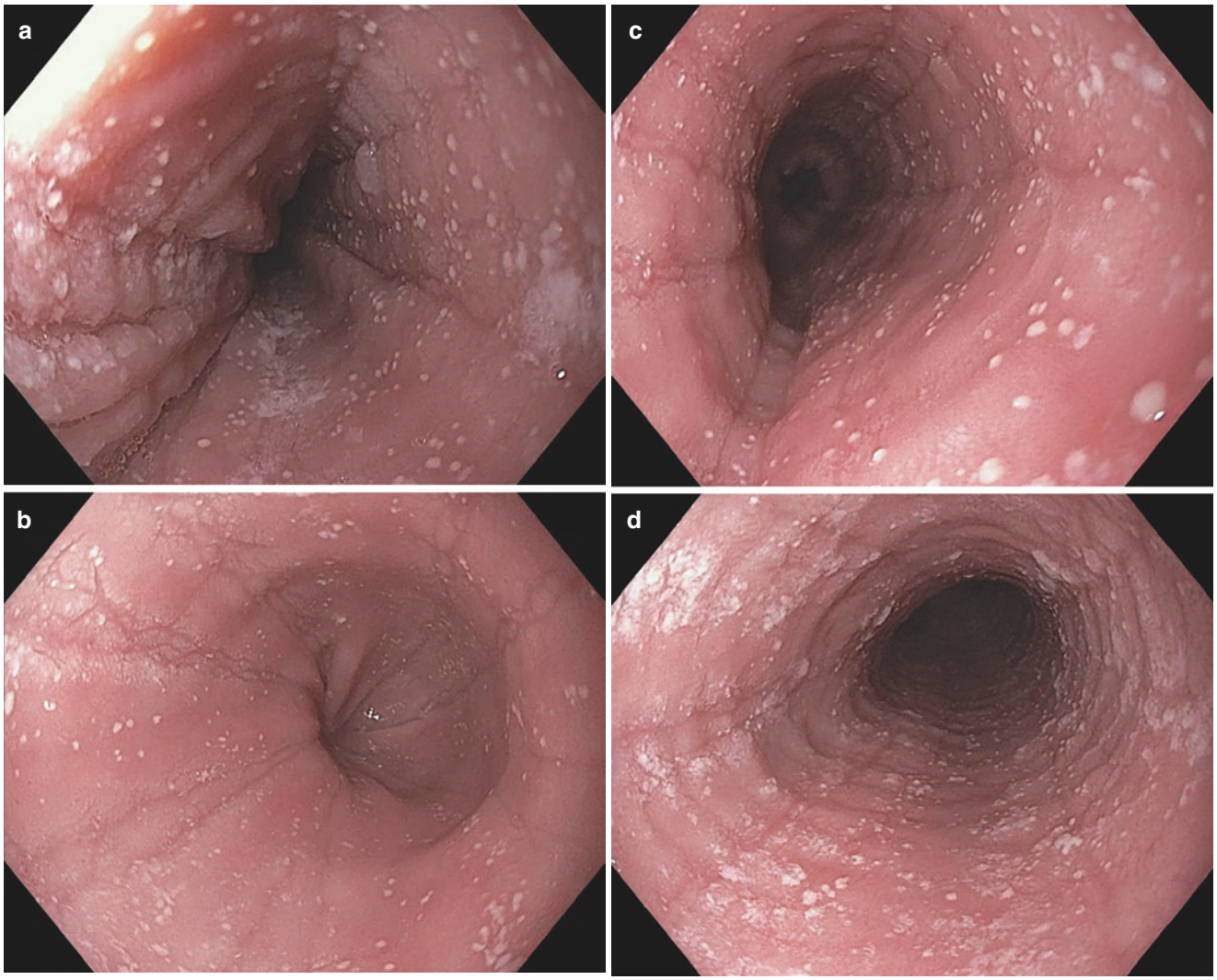

Image 7.2 (**a**–**d**) Endoscopic images of classic EoE findings including edema, fixed rings, exudates, and furrows

Treatment

EoE has not been found to be associated with esophageal malignancy, nor has it shown any evidence of affecting duration of life expectancy. Despite lack of concern for mortality risk, treatment is important not only for improvement in symptoms and quality of life but to prevent remodeling and fibrosis leading to complications and cost. Treatment endpoints in the literature are variable and can be arbitrary due to a number of factors. For example, symptoms can be nonspecific and minimized by compensatory dietary and lifestyle modifications, and histology and symptoms may be discordant. There is also poor correlation of symptoms to eosinophil count. There are also variations in the upper limit of eosinophils per high-power field, due to peak eosinophil count being affected by field size and sampling variability. Other proposed endpoints have been <6 and no eosinophils. This latter measure when occurring with low EREFS score and reduction of symptoms is defined as deep remission. Histology is not perfect in factors such as subepithelial fibrosis, accounting for other cell mediators, and activity level of the eosinophils is difficult to quantify on biopsies. The degree of esophageal fibrosis and determination of decreased esophageal compliance are not easily measured.

The Food and Drug Administration (FDA) recently approved the first pharmacologic therapy for EoE. Dupilumab is a human monoclonal antibody that binds and inhibits the IL-4 receptor alpha subunit interfering with IL-4 and IL-13 signaling and is highly effective in patients with refractory EoE. Although approved for first line therapy, its precise role in the medical treatment of EoE is evolving. Joint task force guidelines have sought to outline management options for EoE and help standardize practice. In patients with confirmed EoE, first-line therapy options in the USA include proton pump inhibitors (PPIs), swallowed topical steroids, empiric elimination diets, and now dupilumab. When one of these treatment options are

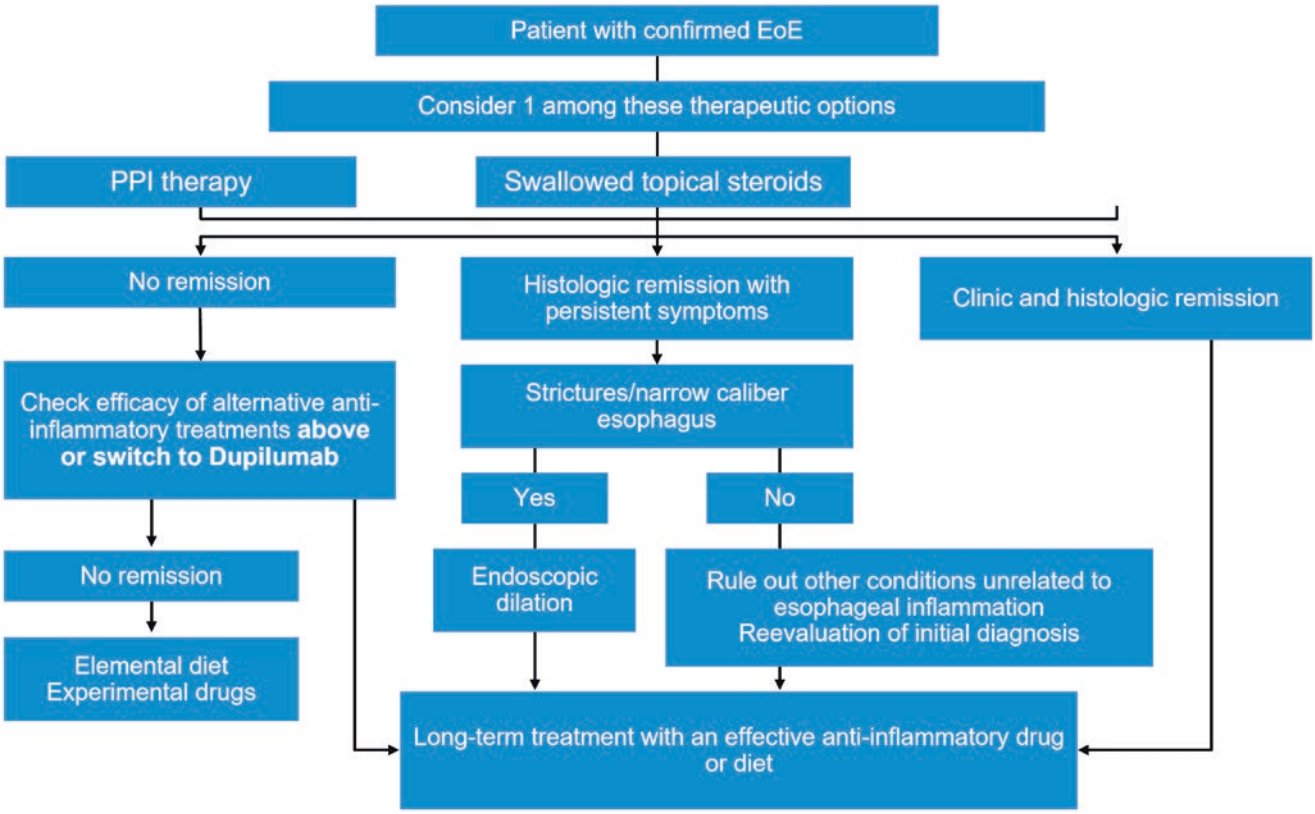

Image 7.3 Proposed treatment algorithm for EoE

undertaken, it is important to evaluate remission and response to therapy both clinically and histologically. If symptoms persist, one should determine if a stricture or narrow-caliber esophagus is present requiring endoscopic dilation. If the patient is not responsive to therapy as defined by persistent eosinophilia on biopsies, then treatment adherence and correct dosing of pharmacologic therapy needs to be assessed, other conditions unrelated to esophageal inflammation should be ruled out, and the initial diagnosis should be reevaluated. If adherence or correct dosing is not an issue and the disease is confirmed, then an alternative anti-inflammatory treatment should be sought. When first-line therapies are not effective and do not result in remission, then dual therapy versus elemental diet or experimental drugs could be considered. Once clinical and histologic remission is achieved, most experts agree that long-term treatment with the effective anti-inflammatory therapy should be continued (Image 7.3).

Initial therapy choice should take into consideration the severity of symptoms, ability to implement the therapy including dietitian counseling availability, cost of medications, therapy effectiveness, and patient and family preference. For simplification and minimization of potential side effects, monotherapy is usually preferred unless true refractory disease is present or in situations where GERD and EoE occur concomitantly and EoE is nonresponsive to PPI. There are no guidelines stating when repeat histologic assessment should be pursued which usually requires upper endoscopy though 6–8 weeks is generally used. When a new management plan is initiated or altered, assessment of response should be considered. This is particularly important to emphasize, as symptoms and histology can be conflicting.

Anti-Inflammatory Treatment and Technical Considerations

PPIs

Proton pump inhibitors (PPIs) are a first-line treatment option. Previously they were used to classify what was considered to be a separate entity termed PPI-responsive esophageal eosinophilia which is now known to be the same disease as EoE. PPIs work through anti-inflammatory effects with inhibition of key cytokines in the EoE pathway. Effectiveness may also be achieved by inhibiting gastric acid. There have been many clinical studies looking at different PPIs, dosing, timing, and methodology leading to a lot of variability in evidence, and ultimately culminating in the recommendation that PPIs are effective when used at "high daily dose." Pooled histology response to PPI treatment in adults varies but estimates are around 40–50%. It is unclear if this applies for long-term therapy. There is some data to suggest a higher histologic response to PPI therapy when administered twice daily compared to once daily administration, but this has been

nonsignificant. When reviewing anti-inflammatory treatment options, advantages of PPIs include favorable safety profile, their simplicity in administration, and that they are cost-effective. A major limitation is their lower response rate and concerns with long-term PPI use risk associations.

Swallowed Topical Steroids

Swallowed topical steroids are currently asthma medications that are repurposed for optimizing esophageal mucosal contact. These are also considered first-line therapy options and are felt to be safe and well tolerated. Without FDA-approved formulations, the two most common options include:

- -Oral aerosolized fluticasone propionate is utilized by puffing a metered dose into the mouth and swallowing. Initial induction dosing for adults is 880 mcg twice daily.
- -Oral viscous budesonide is compounded either by a pharmacy or by the patient at home. If from pharmacy, the slurry comes mixed as oral viscous liquid. If mixing at home, liquid Pulmicort capsules are mixed with sucralose, Splenda, or other sweetened powder to form a 10 cc viscous slurry. Induction dosing is 1–3 mg twice daily.

It is critical to explain to patients how to take the medication correctly. If utilizing aerosolized steroid, patients should breathe, hold, puff, and then swallow to avoid administration into the lungs, which can make the therapy less effective. It should also be used without the spacer. Similarly, budesonide slurry should be placed in and swallowed from the back of the tongue to reduce oral retention. Patients should not eat or drink for 30 minutes after steroid administration. Due to this it is commonly recommended to take medications after an am meal and prior to bedtime. Unfortunately, patients need to be aware of common denial for payment by insurance companies leading to appeals and high out-of-pocket costs for patients. The most common side effect is oral and esophageal candidiasis.

Clinical studies investigating swallowed topical steroids have shown the overall response rate to be 65–70%. A new formulation using an orodissolvable steroid tablet reached 95% efficacy for attaining histologic remission. Steroids are the only treatment option with a strong recommendation in current guidelines due to the availability of randomized controlled trials that demonstrate clear efficacy. When reviewing anti-inflammatory treatment options, the advantage of swallowed topical steroids is a high response rate. Disadvantages to be considered are cost, cumbersomeness of the therapy with no commercially available preparation, and lack of long-term data on adverse events with these preparations. Use of topical steroids in 2–3-month studies have not demonstrated significant adrenal insufficiency or growth suppression. The asthma literature further suggests that these medications are safe for long-term use.

PPIs and steroids together have a potentially synergistic anti-inflammatory response, with PPIs impairing antigen penetration and steroids blunting the allergic inflammatory response. There is data to suggest PPIs inhibit different cytokines than steroids. Given this knowledge combined therapy may be appropriate for patients who have clear GERD overlap with EoE or those that are refractory to monotherapy.

The most current guidelines for treatment of EoE support the need for long-term maintenance therapy. For both PPIs and swallowed topical steroids, practice often involves starting at a high dose to achieve histologic remission followed by step-down to a maintenance dose. Unfortunately, the required maintenance dose is unclear, but studies suggest half to full dose for maintenance. Less than this leads to relapse in most patients. If remission cannot be maintained with a lower dose of PPI or steroid, the standard dose for initial treatment should be resumed. Some factors associated with risk of relapse with PPI use have included concomitant allergic rhinoconjunctivitis, CYP 2C19 rapid metabolizer genotype, and carriers of certain STAT6 gene variants.

Diet Elimination

The current mainstay of diet therapy is empiric elimination diets. An elemental diet is effective but often unpalatable and costly. Food allergy testing directed by skin and serum IgE testing unfortunately is poor in identifying diet triggers in EoE. This has led to empiric elimination diets where food triggers are iteratively excluded and/or reintroduced to determine a patient's individual food triggers. These triggers vary from patient to patient. The most common food triggers in EoE in order are milk, gluten, soy, and eggs. Less likely foods such as legumes, corn, and beef may also trigger EoE (Image 7.4).

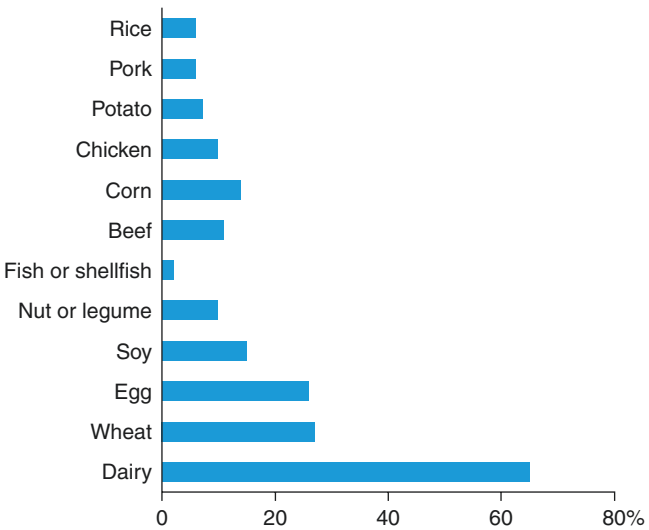

Image 7.4 Pooled rates for EOE food trigger prevalence

Table 7.2 Pros and cons of currently available first-line therapies in EoE

PPI		Steroids		Diet		Dupilumab	
Pros	Cons	Pros	Cons	Pros	Cons	Pros	Cons
Easy to take	PPI risks	Unlimited diet	Expensive	No long term risk	Cost, risks, inconvenience of evaluation period	FDA approved	Expensive
Relatively inexpensive	Lower response rate	Most patients respond	No commercially available preparation	Relatively inexpensive	Long term dietary restriction	Most patients respond	Potential risks
Many of patients also have GERD			Potential risks			Minimal side effects	Insurance coverage

There are a variety of empiric elimination diet strategies currently felt to be acceptable, and choice should be tailored to individual patient preferences, available diet resources, the likelihood of following the diet, and experience. These strategies are based on either step-up or step-down therapy. Various models have been proposed including 1,3-food; 1,4,8-food, 2–4-6 food, milk only, 2-food, 4-food, and 6-food, and extended 6-food elimination diets exist. Step-down approach starting with elimination of six foods typically achieves remission quickly and provides a clear path for reintroduction. While the initial elimination is extensive, it allows subsequent reintroduction, which is encouraging for patients, and clearly identifies triggers when more than one is present. It does, however, require multiple endoscopies to complete. Step-up approach starts with minimal elimination and then increases to more restricted diets in nonresponders. This quickly identifies responders to less restricted diet, and the largest advantage is those who achieve early remission are spared more restrictive diets and endoscopies. Furthermore, some studies suggest that 40% of EoE patients may be effectively treated with elimination of milk and/or gluten only. There is, however, prolonged inflammation in nonresponders due to time requirements which may further impair those patients with severe disease. Further, this approach can include multiple dietary changes to determine triggers, especially if there is more than one.

Regardless of the empiric diet elimination strategy chosen, a registered dietitian can be critical to patient education and compliance. Dietitians can help identify hidden allergens, find suitable food replacements, teach patients to read food labels and understand terminology, and ensure nutritional adequacy when diets are limited. Likely the diet that will be most successful is the one that is personalized in strategy.

Dupilumab

Dupilumab is the first FDA approved therapy for EoE treatment. The clinical trials investigating dupilumab have shown the overall histologic response rate of eosinophils ≤6 per high power field to be 60% at 12 weeks and 85% at 52 weeks. Importantly, patients also demonstrated statistically significant improvement in symptoms during clinical trials. Clinical trial patients were resistant to other medications with all of them failing PPI therapy, 40% having had prior dilation, and 60–70% previously having trialed steroids. This medication is given as a weekly subcutaneous injection. The advantage of dupilumab is it has a high response rate, it is FDA approved, and has minimal reported side effects. Disadvantages to be considered are high cost, and lack of long-term data on adverse events and effectiveness. It's precise role in EoE treatment is evolving but it appears to be an excellent option for those who don't respond to previously considered primary therapy (Table 7.2).

Dilation and Technical Considerations

Dilation is a key tool for treatment of adult patients with EoE and frequently underutilized in practice. It should always be considered in those with severe rings, focal strictures, or narrow-caliber esophagus. It is safe if performed in incremental fashion and discontinued after revisualization of mucosal disruption. Several dilation sessions are often required. Perforation risk is <1% in meta-analysis review. Dilation does not impact the inflammatory nature of the disease but is effective at improving dysphagia.

It is important to note that visualization of subtle esophageal stricture by endoscopy is limited and literature would suggest that esophagram is more sensitive at detecting strictures compared to endoscopy. Fluoroscopic imaging can be an important tool to estimate esophageal diameter and localize the area of greatest concern with barium tablet. It is used frequently in our practices to assess for narrow-caliber esophagus and in attempts to estimate the degree of fibrosis (Images 7.5 and 7.6).

Both bougie (American or Savary) and controlled radial expansion (CRE) balloons can be employed for esophageal dilation in EoE. Choice may be reflected by availability in one's practice and physician experience. When utilizing bougie dilation in EoE, frequent re-examination for mucosal disruption should be employed as there can be more than one stricture and varying severity of strictures. Balloons can be utilized to dilate a focal stricture but also

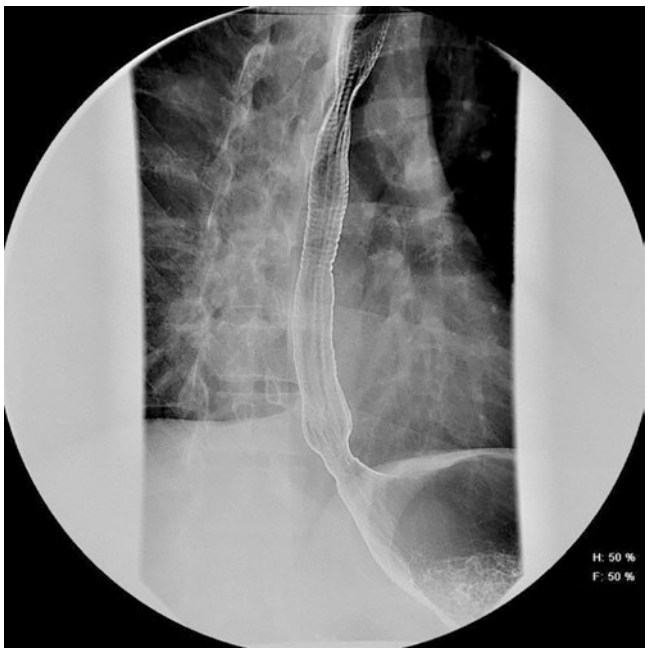

Image 7.5 Fluoroscopic image of patient with EoE. Fine concentric rings are appreciated throughout the upper half of the esophagus

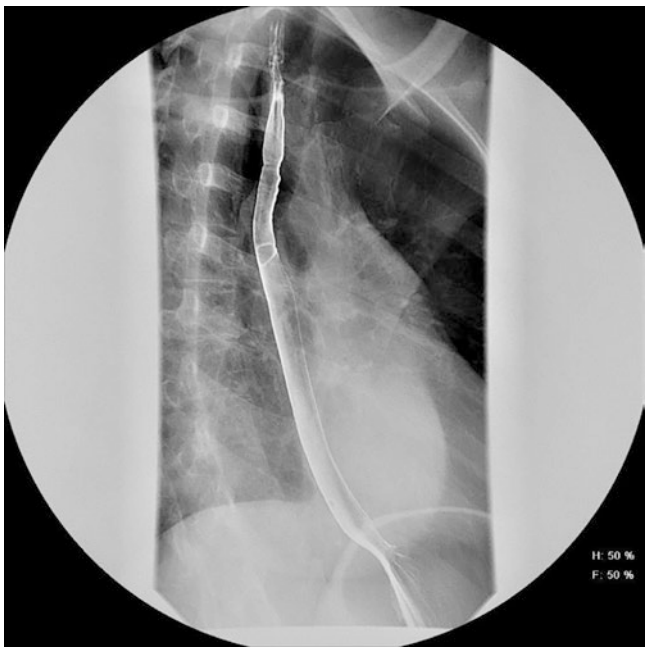

Image 7.6 Fluoroscopic image of patient with EoE. Severe proximal stricture and narrow-caliber esophagus

dilate the entire esophagus via balloon pull-through technique, performed by pulling the inflated balloon from the gastroesophageal junction to the proximal esophagus. Balloon dilation does allow for direct visualization of mucosal disruption during the dilation but could be more costly if multiple sized balloons need to be utilized (Images 7.7 and 7.8).

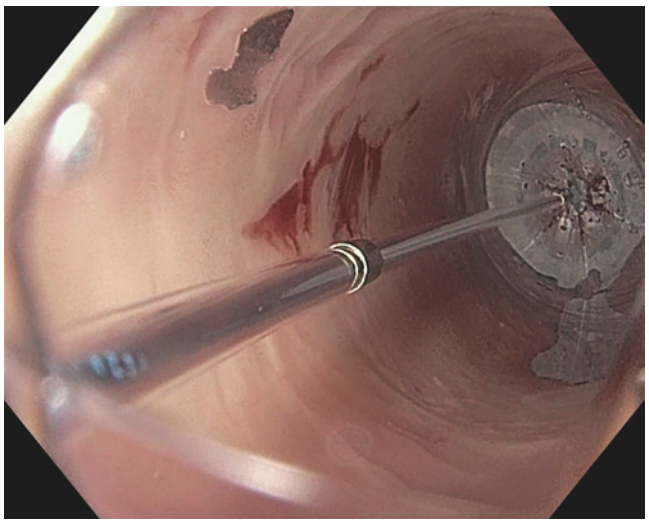

Image 7.7 Dilation with through the scope balloon with direct visualization of tear occurring

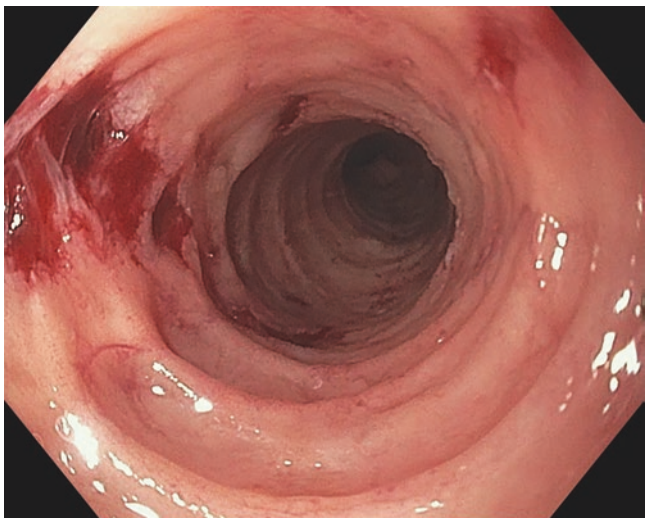

Image 7.8 Post-dilation tear after passing bougie dilator

Future Directions

Multiple advances continue to be made in the diagnosis and treatment of EoE, and the horizon is bright. Alternatives to endoscopy that have shown promise include transnasal endoscopy, the Cytosponge, and the esophageal string test. All of these allow sampling of the esophageal mucosa without performing standard endoscopy under sedation, but have limitations such as patient tolerability and the inability to perform esophageal dilations.

EoE subtypes have been categorized both phenotypically and by genomic markers predicting more progressive disease, medically refractory disease and severe stricture formation. This will hopefully lend itself to more personal-

ized therapy. Noninvasive biomarkers continue to be tested, and discovery of a circulating blood eosinophil progenitor line in the peripheral blood during allergic inflammation brings hope that we may one day have a blood, saliva, or urine test to determine and monitor degree of disease activity.

Functional luminal imaging probe (EndoFLIP) is a balloon-based technology that utilizes high-resolution impedance planimetry to quantify the change in luminal cross-sectional area during distention. It provides esophageal compliance data by generation of volume pressure curves. Decreased compliance measurements have been shown to correlate with risk of future food bolus impaction. This shows promise for determining degree of fibrosis in the esophageal lumen, data which could help guide therapy based on severity of whole organ function.

Many novel treatment options are showing potential in clinical trials. These include standardized topical steroid formulas and biologic therapies. The European Medicines Agency approved an orodispersable budesonide tablet for short-term EoE treatment. Medications targeting IL-13 and the IL-4α receptor subunit blocking IL-4 and IL-13 action have both shown significant promise.

Although EoE is a disease that was initially described only 20 years ago, the degree of understanding that has occurred in this disease is formidable. The inflammatory pathway has been carefully elucidated, diagnostic criteria have been refined, and present and evolving therapies show great promise. Nevertheless, there are improvements to be made, particularly in simplifying diagnosis and endpoints of treatment and in optimizing topical and systemic therapies.

Questions

1. Which of the following is not required to make the diagnosis of EoE?
   A. Clinical symptoms.
   B. Nonresponse to a PPI trial.
   C. ≥15 eosinophils per high-power field on esophageal biopsy
   D. Mucosal eosinophilia isolated to the esophagus
   E. B and D

   Answer: B. PPIs were previously used to classify what was considered to be a separate entity termed PPI-responsive esophageal eosinophilia which is now known to be the same disease as EoE.
2. Which of the following are challenges in diet elimination therapy?
   A. Psychosocial impact of a restricted diet
   B. High cost of allergen-free food products
   C. Patients must be educated on dietary contamination
   D. The process usually requires multiple endoscopies
   E. All of the above

   Answer: E. Dietary elimination therapy can be a lengthy process that has a high up-front cost. Patients need to be educated regarding dietary contamination for strict adherence, and it can require multiple endoscopies depending on the underlying trigger.

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Esophageal Hypersensitivity and Functional Dyspepsia

8

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Objectives

1. To understand the various peripheral and central mechanisms that contribute to esophageal hypersensitivity
2. To formulate an approach to determine whether a patient's symptoms are due to GERD, esophageal motility abnormalities, or a functional disorder
3. To review the different therapeutic options available for the management of esophageal hypersensitivity and functional dyspepsia

Esophageal Hypersensitivity

Introduction

Functional esophageal disorders present with esophageal symptoms (heartburn, chest pain, dysphagia, globus) that are not explained by mechanical obstruction, gastroesophageal reflux disease (GERD), or esophageal motor disorders. The Rome IV diagnostic criteria define five functional esophageal disorders (Table 8.1) [1].

Esophageal hypersensitivity, i.e., abnormal perception of otherwise normal stimuli due to a decreased pain threshold, and the abnormal transmission of stimuli in the peripheral and central nervous system are common underlying mechanisms for functional esophageal disorders. Esophageal hypersensitivity can overlap with GERD in symptom generation (Fig. 8.1).

Table 8.1 The Rome IV diagnostic criteria define 5 functional esophageal disorders

Functional chest pain	Recurring, unexplained, retrosternal chest pain of presumed esophageal origin, not explained on the basis of reflux disease, other mucosal or motor processes, and representing pain different from heartburn
Functional heartburn (FH)	Retrosternal burning discomfort or pain refractory to optimal antisecretory therapy in the absence of GERD, and in the absence of structural, histopathologic, or motor abnormalities
Reflux hypersensitivity (RH)	Typical symptoms of heartburn or chest pain which lack endoscopic evidence of reflux or abnormal acid burden on reflux monitoring, but show triggering of symptoms by physiologic reflux
Globus	Persistent or intermittent non-painful sensation of a lump or foreign body in the throat, unassociated with dysphagia or odynophagia. The diagnosis requires the absence of structural lesions, mucosal abnormalities such as a gastric inlet patch, GERD, or motor disorders
Functional dysphagia	Sensation of abnormal bolus transit through the esophageal body in the absence of structural, mucosal, or motor abnormalities to explain the symptom

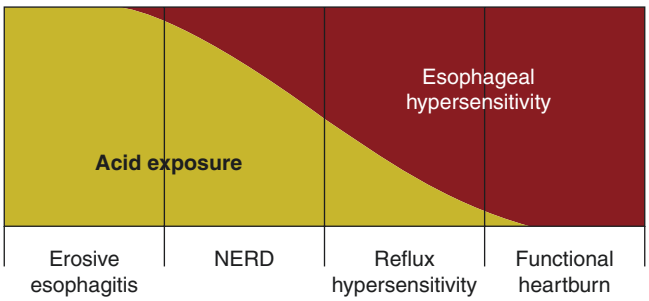

Fig. 8.1 The interplay between esophageal hypersensitivity and acid exposure in the reflux symptom spectrum. Symptoms in erosive esophagitis are dominated by abnormal acid exposure, whereas symptoms in functional heartburn are dominated by hypersensitivity. Symptoms in NERD and reflux hypersensitivity are related to a combination of both acid exposure and hypersensitivity, with a shift reflecting a more pronounced effect of acid exposure along the NERD diagnostic spectrum and a more pronounced effect of esophageal hypersensitivity along the reflux hypersensitivity diagnostic spectrum

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Epidemiology

The incidence and prevalence of different functional esophageal disorders are difficult to assess because of changes in the Rome criteria over various versions and heterogenicity of the inclusion criteria in epidemiologic studies.

The prevalence of functional chest pain is based largely on inferred data from studies assessing noncardiac chest pain (NCCP). Population-based surveys assess the prevalence of NCCP at 19%–33%. In a cohort of patients with NCCP, 50%–60% had GERD, 15%–18% had esophageal dysmotility, and approximately 32%–35% had true functional chest pain.

Functional heartburn is found in approximately 50% of proton pump inhibitor (PPI) nonresponders [1].

The prevalence of reflux hypersensitivity is inferred from the nonerosive reflux disease (NERD) population. In a study of 329 NERD patients who underwent esophageal pH-impedance monitoring, only 40% had true NERD, whereas 36% had RH and 24% had FH [2].

Globus sensation is reported by up to 46% of healthy individuals. It is often chronic, and approximately 45% of the patients may remain symptomatic after 7–8-year follow-up.

The prevalence of functional dysphagia is unknown. A population survey of functional disorders estimated that 7%–8% of dysphagia was unexplained by exclusionary criteria [3].

Pathophysiology

The underlying mechanism of visceral hypersensitivity in functional GI conditions is not fully understood. Studies show that functional esophageal disorders are strongly influenced by both peripheral and central sensitization and viscero-visceral hyperalgesia [4]. In addition, it seems that psychological factors, such as insomnia, stress, and anxiety, cause sensory abnormalities in the esophagus.

Peripheral Sensitization

Esophageal afferent neurons may become sensitized by inflammatory mediators and endogenous substances. A number of ion channels, neurotransmitter receptors, and trophic factors have been implicated in the development of peripheral sensitization. In healthy subjects, a reduction in esophageal pain thresholds to electrical and thermal stimuli following the application of acid and capsaicin demonstrates the presence of peripheral sensitization in response to these noxious stimuli.

Central Sensitization

Increased esophageal afferent input into the spinal cord can induce a complex array of intracellular signaling cascades that lead to neurotrophic changes at the spinal dorsal horn. These, in turn, culminate in enhanced synaptic transmission, leading to central sensitization. Central sensitization means that pain genesis occurs in a site anatomically distinct to the actual injury of noxious stimulus. The effect can also be much more prolonged (up to 5 h) than the initial insult (e.g., 30 min of acid exposure in the esophagus).

Viscero-Visceral Hyperalgesia

Although incompletely understood, viscero-visceral hyperalgesia is considered to be a result of the overlapping innervation and neuronal convergence at the spinal dorsal horn, such that the repeated stimulation of one viscus manifests as heightened sensitivity in another. For instance, distal esophageal acidification in healthy subjects can result in hypersensitivity of the rectum to mechanical distension.

Stress and Esophageal Hypersensitivity

Stress plays a role in esophageal sensitivity. Studies show that GERD patients who were exposed to acute auditory stress experienced increased levels of heartburn induced by intraesophageal acid perfusion, and stress from disturbed sleep has also been shown to cause similar esophageal hypersensitivity. Furthermore, psychological factors, stress, and the intravenous administration of corticotropin-releasing hormone (CRH), known as the master stress hormone, have been shown to influence visceral hypersensitivity in humans [5]. Psychological stress may also induce increased mucosal permeability via release of CRH leading to mucosal barrier dysfunction.

Clinical Evaluation

In addition to a good history and well-performed upper endoscopy, the two essential diagnostic tests used in the evaluation of esophageal symptoms are reflux monitoring (prolonged capsule pH monitoring or 24-hour pH-impedance testing) and esophageal manometry. It is key to differentiate whether the patient's symptoms are due to GERD, esophageal motility abnormalities, esophageal hypersensitivity, or a combination [6].

Functional Chest Pain

Confirmation that symptoms are unrelated to concurrent cardiac disease is a key step and should precede any esophageal workup. Given the high prevalence of GERD as a cause of NCCP, a short course of high-dose PPI therapy is simple and cost-effective in determining whether the chest pain is caused by GERD [7]. The role of gastroscopy is based on limited data available, but it can rule out possible structural causes. Patients not responding to the PPI trial may be referred for ambulatory reflux testing if clinical suspicion for GERD

remains high; this test should be performed off acid suppression. Esophageal manometry should be considered once GERD has been ruled out since esophageal motor disorders can also be a cause of NCCP.

Functional Heartburn and Reflux Hypersensitivity

Most patients are identified with FH or RH when heartburn fails to respond to optimal antisecretory therapy. This is a crucial component of the diagnostic criteria. Endoscopy typically is used in PPI nonresponders as the initial test to evaluate for macroscopic evidence of reflux, or for an alternative diagnosis, such as eosinophilic esophagitis (EoE) or a nonpeptic inflammatory process.

The next step is to determine whether pathologic GERD is present using ambulatory reflux testing. Patients with unproven GERD (i.e., no prior documented evidence of reflux-related pathology on endoscopy or ambulatory reflux monitoring) should be studied off antisecretory therapy. Patients are diagnosed with NERD if esophageal acid exposure is increased, with RH if acid exposure is normal but a positive association with reflux is present, and with FH if none of these conditions are present [1].

Patients not responding to PPI in the context of proven GERD (based on endoscopy and/or ambulatory reflux testing) represent another subgroup with different possible scenarios: truly refractory reflux (if acid exposure is abnormal during pH-impedance testing on PPI), overlap between FH and GERD (if acid exposure is normal with no symptom reflux association on pH-impedance testing on PPI), or overlap between RH and GERD (if acid exposure is normal with positive symptom reflux association on pH-impedance testing on PPI).

Globus

The diagnosis requires a compatible clinical history and ruling out an identifiable cause, such as ENT pathologies, a structural lesion, GERD, or a motor disorder. There must be no dysphagia and no alarm features (e.g., sore throat, odynophagia, weight loss). Physical examination of the neck and laryngoscopic examination of the pharynx are advised as the initial evaluation. Once local structural or inflammatory causes are excluded, the next step is an empiric trial of PPI therapy. If the patient responds, the management shifts to GERD. If the patient does not respond, gastroscopy to assess for a gastric inlet patch or other mucosal processes can be considered [1].

Functional Dysphagia

A careful history is taken to exclude oropharyngeal dysphagia, and to evaluate for conditions mimicking or contributing to dysphagia (globus, xerostomia, odynophagia). GERD and EoE are important conditions to exclude, typically with a combination of a trial of PPI therapy and upper endoscopy with esophageal biopsies. Barium contrast studies, especially using a solid bolus (e.g., tablet, cookie, marshmallow), can evaluate for subtle strictures often overlooked on endoscopy, as well as assess bolus transit through the esophagus. In the absence of structural lesions, esophageal manometry is performed to exclude motor disorders.

Management

For all functional esophageal disorders, the clinician should provide reassurance and counsel the patient that no ominous diagnosis exists. Repetitive invasive testing should be avoided. Esophageal hypersensitivity is primary treated with a variety of pain modulators, mostly in the category of antidepressants. The most commonly used antidepressants in functional esophageal disorders are tricyclic antidepressants (TCAs), selective serotonin receptor inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). These drugs appear to diminish esophageal hypersensitivity through their modulatory effect on central hyperalgesia and to some degree on peripheral hyperalgesia, although other mechanisms of action also have been described.

Behavioral therapies are an important alternative and often are complementary to neuromodulators as they can offer symptom improvement with minimal side effects. Psychological intervention, using cognitive-behavioral therapy, coping skills, and hypnosis, has been shown to be effective and durable in patients both with and without psychological comorbidity.

Functional Chest Pain

Antidepressants have also been found to be beneficial in NCCP. Imipramine, sertraline, and venlafaxine all had significant beneficial effects on chest pain severity or frequency [8].

Functional Heartburn

Therapies for FH remain largely empiric. Escalation of antireflux therapy, particularly to antireflux surgery, should be avoided. Given that abnormal peripheral sensitization and central processing are considered relevant in the pathogenesis of functional heartburn, it is reasonable to consider esophageal pain modulators, such as low-dose TCAs, SSRIs, or SNRIs similar to that described in other functional esophageal disorders.

Reflux Hypersensitivity

Response to antisecretory therapy may be better in RH than in other functional esophageal disorders. However, patients with nonacid reflux-triggered symptoms generally are refrac-

tory to PPIs. There is very limited evidence suggesting that acid reflux-triggered symptoms refractory to PPI can respond to antireflux procedures [9]. The mainstay of treatment remains pain modulators including TCAs, SSRIs, and SNRIs. However, the level of evidence is not very strong [10].

Globus

Given the benign nature of the condition and absence of data on highly effective therapy, the main treatment is reassurance and explanation. There are no placebo-controlled trials of antidepressants and behavioral therapy for globus, but there is anecdotal evidence for their utility [1].

Functional Dysphagia

Few studies have been done to assess treatment option for functional dysphagia. In addition to reassurance, simple non-pharmacologic measures such as eating in the upright position, avoiding precipitating foods, careful chewing of food, and chasing food with liquids may be enough in mild cases. Since dysphagia can be part of the reflux spectrum, a short trial of PPI can be used. Empiric bougie dilation of the esophagus can be considered. Despite a lack of proven efficacy, a trial of antidepressants, particularly TCAs, can be used.

Conclusion

Esophageal hypersensitivity can contribute to symptom generation in functional esophageal disorders or can coexist with GERD or esophageal motor disorders. PPI therapy is often insufficient to control symptoms, and antidepressants can be used for modulation of the "brain-gut axis."

Functional Dyspepsia

Introduction

The term dyspepsia refers to upper gastrointestinal symptoms, such as upper abdominal pain or discomfort, which can occur in the presence or absence of organic disease. Causes for dyspepsia include peptic ulcer disease, gastroesophageal reflux disease (GERD), and functional dyspepsia (FD). The latter, also known as non-ulcer dyspepsia, is a common etiology for dyspepsia symptoms with growing prevalence within the United States and worldwide [11].

Most common symptoms of FD include postprandial fullness, early satiety, upper abdominal bloating, epigastric pain, and nausea and vomiting. There are two subtypes of FD based on predominant symptoms: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). The most common mechanisms implicated in symptom development include impaired gastric accommodation to a meal, delayed gastric emptying, and/or hypersensitivity to gastric distension. Recent data has further suggested that duodenal mucosal inflammation and duodenal response to acid and fat may also play a role [12].

Like other functional GI disorders, FD has a negative effect on health-related quality of life in all domains, including physical mental and social aspects.

Epidemiology

The prevalence of FD is estimated between 10% and 16%, though FD remains an underdiagnosed condition. Approximately 12.5% of patients with symptoms will receive the accurate FD diagnosis, whereas many will be labeled with GERD or other functional gastrointestinal disorders such as gastroparesis or irritable bowel syndrome (IBS) [11].

Unlike some gastrointestinal conditions, FD does not favor any particular age group. Studies around the world have demonstrated various age trends, such as 45–54 years of age among Canadian, 41–50 years among Chinese, and 50–59 years among Japanese patients. Further, age trends have been noted among dyspepsia subtypes, such as ulcer-like predominant symptoms among patients aged <39 years in contrast with dysmotility-like symptoms among those <59 years.

FD remains more prevalent among females, and female sex was found to be an independent risk factor for developing FD in a 2018 Taiwanese health check-up study [13]. The role of ethnicity has not been assessed as accurately. Most surveys have included patients with Caucasian or Asian background.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) was an independent risk factor for FD in a survey of American and British adults. While dyspeptic symptoms occur in up to 40% of patients with *Helicobacter pylori* infection, the relationship between FD and *Helicobacter pylori* is unclear. Smoking and alcohol have not been strongly associated with FD [13].

Pathophysiology

The pathogenesis of functional dyspepsia is thought to be heterogenous and multifactorial, including an underlying motility disorder (e.g., impaired fundic volume accommodation), sensorimotor disorders (e.g., reduced excitability of enteric nerves in the duodenum), visceral hypersensitivity (e.g., heightened sensitivity after stomach expansion), and psychosocial factors (e.g., increased anxiety, depression, somatization). More recently, loss of integrity of duodenal mucosa has

been thought to contribute to functional dyspepsia symptoms, particularly when found with low-grade mucosal inflammation primarily with eosinophils and mast cells.

Impaired gastric accommodation and visceral hypersensitivity remain the predominant proposed pathophysiological mechanisms for FD. Approximately 50% of patients with FD experience impaired gastric accommodation. Normally the gastric fundus relaxes during an increase in gastric volume (e.g., food intake), in order to avoid an increase in gastric pressure. When gastric accommodation is impaired, gastric pressure rises and food redistributes to the distal stomach, resulting in more rapid gastric emptying. Patients can therefore experience symptoms of early satiety, epigastric pain, bloating, and nausea and vomiting. Visceral hypersensitivity occurs via sensory nerves connecting the gut to the central nervous system, creating the "brain-gut axis." Hypersensitivity is thought to occur more often with comorbid psychosocial disorders, including anxiety, depression, and somatization.

Factors outside the stomach may also contribute to the pathophysiology of FD. For example, acid in the duodenum can lead to functional dyspepsia symptoms, possibly related to sensitized pH sensors or impaired motor function in the proximal duodenum. Also, intraduodenal infusion of fat has been shown to trigger symptoms in patients with FD. This relationship is thought to be associated with direct neural action, increased enteroendocrine cell sensitivity, and/or increased cholecystokinin-A receptor sensitivity.

As with many other functional gastrointestinal disorders, an episode of bacterial, protozoal, or viral gastroenteritis increases the risk of developing FD 2.5 times. Risk factors for developing postinfectious FD include smoking and psychological stress. Patients with postinfectious FD have been found to have an abundance of eosinophils in the duodenal mucosa and proximal gastric dysfunction [14].

Diagnosis

Diagnosis of FD relies on clinical symptom presentation. Rome IV criteria define functional dyspepsia as any combination of four symptoms, early satiety, postprandial fullness, epigastric pain, and epigastric burning, occurring at least 3 days per week over the last 3 months, with an onset occurring at least 6 months in advance. In the absence of alarm features in a patient under 60 years of age, no further diagnostic tests are necessary to make a diagnosis of FD. In patients 60 years or older, an upper endoscopy should be performed. Once a diagnosis of FD is made, the patient can be further assigned to one of two subgroups of FD: (1) epigastric pain syndrome (EPS) and (2) postprandial distress syndrome (PDS). EPS refers to patients experiencing epigastric discomfort (e.g., pain, burning sensation) unrelated to meal ingestion, whereas PDS is characterized by symptoms related to immediate meal ingestion and suggestive of gastric motility disturbance [15].

Many patients with FD can experience symptoms which can overlap with other conditions such as gastroparesis, GERD, and IBS. For example, 25% of FD patients can present with delayed gastric emptying, a fundamental component of gastroparesis. Similarly, a subset of patients with FD have pathologic acid reflux and symptoms of heartburn and/or regurgitation. Further, approximately 30% of patients with FD experience symptoms consistent with IBS, a functional gastrointestinal disorder characterized by recurrent abdominal pain associated with alterations in bowel movements. As patients with FD can present with abdominal pain, physicians are often challenged in trying to distinguish if patients' symptoms are a reflection of FD, IBS, or both. However, further investigations, such as with a gastric emptying study or 24-h pH-impedance study, are not routinely necessary unless they will alter management.

Management

Once a diagnosis of FD is made, the first priority is explaining the condition to the patient, including the nature and cause of symptoms and providing reassurance. Creating a treatment alliance with the patient is key. Management of FD includes both pharmacologic and nonpharmacologic options.

Pharmacologic management in functional dyspepsia focuses on symptomatic improvement. Duration of treatment is not defined, but a period of 8–12 weeks is recommended.

Helicobacter pylori Eradication

The presence of *Helicobacter pylori* infection increases the risk of dyspeptic symptoms. Patients with FD should be tested for active *Helicobacter pylori* infection (stool antigen or urea breath test) and should receive eradication therapy, if positive. The success of eradication should be subsequently confirmed. While the effect of *Helicobacter pylori* eradication in FD is small, it is statistically significant with a NNT of 13 [16].

Acid Suppression

Proton pump inhibitor (PPI) therapy can be effective in FD, especially in the EPS subtype. Interestingly, histamine receptor-2 (H2) blockers may be slightly more effective than PPIs (NNT of 11 for PPIs vs. NNT of 7 for H2 blockers). The effect of H2 blockers may go beyond acid suppression and also include symptoms related to mast cell infiltration leading to histamine release. However, the quality of the data is poor, and studies may have included patients with GERD misclassified as FD [16].

Antidepressants

A variety of antidepressant agents have been evaluated in the treatment of FD. These agents are thought to work by reducing psychological symptoms, including anxiety and depression, as well as via central analgesic effects and sleep restoration. Low-dose tricyclic antidepressants (TCAs), including amitriptyline, imipramine, and desipramine, have been shown to have benefit for relief of global symptoms in patients with FD. Generally, dose should not exceed 75 mg per day as higher doses do not have greater benefit in FD and may cause side effects [16].

Selective serotonin reuptake inhibitors (SSRIs) have not been shown to have an effect on FD symptoms, but can be used in patients with concomitant depression to address underlying mental health contributors to a patient's FD.

Mirtazapine has been shown to benefit patients with FD with unintentional weight loss. Its effect is on global FD symptoms as well as depression and has been associated with improved quality of life and weight gain.

Prokinetic Agents

Since impaired gastric emptying is present in some patients with FD, prokinetic agents have been used to address this possible pathophysiologic mechanism. Metoclopramide and domperidone are associated with global symptom improvement in FD, though the quality of the evidence is low. Patients with PDS subtype may be more likely to benefit from prokinetics [16].

5-Hydroxytryptamine (5-HT)$_{1A}$ Receptor Agonist

Impaired gastric accommodation has been reported in approximately 40% of functional dyspepsia patients. Buspirone, a 5-hydroxytryptamine (5-HT)$_{1A}$ receptor agonist, has been shown to reduce the severity of FD symptoms, including postprandial fullness, early satiety, and upper abdominal bloating while quantitatively increasing gastric accommodation [16].

Phytotherapy

Phytotherapy is the use of plant-derived medications in the management of symptoms. A variety of formulations exist, including a preparation called STW5 (Iberogast), which contain various combinations of peppermint, caraway oil, bitter candytufts, wormwood, gentian, angelica root, chamomile, and lemon balm. Small studies have shown symptom relief which may occur through a spasmolytic and/or sedative effect on the gastrointestinal tract.

Psychological Therapy

Psychological factors are known to play a role in FD. Psychological therapy (cognitive-behavioral therapy, relaxation therapy, hypnosis, psychotherapy, etc.) has been assessed in small studies and may be beneficial in FD in motivated patients [16].

Dietary Modification

Diet plays a minor role in FD. If a patient can identify a particular trigger food(s), trial of elimination can be considered. Dietary modification can also include changing the timing and amount of food ingested, such as multiple small meals throughout the day or grazing.

Conclusion

Functional dyspepsia remains a common functional gastrointestinal disorder characterized by abdominal discomfort, postprandial fullness, and early satiety. Diagnosis is based on symptom assessment set out by Rome IV criteria, separating functional dyspepsia into epigastric pain syndrome and postprandial distress syndrome. Management options include reassurance, eradication of *Helicobacter pylori* infection, acid suppression, antidepressants, and complementary options like phytotherapy and dietary modification.

Questions

1. All of the following therapeutic options have good data supporting their use in the management of esophageal hypersensitivity, except:
   A. Tricyclic antidepressants
   B. Selective serotonin receptor inhibitors
   C. Serotonin-norepinephrine reuptake inhibitors
   D. Antireflux surgery

Answer: D.

2. Regarding functional dyspepsia, which of the following is false:
   A. Functional dyspepsia is more common in women
   B. NSAIDs are an independent risk factor for functional dyspepsia
   C. A gastric emptying study is required as part of the diagnostic workup of functional dyspepsia
   D. Mirtazapine alleviates symptoms in functional dyspepsia and helps patients gain weight

Answer: C.

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Endoscopic GERD Therapies

9

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Introduction

Gastroesophageal reflux disease (GERD) is one of the most common chronic gastrointestinal conditions. Anti-reflux medications, especially proton pump inhibitors (PPIs), are first-line therapy for GERD. However, a significant proportion of patients may have incomplete or no response to therapy, and PPIs are ineffective in managing regurgitation-type symptoms. Further, there has been increased recognition of the potential adverse effects of chronic PPI use. Laparoscopic anti-reflux surgery (LARS) remains the gold standard for patients who have failed medical therapy or have complicated GERD. However, more widespread use is limited by the invasiveness of the procedure and postsurgical risks (albeit low) and adverse events (AEs) including de novo dysphagia and gas bloat. Endoscopic therapies have the potential to bridge the gap between medications and surgery, thus providing a minimally invasive option for patients unwilling or unable to continue indefinite medical therapy. This review will summarize the most promising currently available endoscopic GERD treatment including transoral incisionless fundoplication (TIF) and endoscopic augmentation of the gastroesophageal junction (GEJ).

Pre-Procedure Evaluation

GERD is a spectrum disorder with complex pathophysiology. As such, treatment should be tailored not only to the phenotype but also the anatomic or physiologic alterations of the individual patient. Although endoscopic GERD treatments are now considered appropriate options early in the GERD spectrum, a major difference remains when compared with LARS. In LARS, the anti-reflux barrier is restored by reducing the hiatal hernia, restoring the crural defect, and creating a flap valve via fundoplication. In contrast, endoscopic GERD therapies alone are unable to perform crural repair, and although TIF can lengthen the intra-abdominal esophagus, it can only repair small hiatal hernias. Hence, the ideal application of endoscopic GERD treatments lies in those patients with largely intact crural sphincters.

Esophagogastroduodenoscopy is fundamental to identify the presence of GERD complications (esophagitis and Barrett's esophagus) and anatomic alterations. The importance of accurately assessing (1) the presence and length of any hiatal hernia, and (2) the crural opening, cannot be emphasized enough. The Hill classification provides an endoscopic grading system for the gastroesophageal flap valve (Fig. 9.1) but is often underestimated due to insufficient time and/or insufflation during retroflex, or the presence of a "fat pad" filling the open hiatus. We recommend 60 s in retroflexion with active insufflation before determining the Hill classification.

In patients without definitive endoscopic evidence of GERD (erosive esophagitis and/or Barrett's esophagus), ambulatory pH testing should then be performed to confirm the presence of pathologic reflux. High-resolution esophageal manometry should be considered in patients with dysphagia or other suspicion for an esophageal motility disorder. At this stage, we recommend endoluminal GERD therapy be limited to patients with confirmed pathologic GERD.

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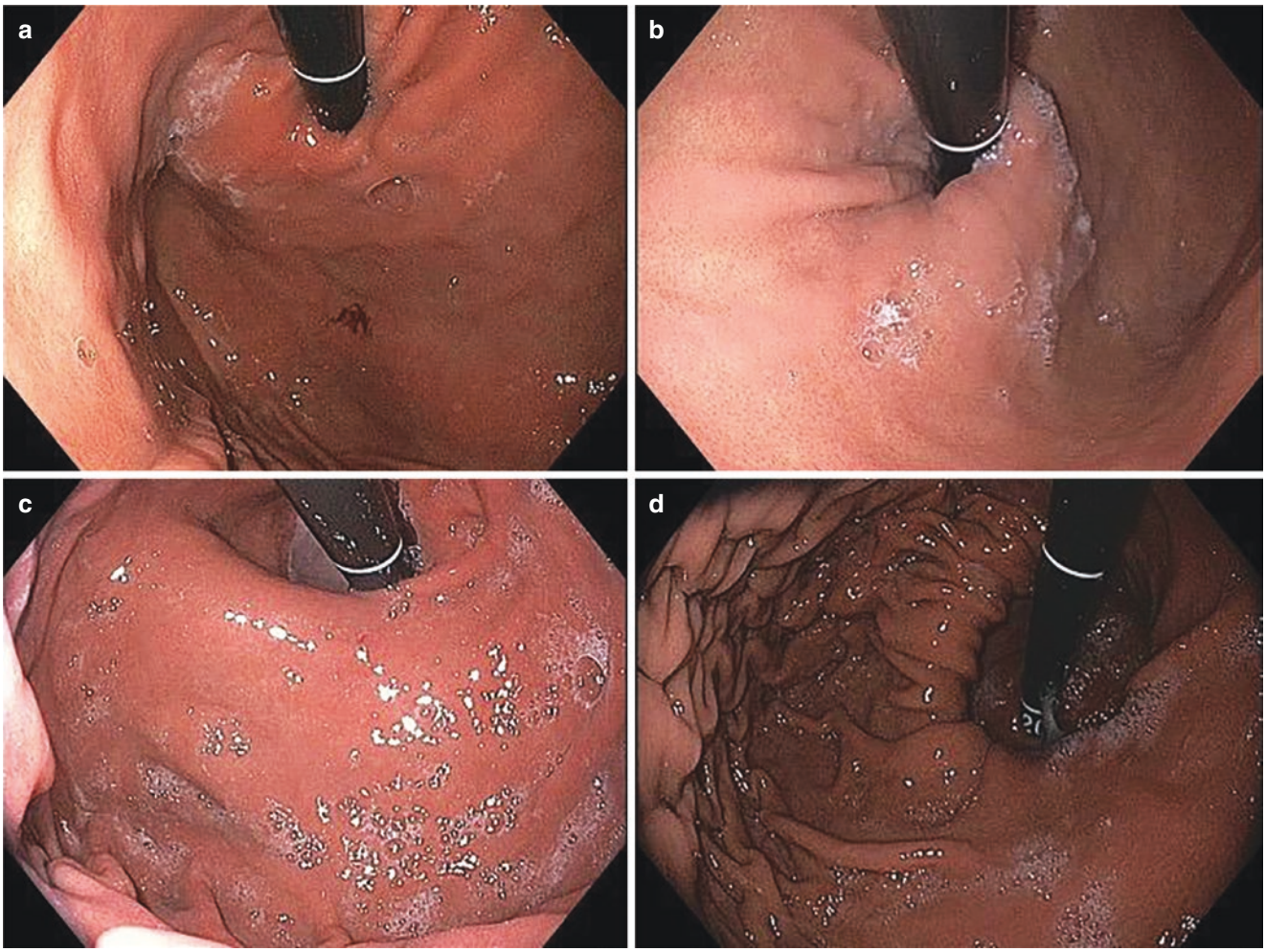

Fig. 9.1 Hill classification viewed with the endoscope in retroflexed position after at least 45 s of insufflation (**a**) Hill grade I (**b**) Hill grade II (**c**) Hill grade III (**d**) Hill grade IV

Transoral Incisionless Fundoplication

Transoral incisionless fundoplication (TIF) is a minimally invasive anti-reflux procedure, most commonly performed using the EsophyX-Z device (EndoGastric Solutions, Inc. Redmond, WA). Originally Food and Drug Administration approved in 2006, the all-inclusive system has evolved through several different iterations to arrive at TIF2.0 which achieves outcomes morphologically and physiologically comparable to the operative partial anterior fundoplication (Toupet procedure). During the TIF procedure, the intra-abdominal portion of the distal esophagus is lengthened, and a 2–cm length rotational wrap of the cardia and fundus is performed using polypropylene fasteners (Fig. 9.2). In doing so, TIF accentuates the cardiac notch, steepens the angle of His, and re-establishes the flap valve mechanism.

TIF Mechanism of Action

TIF is the endoscopic treatment which most closely mirrors LARS. In early explorative studies, TIF significantly reduced both the number of transient lower esophageal sphincter relaxations (tLESRs) and the number of tLESRs associated with liquid-containing reflux. TIF also decreased the number and proximal extent of reflux episodes, and improved acid exposure time (AET) in the upright position. Importantly, TIF had no effect on the number of gas reflux episodes, therefore substantiating the reported low incidence of post-procedure gas bloat. Finally, TIF significantly reduced GEJ distensibility as measured by impedance planimetry.

The rotational wrap in TIF creates a 3 cm flap valve, or high-pressure zone at the distal esophagus which should decrease upright and supine reflux. In creating a 270° partial

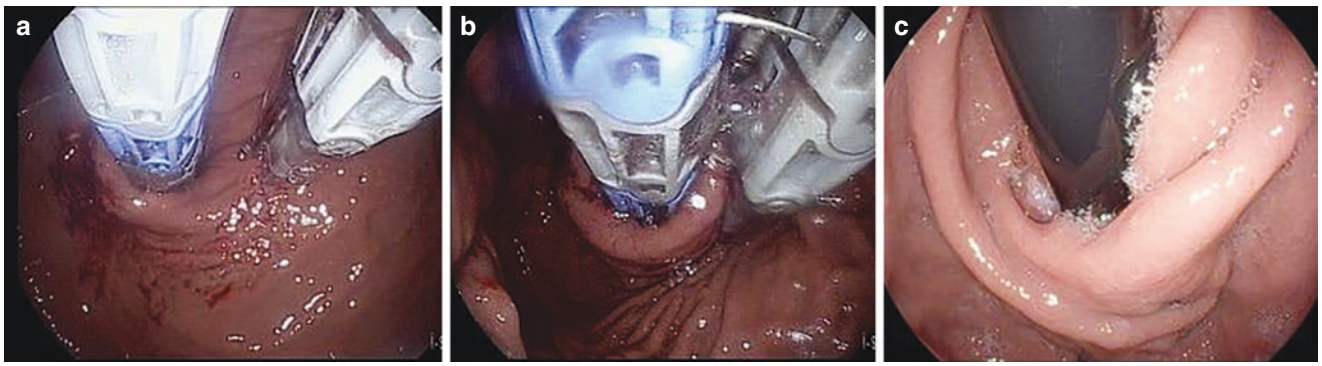

Fig. 9.2 Transoral incisionless fundoplication (TIF) using EsophyX-Z device. (**a**) The device is advanced into the stomach, and the endoscope is retroflexed to visualize the gastroesophageal junction. The helical retractor is advanced to grasp tissue. (**b**) The tissue is pulled in between the tissue mold and the chassis while suction is applied to deflate the stomach. Once adequate length (around 3 cm) is created, the device is rotated toward the lesser curve to create the wrap. The sequence is repeated to create a 270° circumferential wrap. (**c**) Intact TIF wrap is seen at follow-up EGD

wrap, TIF allows gas escape from the stomach, minimizing the gas bloat side effect. Further, the wrap is performed against the shaft of the device, minimizing post-procedure dysphagia.

TIF Patient Selection

As TIF does not address crural defects, ideal candidates for TIF are those with pathologic GERD and small crural defects who fit within the "2 by 2" rule, defined as hiatal hernia of axial length ≤2 cm and Hill grade ≤2. This is critical as underestimated Hill grade is the most common reason for TIF failure. In practice, a significant proportion of patients do not meet these criteria, and the addition of a concomitant hiatal hernia repair to TIF (or cTIF) allows a greater number of patients to become candidates for LARS without traditional AEs such as gas bloat and dysphagia. This will be discussed in detail later in this chapter.

TIF Technical Considerations

TIF2.0 is performed using the disposable EsophyX-Z device which is comprised of an 18-mm-diameter frame through which a standard gastroscope can be introduced. There is a handle with controls, a tissue invaginator (with side holes at the distal end to which external suction can be applied), a tissue mold, a helical retractor, and two stylets which puncture plicated tissue to deploy polypropylene H-shaped fasteners.

TIF is performed under general anesthesia with muscle relaxation. Positioning the patient in left lateral position aids device introduction, although a supine position can decrease pressure on the GEJ from the liver. Both positions have been safely used in clinical practice. Generally, TIF involves two operators: one to handle the device and the other the endoscope. A diagnostic EGD is performed immediately before to verify that the stomach is free of food, measure landmarks (specifically the GEJ), check Hill grade, and confirm the size of any hiatal hernia. An 18 mm dilation can be performed of the upper esophageal sphincter to facilitate device passage. Lubricant is liberally applied to the endoscope and device channel, before advancing the endoscope through the device until the distal tip emerges. The device and endoscope are then advanced together, carefully under direct visualization, into the stomach. Resistance is often encountered at the oropharynx and upper esophageal sphincter, which is usually overcome by jaw thrust and deflation of the endotracheal tube. The endoscope is then retroflexed to visualize the device, which is advanced until the second blue segment is seen to enter the stomach. The endoscope is then withdrawn into the chassis until the gray segment is visualized and the tissue mold is closed. The endoscope is then readvanced through the side hole and once again retroflexed in the stomach. Now in reference to a clock face, starting with 12 o'clock at the lesser curvature, we describe plication positions. First, the device is rotated to the posterior corner (11 o'clock position). The helical retractor is advanced, just distal to the squamocolumnar junction, and rotated clockwise to engage the tissue. The helical retractor is then released from the tissue mold by a slight device advancement and opening of the tissue mold. The entire device is then adjusted such that the proximal blue segment is within the esophagus, a step we refer to as "burying the blue." Next, the stomach is desufflated while the retractor is pulled back maximally, thereby drawing tissue into the mold, and attaining the valve length. A valve length of 3 cm should be targeted. Once fully retracted, the device is rotated toward the lesser curve to create the "wrap." The next sequence of steps is then "lock,

lock, suck" referring to (1) locking the helical retractor, (2) closing tissue mold completely and locking it in place, and (3) turning on the invaginator suction. The stomach is then reinsufflated to confirm the device and endoscope are below the diaphragm, or the initial location of the GEJ. The double fasteners are then "fired" by holding the safety button and squeezing the trigger. The invaginator is then turned off and fasteners are reloaded. The device is unrotated, helical retractor unlocked and the tissue mold opened. The process is repeated for a total of three plications at the posterior corner. The helical retractor is then removed from the tissue by an anticlockwise rotation, retracted back into the device which is rotated to the anterior corner (1 o'clock position) for a further three plications. These initial plications form the wrap. The device is then positioned in the 5 and 7 o'clock positions for two plications each. Here, no rotation is performed, only desufflation and retraction to create length. At this point, following a total of 10 plications with placement of 20 fasteners, a visual inspection is made. The valve can be "touched up" with additional 2–5 plications. Finally, the endoscope is straightened and retracted into the device frame, the tissue mold is straightened, and the helical retractor is placed in the safety position for removal of the entire device and endoscope. A relook is performed to assess the degree of wrap, valve length, and fastener placements.

TIF Outcomes

We will summarize the three randomized controlled trials (RCTs) evaluating TIF2.0 to date. The TEMPO trial by Trad et al. randomized 63 patients to TIF ($n = 40$) and high-dose PPI ($n = 23$). At 6-month follow-up, troublesome regurgitation was eliminated in 97% of the TIF cohort vs 50% of the PPI cohort (RR = 1.0, 95%CI: 1.2–3.11, $p = 0.006$). Overall, regurgitation and extraesophageal symptoms were eliminated in 62% following TIF compared with 5% on PPI (RR = 12.9, 95%CI: 1.9–88.9, $p = 0.009$). In TIF patients, esophageal AET was normalized in 54% and 90% were off PPIs. Following the 6-month evaluation, all patients in the PPI group elected to cross over to TIF, and a follow-on paper reported 5-year outcomes. Of the initial 63 patients, 60 were available for follow-up at 1 year, 52 at 3 years, and 44 at 5 years. Troublesome regurgitation was eliminated in 88% at 1 year, 90% at 3 years, and 86% at 5 years. At 5 years, 34% of patients were on daily PPI therapy, compared with 100% at baseline. Improvement in GERD-health-related quality of life (HRQL) was sustained at 6.8 at 5 years, compared with 22.2 at baseline ($p < 0.001$). Three patients (5%) underwent reoperation.

RESPECT was a prospective sham-controlled trial comparing TIF2.0 to PPI. The study randomized 129 GERD patients to TIF with 6 months of placebo ($n = 87$), or sham surgery with 6 months of PPI ($n = 42$). By intention-to-treat analysis, TIF eliminated troublesome regurgitation in 67% of patients compared with 45% with PPIs ($p = 0.023$). A higher proportion of patients reported no response at 3 months in the PPI group (36%) compared with TIF (11%, $p = 0.004$). Esophageal AET improved after TIF from mean 9.3% before to 6.3% after ($p < 0.001$), but not after sham surgery (mean 8.6% before and 8.9% after). TIF provided equivocal symptom score improvement to sham/PPI.

The final study by Hakansson et al. was a double-blind sham-controlled trial in chronic PPI users with GERD. The study randomized 44 patients to TIF ($n = 22$) and sham procedure ($n = 22$). Time in remission was significantly longer in the TIF group than the sham cohort (197 vs 107 days, $p < 0.001$). At 6 months, 59% of the chronic GERD patients remained in clinical remission without PPI following TIF. Other secondary outcomes including PPI consumption, AET, and GERD symptom scores were all in favor of TIF.

A meta-analysis of the 3 RCTs ($n = 233$) demonstrated improved esophageal pH, decreased PPI utilization, and improved quality of life. Since then, publications by Testoni et al. and Bell et al. have reported durability out to 10 years. Serious AEs incorporating multiple versions of TIF are approximately 2–2.5% but lowered to <0.5% since TIF2.0 was introduced. There are no direct comparisons to magnet sphincter augmentation (MSA) or surgical fundoplication. However, a recent systematic review by Chandan et al. comparing MSA and TIF2.0 found comparable technical success and clinical success based on GERD-HRQL scores. However, although a significantly greater proportion of patients reported improvement in regurgitation and were able to completely discontinue PPI therapy with MSA compared to TIF2.0 (91.3% (CI 81.5, 96.2) vs 63.8% (CI 51.6, 74.4)), there was also a higher proportion of patients with postoperative dysphagia following MSA compared with TIF (9.1% (CI 4.2, 18.8) vs 3.6% (CI 1.4, 8.8)). Another systematic review and network analysis by Richter et al. compared laparoscopic Nissen fundoplication (LNF) vs TIF or PPI and showed that although HRQL improved post-TIF, LNF was more effective in increasing LES pressure and decreasing esophageal AET. Notably, concerns were raised regarding the analysis methodology and head-to-head trials are eagerly awaited.

Concomitant Laparoscopic Hernia Repair and TIF (cTIF)

As mentioned previously, a significant proportion of GERD patients will not be suitable for TIF alone due to Hill grade ≥2 and/or hiatal hernia length ≥2 cm. A concomitant HH

repair with TIF (cTIF) was proposed and carries several advantages to traditional LARS. In repairing the hiatal defect alone, the more extensive dissection for fundal mobilization is avoided. Further, emerging cTIF data also suggests reduced gas bloat than standard LARS.

So far, cTIF has been evaluated in several non-comparative studies. Ihde and colleagues reported 2 retrospective studies, first with 18 patients in 2011 and then with 55 patients in 2019. In the more recent study, 29 patients (53%) had matched pre- and postoperative validated surveys and pH testing. There was significant improvement in GERD-HRQL from 33.7 (SD 22.0) to 9.07 (SD 13.95) ($p < 0.001$), and 22 patients (76%) normalized their pH exposure. A prospective trial by Janu et al. evaluated cTIF in 99 patients and demonstrated significant improvement in symptom scores with 74% of subjects off PPIs at 12 months. More recently, Choi et al. reported on 60 patients treated by cTIF noting significantly improved symptom scores and AET decreasing from 12.7% to 1.28% post-cTIF ($p = 0.06$). RCTs comparing cTIF with traditional LARS and fundoplication are eagerly awaited.

Emerging Applications for TIF

Novel applications of TIF include the treatment post-peroral endoscopic myotomy (POEM) GERD. The first published case series ($n = 5$) showed discontinuation of PPI in all patients at an average follow-up of 27 months (range 5–34) with no AEs. An emerging possibility is concomitant POEM plus TIF in a select cohort of achalasia patients. Further, as TIF does not incorporate much of the gastric fundus into the fundoplication, it is also being considered in obese patients prior to sleeve gastrectomy. There is increasing recognition of the link between chronic respiratory disease and lung transplant outcomes with GERD, with recent recognition for early diagnosis and management of GERD in lung transplant recipients. As such, the role of TIF is being explored in such patients. Finally, TIF can also be used as salvage following failed prior therapy including TIF or LARS.

TIF Summary

TIF is an emerging endoscopic GERD treatment which is most morphologically and physiologically identical to LARS without traditional side effects such as gas bloat and dysphagia. With careful patient selection, TIF and cTIF are safe and effective GERD treatments.

Endoscopic Anti-Reflux Gastroesophageal Junction Augmentation

Various techniques have been reported which utilize endoscopic tools to augment the GEJ. We will discuss these from their inception with anti-reflux mucosectomy (ARMS) and the modifications which followed.

Mechanism of Action

The rationale is that by inducing mucosal injury at the gastric cardia around the GEJ, as healing and scar occur, the tissue augments the natural anti-reflux valve, thereby reducing the opening and sharpening the angle of His. These procedures cannot reduce hiatal hernias. A porcine model by Li et al. demonstrated significantly higher gastric yield pressure (i.e., intragastric pressure until esophageal fluid reflux is noted) ($p = 0.004$) and reduced cardia width ($p = 0.032$) following ARMS.

Patient Selection

Ideal patients are those with minimal or no hiatal hernias, minimal crural defect, and the absence of an esophageal dysmotility disorder. As with TIF, accurate pre-treatment evaluation must be performed to assess for any anatomic abnormalities or GERD complications. There should be a low threshold for high-resolution manometry to rule out dysmotility disorders.

Anti-Reflux Mucosectomy (ARMS)

ARMS was first reported in 2014 by Inoue's group after incidentally noting that some patients who underwent resection for gastric cardia neoplastic lesions reported improved reflux symptoms. They subsequently evaluated the technique in a pilot study of ten patients. The group aimed to perform at least hemi-circumferential resection of the gastric cardia. The mucosa was first marked along the lesser curve of the gastric cardia with the gastroscope in retroflexed position, in order to protect the mucosal flap valve at the greater curve. The cardial mucosa was then lifted with a submucosal injection before resection using either endoscopic mucosal resection (EMR), cap-assisted EMR, or endoscopic submucosal dissection (ESD). In their pilot study, eight underwent 270° resection, while two had circumferential mucosectomies.

They demonstrated significant improvement in GERD symptoms, esophageal AET from 29.1% to 3.1% ($p = 0.01$) and flap valve grade from 3.2 to 1.2 ($p = 0.0152$). However, balloon dilation was required in the two patients who had circumferential mucosectomy. Since then, several further studies have reported promising outcomes with 270° resection by cap-assisted EMR (or ARMS-c). The larger study by Sumi and colleagues evaluated 109 patients and noted durable symptom improvement to 3 years with 40–50% of patients able to discontinue PPI. There were minimal AEs with postoperative bleed was noted in 2 (1.8%) and perforation in 1 (0.9%), all managed endoscopically. However, the authors noted a high incidence of stricturing in an earlier cohort treated with standard 270° resection with 13 of 88 patients requiring dilation more than 3 times. They noted, however, that after switching to a "butterfly" method (leaving a small amount of mucosa in the lesser curvature), only 1 patient of the subsequent 21 required dilation.

ARMS can also be performed by band-EMR (or ARMS-b). Monino et al. reported on 21 patients who underwent the procedure with decrease/discontinuation of PPI in 76% at 3 months and 72% at 6 months. There was statistically significantly improvement in GERD symptom scores. One patient underwent LARS during mean follow-up of 10 ± 5 months. ARMS has been compared with LNF in a retrospective review of prospective data by Wong et al. The group matched patients who underwent ARMS ($n = 33$) to LNF patients ($n = 67$) and demonstrated shorter procedure time ($p < 0.001$), post-procedure hospital stay ($p < 0.001$), post-discharge pain ($p = 0.007$), and earlier return to activities of daily living ($p < 0.001$) in the ARMS cohort. There was no difference in GERD-HRL, reflux symptom index (RSI), or dysphagia scores at 2-year follow-up. However, the ARMS group reported less gas and bloating at all time points (all $p < 0.05$). Both groups reported increased dysphagia at 3 weeks, but this did not persist at beyond 6 months. Notably, ten patients (30.3%) in the ARMS group underwent additional LARS during follow-up. The authors concluded that although ARMS had better perioperative outcomes, GERD quality of life outcomes were comparable. Hence, ARMS can be effective for GERD when performed on appropriately selected patients without limiting future LARS.

Anti-Reflux Mucosal Ablation (ARMA) and Cardia Ligation Endoscopic Anti-Reflux (CLEAR) Procedure

Although early trials have shown ARMS to be effective with a good safety profile, significant technical expertise is required in such an extensive resection. Mucosal ablation and endoscopic band ligation (EBL) with or without resection (CLEAR or cardia ligation endoscopic anti-reflux technique; Fig. 9.3) or the use of clips have been suggested as potential alternatives to EMR/ESD.

The anti-reflux mucosal ablation (ARMA) procedure utilizes a similar technique to ARMS with ablation instead of mucosectomy. First used in a patient with insufficient response to ARMS where post-resection scarring limited further mucosectomy, Inoue's team describe the application of a submucosal cushion before using a triangle-tip knife in spray coagulation to ablate the mucosa around the cardia in a "butterfly" shape. In their pilot study, 12 patients with PPI-refractory GERD successfully underwent ARMA with significant improvements in GERD symptoms, quality of life, and objective parameters including Hill grade and esophageal AET. One patient developed symptomatic stricture requiring balloon dilation; no other AEs were seen.

The CLEAR procedure was studied by Seleem et al. in a relatively large RCT assigning 150 patients with refractory GERD to EBL ($n = 75$) or optimized PPI therapy ($n = 75$). EBL was performed at four quadrants at the GEJ. Patients

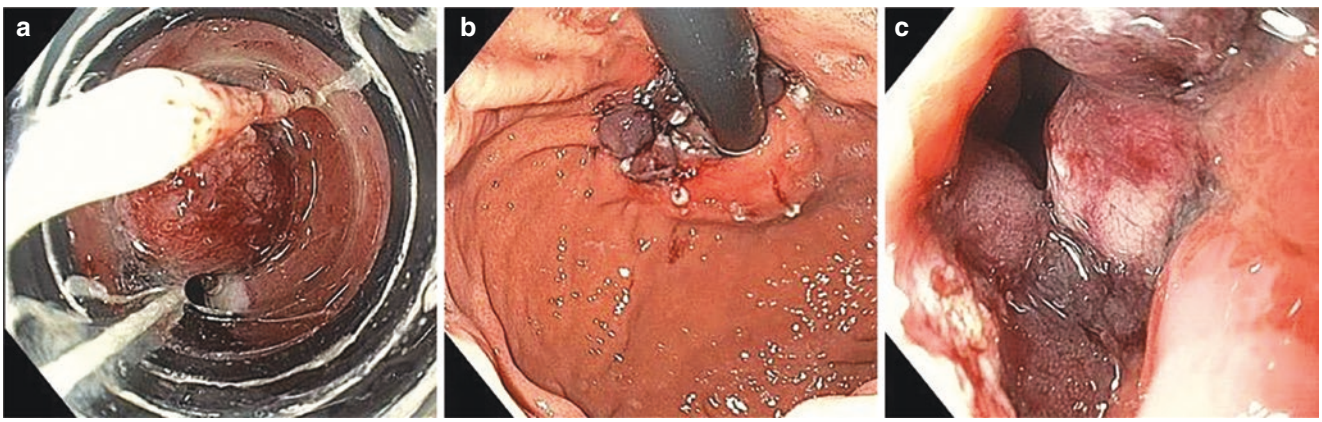

Fig. 9.3 Cardia ligation endoscopic anti-reflux (CLEAR) technique. (**a**) A band is placed to constrict the cardial mucosa. (**b**) Retroflexed view of the cardia with one band in situ. (**c**) Antegrade view of the gastroesophageal junction following placement of two bands

subsequently underwent follow-up endoscopy and pH-impedance monitoring every 3 months for 1 year. If the GEJ was still dilated at follow-up endoscopy, further EBL was performed. The CLEAR-treated patient group showed highly significant improvement in GERD quality of life score, RSI, and number of reflux events without major AEs (including bleeding, post-band ulcers, or stenosis). This clinical trial provides high-quality evidence of the potential for CLEAR as a safe and cost-effective approach for refractory GERD, but results need to be confirmed.

Novel Applications of Endoscopic GEJ Augmentation

ARMS has been reported in treatment of refractory GERD following sleeve gastrectomy in a case series of six patients who were unable to or declined conversion to Roux-en-Y gastric bypass. Debourdeau et al. performed ARMS using band-EMR (or ARMS-b) to resect 270° around the GEJ and demonstrated >50% in GERD-HRQL score in 5 patients (83%). One patient developed a stricture and another had benign bleeding. Although further clinical trials are warranted, endoscopic GEJ augmentation likely has a role in patients with altered anatomy where other endoscopic methods and LARS are limited.

GEJ Augmentation Summary

The above-discussed procedures are promising but limited to patients with minimal or no hiatal hernia and minimal crural defects. Although the original procedure required extensive resection and therefore technical expertise, recent modifications have significantly reduced the requisite endoscopist skillset. Despite this, the lack of procedure standardization limits large-scale outcome assessment. Future research efforts should aim to identify the optimal technique. In addition, stricture formation is a concern which appears to be improved by the "butterfly technique." Nevertheless, further refinements should be made to the procedure to minimize this outcome. These techniques likely have a role in GERD patients with altered anatomy. However, additional research is needed to determine their safety, efficacy, and clinical utility.

Conclusion

Endoscopic therapies are well positioned to fill the gap between medical therapy and more invasive surgical procedures. Although there has been significant progress in endoscopic therapies for GERD, GERD is a spectrum disorder, and it is likely that at this stage endoluminal therapies are most appropriate early in the spectrum. Long-term durability data and comparative studies of not only these techniques but also in relation to LARS are eagerly awaited.

Questions

1. Which of the following patients are appropriate for transoral incisionless fundoplication (TIF)?
   A. A 35-year-old male with heartburn and regurgitation not responsive to proton pump inhibitor (PPI) therapy. Upper endoscopy shows no hiatal hernia, Hill grade 1. Impedance-pH testing off PPI showed esophageal acid exposure time of 2.5%
   B. A 72-year-old female with chronic cough and globus. Upper endoscopy shows a 1 cm hiatal hernia and Hill grade 2. Impedance-pH testing off PPI showed esophageal acid exposure time of 1.8%
   C. A 42-year-old male with chest pain and regurgitation, partially responsive to PPI therapy. Upper endoscopy shows a 3 cm hiatal hernia and Hill grade 2. Impedance-pH testing off PPI shows esophageal acid exposure time of 7.8%
   D. A 60-year-old female with heartburn and regurgitation, responsive to PPI therapy. Upper endoscopy shows a 1 cm hiatal hernia and Hill grade 2. Impedance-pH testing off PPI shows esophageal acid exposure time of 7.2%

Answer: D.

2. All of the following techniques have been used to augment the gastroesophageal junction for treatment of gastroesophageal reflux disease, except:
   A. Mucosal ablation
   B. Endoscopic submucosal dissection
   C. Band ligation
   D. All the above techniques have been used

Answer: D.

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Conflicts of Interest Marcia Canto has received research grants from EndoGastric Solutions, Pentax Medical Corporation, Lucid, Inc., and royalties from UpToDate, Inc. Linda Zhang has no conflicts of interest to report.

Suggested Readings

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EGJ Augmentation

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Understanding the Optimal Gastroesophageal Flap Valve: The Omega Flap Valve

10

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Objectives

1. Recognize the importance of collaboration between GI surgeons and gastroenterologists to move the field of foregut disease to the next level.
2. Understand the importance of the crura and reestablishment of the native gastroesophageal flap valve (GEFV) to create an effective antireflux barrier.
3. Understand the concept of an "omega" flap valve.
4. Recognize the outcome data and geometric limitations of the GEFV constructed by the current total and partial fundoplication techniques.
5. Learn the proposed technical modification of the current fundoplication technique to optimize the construct of the surgical GEFV—the omega fundoplication.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common chronic conditions that can severely affect one's quality of life. GERD is a spectrum of disease that includes esophageal hypersensitivity, delayed gastric emptying, genetic variability, obesity, poor esophageal clearance, and a defective antireflux barrier (Fig. 10.1). Management of GERD consists primarily of the use of proton pump inhibitors and, in a subset of patient with symptoms refractory to medical therapy, the use of some form of endoscopic or laparoscopic antireflux surgery [1]. Goals for most antireflux procedures include reduction of hiatal hernia, reestablishment of the intra-abdominal esophageal length, closure of concomitant hiatus hernia or crura separation, and performance of a partial or total fundoplication. The underlying pathophysiologic mechanisms of the surgical fundoplication are multifactorial. These factors include restoration of the crural function with a hiatal hernia repair, restoration or augmentation of the lower esophageal sphincter (LES) function, and reestablishment of a functioning musculomucosal, gastroesophageal flap valve (GEFV) [2]. In this chapter, we aimed to:

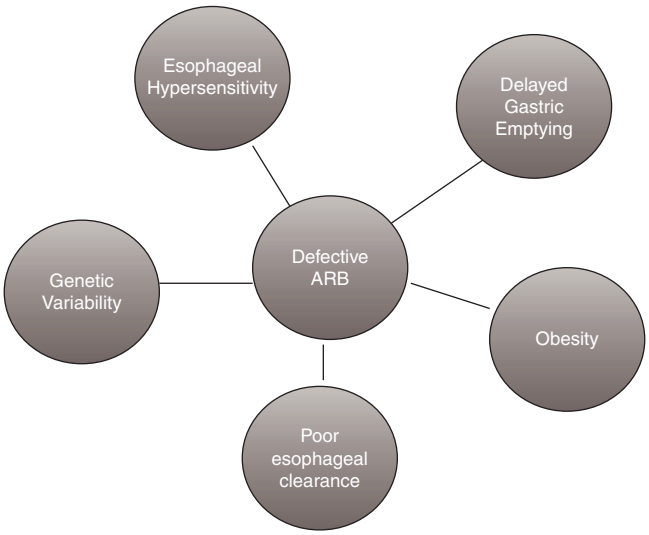

Fig. 10.1 GERD spectrum of the disease

1. Stress the importance of collaboration between gastroenterologists and the gastrointestinal (GI) surgeons for the treatment of GERD.
2. Discuss elements that define an effective and desirable GEFV.
3. Emphasize the importance of the crura, the LES, and the GEFV as components of the antireflux barrier.
4. Understand the concept of the omega flap valve.

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5. Discuss the potential geometric limitations of the GEFV constructed by the current total and partial fundoplication.
6. Learn the proposed technical modification of the current fundoplication technique to optimize the construct of the surgical GEFV.

Collaboration of Gastroenterology and GI Surgery

Management of GERD is a combined effort between the primary care physicians, the gastroenterologists, and the GI surgeons. The GERD management scheme ranges from medical therapy and endoscopic antireflux procedures to surgical fundoplication. One of the most effective endoscopic antireflux procedures that recreate and accentuate the GEFV is the transoral incisionless fundoplication (TIF) [3–4]. Endoscopic TIF is reserved for a small subset of patients presenting with documented GERD but without the presence of a hiatal hernia or crura separation. Therefore, patient selection is key for the primary TIF procedure. Although the TIF procedure is indicated for patients up to 2 cm hiatal hernia, it is critical to address and repair hiatal hernia of any size prior to construction of the new GEFV. Primary endoscopic TIF is best indicated for patients with an endoscopic Hill grade 1 with no hiatal hernia or crura separation observed on an upper GI study. In our practice, a Hill grade 2 is part of a spectrum of GERD and signify the presence of a sliding hiatal hernia with esophageal foreshortening and crura separation. It is important to note that we tend to underestimate the presence of a hiatal defect on preoperative studies. For patients with any size hiatal hernia or crura separation (Hill grades 2–4), current surgical options include a laparoscopic hiatal hernia repair with a total or partial fundoplication.

As one of the most common chronic conditions, the mainstay management scheme for GERD has been through the primary care physicians and the gastroenterologists with the use of medical therapy. For a small subset of patients with refractory symptoms, the gastroenterologist considers performance of the endoscopic TIF, and for a group of patients with hiatal hernia or refractory symptoms to medical therapy, the foregut or GI surgeons will care for the patient with performance of a laparoscopic hiatal hernia repair with a total or partial fundoplication. Different treatments are often managed by different providers accordingly during different phases of treatments. Recently the University of California Irvine (UCI) has championed the combined laparoscopic hiatal hernia repair with TIF performed in the same session otherwise known as concomitant TIF (cTIF) for the treatment of GERD. The cTIF procedure is a collaboration between the GI surgeon performing a laparoscopic hiatal hernia repair and the gastroenterologist performing the TIF procedure sequentially at the same session. Unlike the surgical fundoplication that is performed externally with much less emphasis on the resulting GEFV configuration, the cTIF is unique in that the fundoplication is created endoscopically where the entire emphasis is on forming a symmetrical, near-circumferential GEFV. Therefore, our experience with cTIF collaboration at UCI provides a different perspective and understanding of what constitutes an optimal surgically constructed GEFV. This understanding came about from our collaboration whereby the gastroenterologist learned the importance of the crura contribution to the antireflux barrier from the laparoscopic view and the GI surgeon learned the important elements in endoscopic construction of a GEFV from the endoscopic view. This collaboration has led to our improved understanding of the critical elements in constructing of the optimal GEFV, the geometric limitations of the current total and partial fundoplication, and proposal for modification of the partial fundoplication technique to optimize the construct of the GEFV. We believe that collaboration between specialists is the key to move the field of foregut disease forward.

Concomitant Transoral Incisionless Fundoplication (cTIF)

The cTIF is gaining interest and popularity among gastroenterologists and GI surgeons as an alternative to the current surgical fundoplication. A head-to-head multicenter, randomized clinical trial between cTIF and laparoscopic Nissen fundoplication is currently underway. With the progression of GERD and as the hiatus widens, the angle of His also widens and becomes obtuse as the gastroesophageal junction intermittently or permanently herniates into the mediastinum. With cTIF, the hiatal hernia is repaired laparoscopically with esophageal mobilization to increase the intra-abdominal esophageal segment and crura closure, followed with construction of a new GEFV using the TIF device. This newly constructed 270° musculomucosal flap valve is 2–4 cm in length and is formed by wrapping the gastric cardia in a 270° fashion around the distal esophagus while leaving an area of opening along the right lateral aspect of the distal esophagus and gastroesophageal junction. This open area serves as a "backstop" plate to oppose and receive the newly constructed GEFV. Figure 10.2 shows (a) the endoscopic retroflex view of a Hill grade 4 flap valve, (b) the endoscopic view after laparoscopic hiatal hernia repair with esophageal lengthening and recreation of the native musculomucosal GEFV, and (c) the newly constructed 270° GEFV that is 2–3 cm in length. Understanding the concept of the GEFV constructed by cTIF has improved our conceptualization of the optimal antireflux valve and provided a crucial understanding of the geometric limitations of the surgical

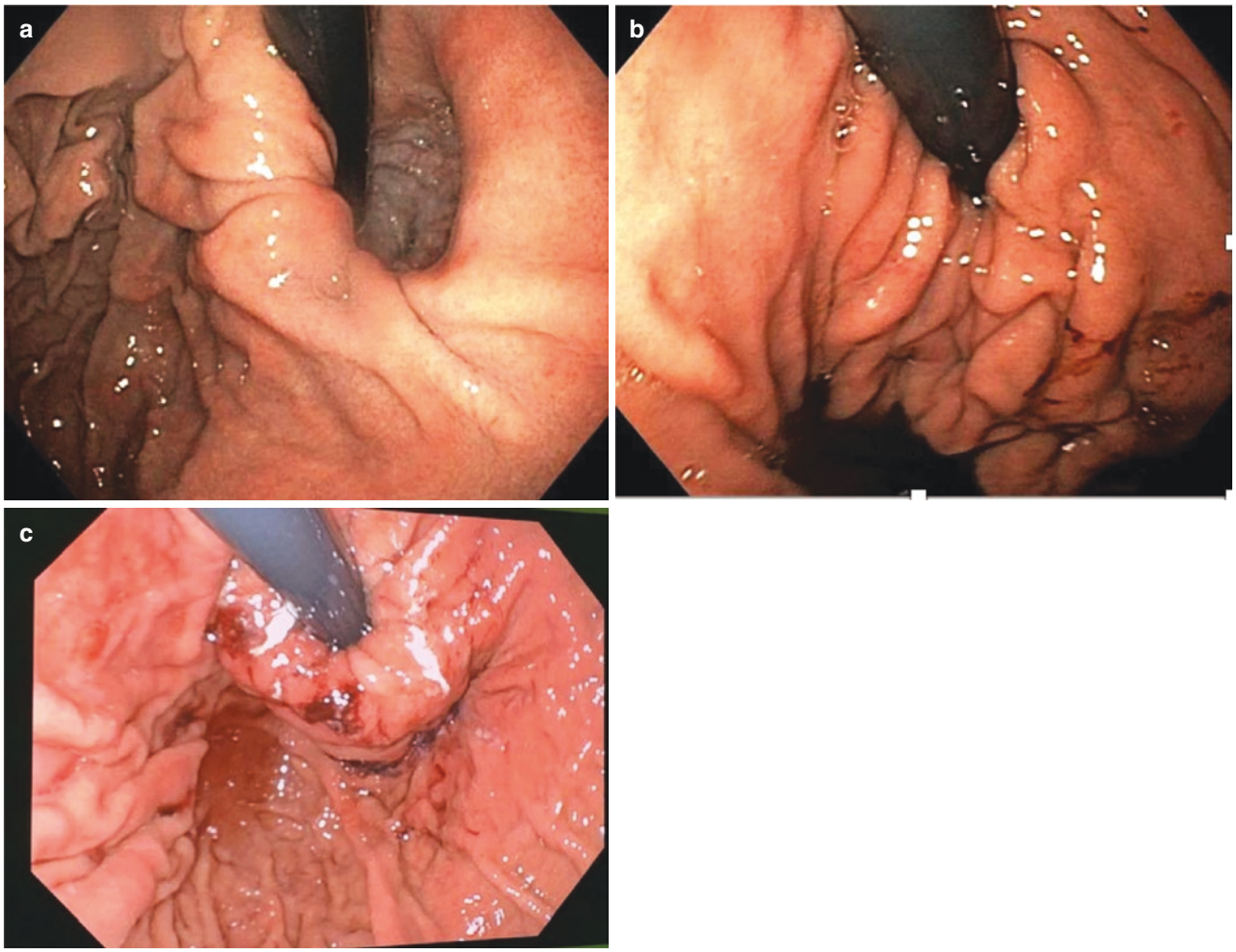

Fig. 10.2 Endoscopic view showing (**a**) a defective GEFV (Hill grade 4), (**b**) endoscopic view of the GEFV after laparoscopic hiatal crural repair, and (**c**) a newly constructed 270° GEFV after cTIF

GEFV created by the current fundoplication techniques. In a recent study from the University of California Irvine on the short-term outcomes of cTIF, the authors reported technical success in all 60 patients who underwent cTIF [5]. The GERD health-related quality of life index significantly decreased from 23.3 at baseline to 7.4, and regurgitation was reduced from 14.3 at baseline to 0 at follow-up. Additionally, the reflux symptom index similarly decreased from 17.7 at baseline to 8.1 at follow-up.

The Optimal Antireflux Valve

The optimal antireflux barrier should be similar to the native GEFV that is formed from opposition of the gastric cardia and the distal esophagus at the angle of His, resulting in a musculomucosal flap or fold. This native fold is approximately 1–2 cm in length and 180° in circumference. This naturally occurring musculomucosal fold acts as a flap valve that closes against the backstop area along the right lateral aspect of the distal esophagus and gastric cardia to prevent reflux. As GI contents enter the stomach, the intraluminal pressure exerts forces that act upon the musculomucosal GEFV that serves to close the valve against the backstop region of the distal esophagus [6–8]. This naturally occurring valve, however, deteriorates over time. This deterioration in combination with crura separation, foreshortening of the esophagus, and development of a hiatal hernia leads to a defective GEFV and varying degree of reflux disease. Dysfunction of this mechanical antireflux barrier is considered to be the main cause of GERD. When this happens, procedures such as cTIF repair the hiatal hernia, lengthen the intra-abdominal esophageal segment, and reconstruct a new GEFV. In an effort to understand the optimal antireflux valve, it is important to understand the endoscopic nomenclature in assessment of the GEFV. In a study examining the endoscopic gastroesophageal valve after antireflux surgery, Jobe B and colleagues reported important endoscopic characteris-

tics in assessment of the GEFV to include the presence of prominent anterior and posterior grooves, the presence of an omega shape valve, and a lengthy body of the valve [9]. The authors suggested a link between the valve appearance and the overall function of the antireflux barrier. Lastly, it is important to note that the native GEFV function as a "one-way" valve based on the geometric mechanism of the musculomucosal fold without external forces exerting on the backstop area of the right lateral aspect of the distal esophagus.

Understanding the Omega Gastroesophageal Flap Valve

The valve constructed during cTIF is a 270° near-circumferential wrap of the gastric cardia around the distal esophagus, creating a musculomucosal flap valve that is 2–4 cm in length using through-and-through, double-sided T tags (Fig. 10.2c). The only esophageal area that is not covered by the wrap is along the right lateral aspect of the distal esophagus and gastric cardia. In essence, cTIF fundoplication replicates and accentuates the native GEFV. Therefore, this newly constructed GEFV formed by cTIF has all of the above-listed characteristics and resembles the omega sign configuration (Fig. 10.3a). The omega configuration consists of approximately 270° semicircle that ends in a flat backstop (Fig. 10.3b). An important point to note is that the omega configuration must be positioned specifically in a direction from the left side wrapping toward the right side. This contrasts with the current fundoplication technique whereby the wrap is start posteriorly and wrap anteriorly. The omega configuration is what we believe should be achieved in construction of an optimal surgical GEFV. In a three-dimensional view, this flap valve looks like a series of consecutive omega signs, hence creating a tubular 270° flap valve that we have coined the "omega flap valve" (Fig. 10.3c). The omega flap valve is characterized by prominent anterior and posterior grooves which represents accentuation grooves of the GEFV. The length of the valve is another important factor to improve the efficacy of the antireflux barrier, with an optimal length ranging between 2 and 4 cm, with longer lengths resulting in better reflux control. This concept of omega flap valve is important to reinforce the principles for (1) the need for esophageal lengthening to obtain at least 2–3 cm of intra-abdominal esophageal in an effort to reestablish the GEFV, (2) which region of the esophagus and gastric cardia need to be used for the fundoplication, and (3) which region should be voided of any fundoplication. Understanding these principles will also lead to an understanding of the geometric limitations of the current surgical fundoplication techniques.

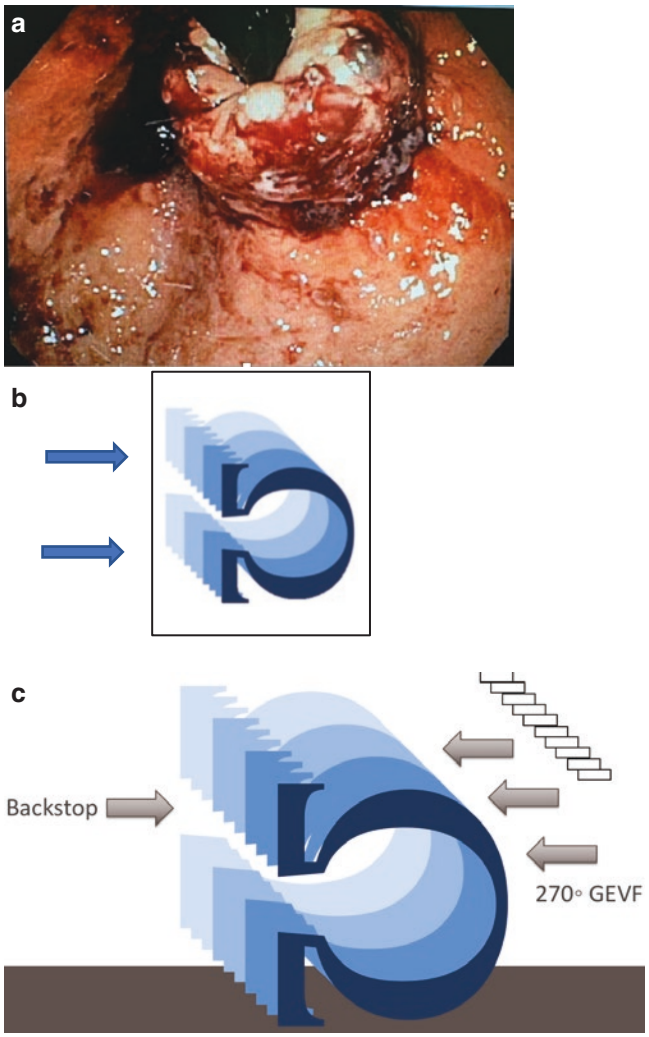

Fig. 10.3 Concept of an omega flap valve (**a**) with an endoscopic view of the newly constructed GEFV after cTIF, (**b**) resembling the GEFV configuration of an omega sign that can oppose against the backstop (blue arrow), and (**c**) consecutive omega signs to demonstrate a three-dimensional view of a 270° circumferential flap valve otherwise referred to as the omega flap valve

Understanding the Outcome and Geometric Limitations of the Surgical Fundoplication Techniques

There are many surgical fundoplication techniques that have been described in the literature. Surgical fundoplication can be divided into either total or partial fundoplication. All current fundoplication procedures including cTIF produce variations of the GEFV. Total fundoplication represents the Nissen fundoplication which is a 360° wrap. However, there are many variations of the Nissen technique, including division of the short gastric vessels or not, but more importantly, which part of the gastric fundus is used to perform the wrap. With regard to the partial fundoplication, there are many

described procedures including the Toupet (270° posterior), the Watson (120° anterolateral), the Lind procedure (300° posterior), and the Dor (180° anterior) fundoplication. A comparison in the outcome for these operations was best summarized by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines for surgical treatment of GERD published in 2010 [10]. In this original guideline, the view of the antireflux barrier included the LES, diaphragmatic crura, and the phrenoesophageal ligament. The recommendations from this guideline state that surgical therapy for GERD is an equally effective alternative to medical therapy and should be offered to appropriately elected patients. With regard to the type of fundoplication, partial fundoplication was found to be associated with less postoperative dysphagia with similar patient satisfaction and effectiveness in controlling GERD compared with total fundoplication up to 5 years. The guideline also noted that anterior partial fundoplication may be less effective in the long term compared to Toupet fundoplication. In 2021, SAGES published another guideline on the surgical treatment of GERD based on 105 reviewed studies [11]. In this latest guideline, it was noted that the mechanism of antireflux surgery was to augment the LES to prevent abnormal reflux of gastric contents into the esophagus. In this latest version, there were no mentions on the role of the crura of the diaphragm or the GEFV as a mechanism for antireflux barrier. There were 4 key questions addressed, and one of the questions was complete versus partial fundoplication which was reviewed based on 26 randomized controlled trials and 17 cohort studies. On pooled analysis, patients who underwent partial fundoplication had lower risk of long-term dysphagia than patients who underwent complete fundoplication. There was no significant difference between groups for short- or long-term symptom control or quality of life. However, prolonged proton pump inhibitor (PPI) use was higher in patients who underwent partial fundoplication. With regard to clinical practice, the guideline suggests that surgeons may discuss the risk for dysphagia with complete fundoplication and address the patient's preferences and trade-offs with regard to PPI usage versus dysphagia symptoms. Based on these data, it appears that we cannot have our cake and eat it too. Achieving optimal GERD control will be adversely affected by side effects such as dysphagia and gas bloat symptoms. Therefore, it is important to evaluate the fundoplication techniques that were used in these trials. Based on our experience with cTIF and learning the geometry of the GEFV, we believes that alteration in surgical technique of the partial fundoplication can be done to accentuate the geometry of the GEFV to maximizing the efficacy of GERD control while minimizing the side effects of the total fundoplication.

The goals of the total and partial fundoplication include increasing the intra-abdominal esophageal length (3 cm), hiatal crural closure, and the construction of a 2–3 cm wrap to augment the LES competency and formation of some form of a GEFV. These fundoplications are performed based solely on the laparoscopic view, and the resulting GEFV after surgical fundoplication is not commonly reviewed or critically analyzed. Based on our experience in constructing the GEFV with cTIF, we have begun to understand and recognize the limitations of the GEFV constructed by the current surgical fundoplication techniques. Figure 10.4 shows the transverse anatomic plane depicting the GEFV formed by the three commonly performed fundoplication techniques in contrast with the omega configuration constructed by the cTIF. In the Nissen fundoplication, the technique most commonly used is to swing the anterior wall of the gastric fundus greater curvature under and around the retroesophageal space, perform the "shoeshine" maneuver, and place three anterior plication sutures to complete the wrap (Fig. 10.4a). This technique is often called the Rossetti-Nissen technique which is different than the wrap performed in cTIF, and therefore the resulting GEFV of the Nissen is also quite different. The GEFV created by the Nissen is looser, is floppier, and often contains transverse gastric folds (Fig. 10.5a). These transverse gastric folds are classic sign of a Rossetti-Nissen and mentioned within Jobe B and colleagues' publication as "stacked coils" along the body of the valve [9]. Conversely, the GEFV constructed by cTIF appears uniformly snug but without the presence of transverse gastric folds as observed on endoscopic view. Additionally, the main criticism in the technique of the Nissen is a 360° wrap which by definition exerts external pressure upon the "backstop" region along the right lateral aspect of the distal esophagus and the gastric cardia. We hypothesize that the additional external pressure specifically along the backstop region created from the Nissen fundoplication likely contribute to the higher dysphagia symptoms and reduced ability to physiologically vent the stomach. Additionally, if there is a hiatal recurrence after a Nissen in the future, that can lead to changes in the geometry of the transverse gastric folds which contributes to the late dysphagia symptoms (Fig. 10.5b). Alternatively, some surgeons perform the Nissen fundoplication with a different surgical technique by using the anterior and posterior gastric wall to construct the wrap rather than only the anterior wall of the gastric fundus (Nissen-Rossetti) [12]. This approach actually bears a closer resemblance to the cTIF procedure used in construction of the omega flap valve. The Toupet partial fundoplication is limited with regard to the geometric formation of the omega GEFV valve (approximately 180° of the 270° valve). These deficiencies are related to the location of the 90° open area being anteriorly on the esophagus anteriorly, while a portion of the fundoplication exerts unnecessary external pressure along the backstop region on the right aspect of the distal esophagus (Fig. 10.4b). The Toupet fundoplication also limits the for-

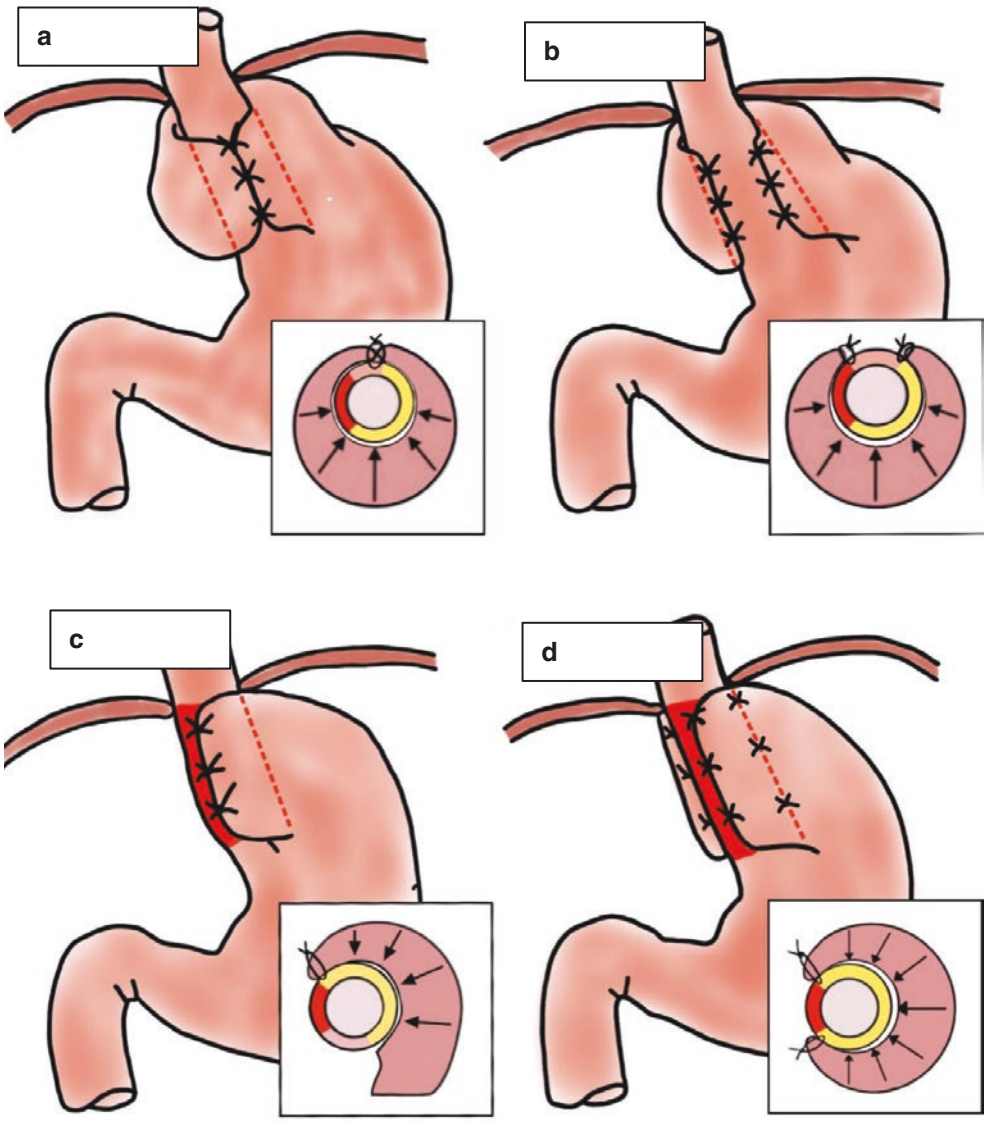

Fig. 10.4 Transverse plane view depicting the anatomic configuration of the (**a**) Nissen fundoplication, (**b**) Toupet fundoplication, (**c**) Dor anterior fundoplication, and (**d**) omega configuration as constructed by cTIF. The red area represents the distal esophagus region that acts as a backstop to appose against the newly constructed GEFV. The yellow area represents the region of the distal esophagus with formation in varying degree of the GEFV. The arrow represents intraluminal pressure exerting forces upon GEFV and the distal esophagus with a goal to avoid external forces acting upon the backstop region (red area)

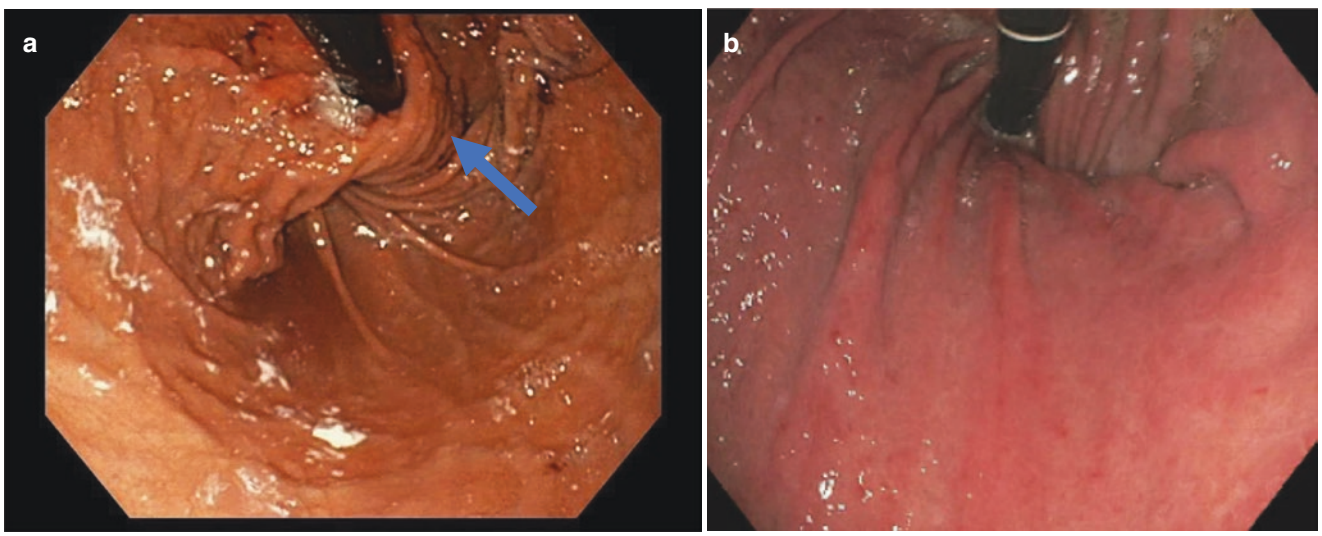

Fig. 10.5 (**a**) Endoscopic view of the Nissen fundoplication showing transverse folds (arrows) observed after construction of a Rossetti-Nissen fundoplication, (**b**) endoscopic view of a Nissen fundoplication showing a herniation of the wrap with the loss of the GEFV, change of geometry and orientation of the transverse gastric folds that impinges on the esophageal lumen

mation of a posterior groove. The anterior Dor fundoplication and the Watson fundoplication are both similarly limited by only forming approximately 180° of the potential 270° omega GEFV valve (Fig. 10.4c) but fail to form the posterior grooves. Lastly, the optimal omega flap valve as constructed by cTIF is a fully formed 270° GEFV with intraluminal pressure exerting forces in the ideal manner, to push the GEFV against the distal esophagus backstop plate without any opposing external pressure acting against the valve (Fig. 10.4d). Important characteristics of the omega flap valve are distinct anterior and posterior grooves in the presence of an omega shape valve.

Proposal of the Omega Fundoplication

With cTIF, many surgeons have raised the question: since a laparoscopic hiatal hernia repair is required, why not continue to perform a laparoscopic partial fundoplication instead of the TIF procedure? The answer is that such a feat would be possible as long as we can reliably perform a laparoscopic fundoplication that replicates the principles set forth in construction of an omega flap valve similar to that formed by the TIF procedure. Currently, none of the current fundoplication configurations (Nissen, Watson, Dor, and Toupet) replicate the construction of the omega flap valve observed in the cTIF procedure. To replicate construction of the omega flap valve using laparoscopic technique, all surgical principles need to be adhered to including the need to restore intra-abdominal esophageal length and snug hiatal crura closure. With respect to the fundoplication technique, we describe technical modification of the current partial fundoplication technique to achieve maximal construct of the 270° omega valve while avoiding wrapping of the backstop region in an effort to avoid external pressure on this region [13]. It is important to understand that the proposed technique is not meant to be a new fundoplication operation but truly a modification of the existing partial fundoplication to achieve the principles of an optimal GEFV. We called this modification technique the "omega fundoplication" as we wanted to emphasize that the technique will focus to achieve the principles of an omega flap valve. The omega fundoplication is a partial 300° fundoplication using the anterior and posterior wall of the gastric fundus to wrap the distal esophagus starting at the 3 o'clock position. The technique begins first with the posterior wrap that is sutured to the right crura of the diaphragm and the right lateral border of the esophagus. A total of three sutures are placed for fixation (Fig. 10.6a). Next, the gastric cardia is elevated and sutured to the left border of the distal esophagus to the left crura of the diaphragm to recreate the angle of His (Fig. 10.6b). Lastly, the anterior wrap is formed using the anterior gastric wall to perform the wrap similar to that of the Dor or Watson fundoplication with three fixation sutures

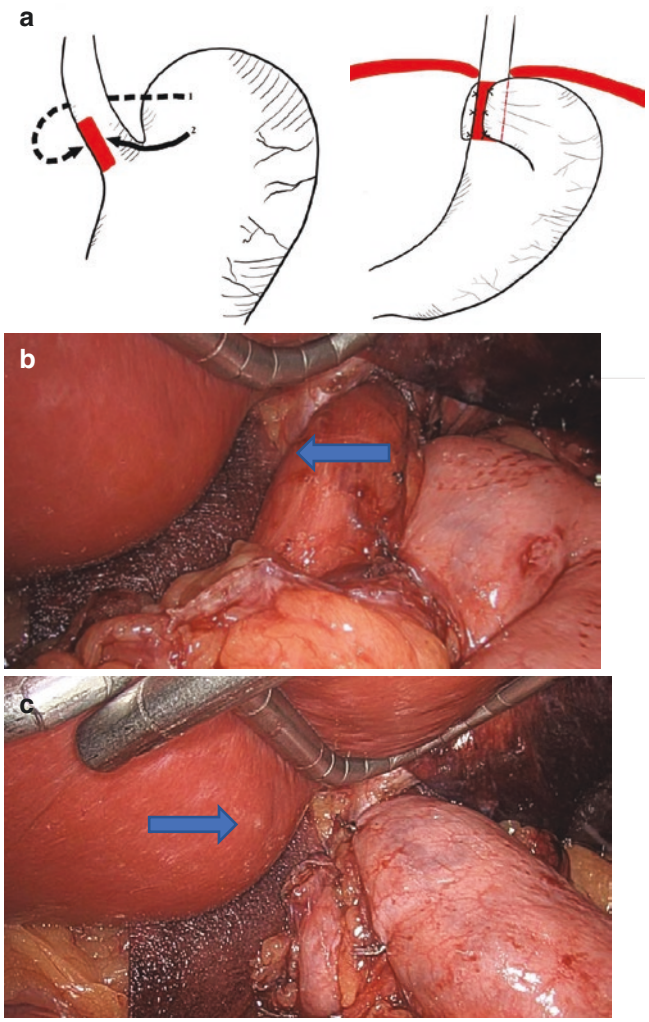

Fig. 10.6 The omega fundoplication: (**a**) drawing showing the location of gastric cardia used to perform the wrap starting at the 3 o'clock position in a reverse C fashion resulting in a 300° wrap with an open area along the backstop plate (red area), (**b**) laparoscopic view showing sutures placed to reestablish the acute angle of His (arrow), and (**c**) laparoscopic view of the omega fundoplication showing a 300° wrap with a 60° open area positioned at 9 o'clock along the lesser curvature aspect of the distal esophagus (right side) and gastric cardia (arrow)

starting on the superior aspect of the right crus. Additional fixing between the wrap and the crura anteriorly is performed. In summary of the technique, this is a gastric cardia wrap that begun at the 3 o'clock position and wraps the distal esophagus 150° anteriorly and 150° posteriorly in a reverse C fashion, leaving approximately a 60° area of the lesser curvature of the distal esophagus/gastric cardia region open (Fig. 10.6c). Unlike conventional fundoplication technique, there are more plication sutures used to construct the valve and secure the valve to the left and right crura in an effort to minimize acute and late herniation of the valve. Endoscopically, this modified partial fundoplication technique creates a symmetrical omega flap valve that is similar

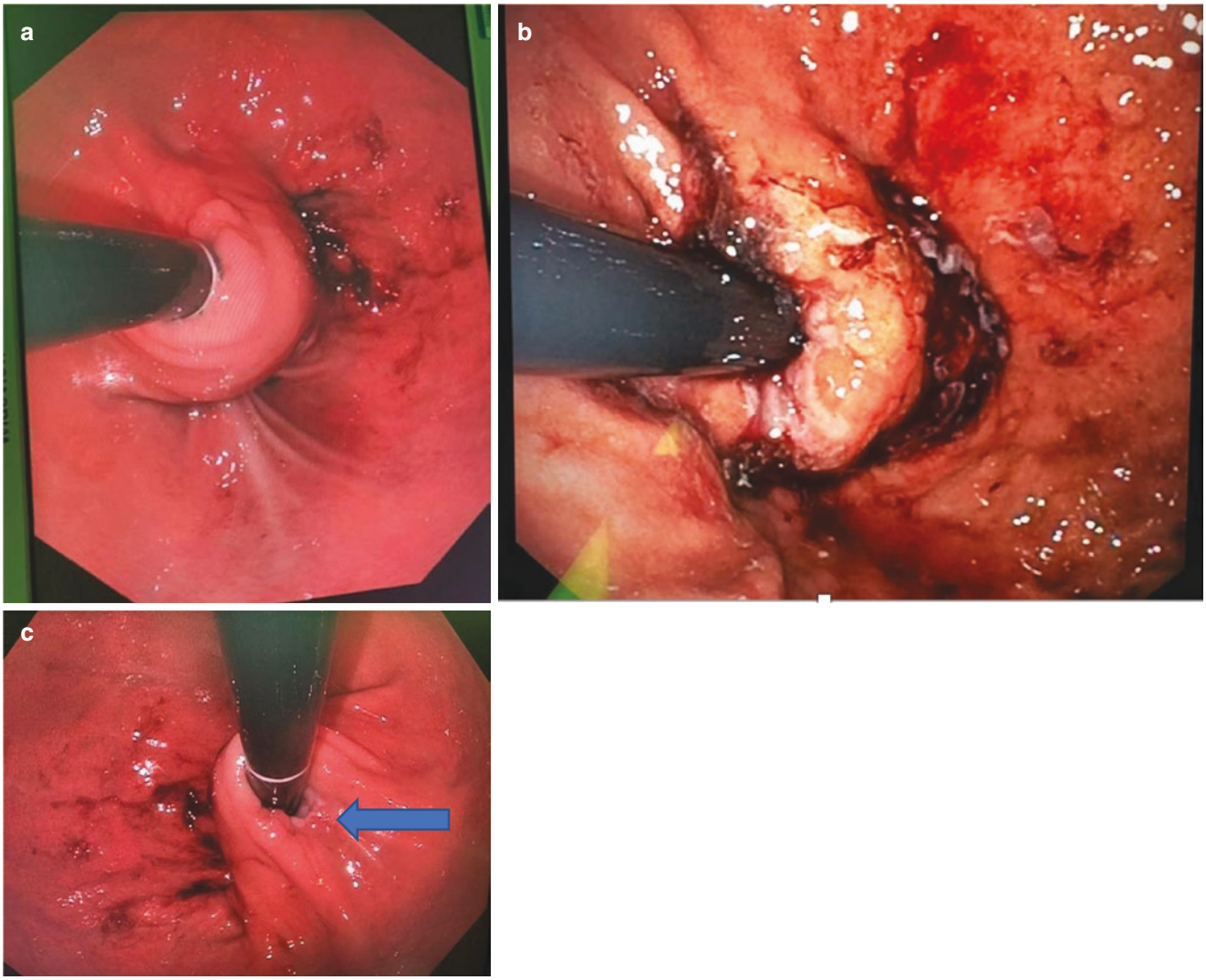

Fig. 10.7 (**a**) Endoscopic view of the laparoscopic omega fundoplication showing a newly constructed GEFV similar in configuration to the omega valve constructed by cTIF, (**b**) endoscopic view of the omega valve constructed by cTIF, (**c**) endoscopic view of the omega fundoplication showing the open backstop plate along the lesser curvature aspect of the distal esophagus and cardia (arrow) without the issue of external pressure acting upon this region

in geometry to that created by the cTIF procedure (Fig. 10.7a–c).

Again, it is important to reemphasize the two important technical differences of the omega fundoplication vs. current fundoplication techniques. Toupet and Nissen fundoplications are posterior wraps that are oriented toward the 11 or 12 o'clock position. The first key point for omega fundoplication is that it is a partial fundoplication with attention to formation of the wrap starting at the 3 o'clock position with formation of the wrap in a reverse C fashion. This reconfiguration will maximize the formation of the omega valve. The second key point is the omega fundoplication is a partial fundoplication with an open area specifically positioned at the right lateral aspect of the distal esophagus. By having this area open, it avoids external pressure on this area which would act to oppose the forces achieved from the GEFV and therefore minimize the issue of dysphagia symptoms. Both of these principles can be observed on endoscopic examination of the newly constructed GEFV which reflects (a) an omega shape valve and (b) gap between the backstop plate and the endoscope which represents looseness in this region which likely is important to minimize dysphagia and allow the stomach to vent.

Conclusion

Collaboration between a GI surgeon and a gastroenterologist has led to new perspectives on the optimal surgically constructed GEFV. We describe the concept of constructing an omega flap valve during cTIF that can oppose against a distal esophagus backstop to provide an optimal antireflux barrier. Experience and understanding of the omega flap valve has led us to alter our current laparoscopic fundoplication technique in an effort to achieve the desirable principles of the omega flap valve. We have termed this new laparoscopic fundoplication technique the "omega fundoplication."

Questions

1. Which of the following patients would be an appropriate candidate for a primary transoral incisionless fundoplication?
   A. Patient with Hill grade 2 with a 2.5 cm vertical length hiatal hernia
   B. Patient with Hill grade 3
   C. Patient with Hill grade 1 and no evidence of a hiatal hernia
   D. Patient with Hill grade 4

Answer: C. Although the TIF procedure is indicated for patients up to 2 cm hiatal hernia, it is critical to address and repair hiatal hernia of any size prior to construction of the new GEFV. Primary endoscopic TIF is best indicated for patients with an endoscopic Hill grade 1 with no hiatal hernia or crura separation observed on an upper GI study.

2. What are documented adverse effects of a complete fundoplication compared to a partial fundoplication?
   A. Prolonged usage of protein pump inhibitor
   B. Dysphagia and gas bloat
   C. Higher rates of reoperation
   D. Increased rates of regurgitation

Answer: B. Total fundoplication represents the Nissen fundoplication. Partial fundoplication includes the Toupet (270°posterior), the Watson (120° anterolateral), the Lind procedure (300° posterior), and the Dor (180° anterior) fundoplication. Total fundoplication is associated with higher postoperative dysphagia and gas bloat symptoms, while partial fundoplication is associated with higher rate of prolonged usage of protein pump inhibitor at late follow-up.

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Laparoscopic Fundoplication

11

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Objectives

1. Know that gastroesophageal reflux disease (GERD) is an abnormal esophageal exposure to acid and other gastric contents caused by dysfunction of the antireflux barrier.
2. Understand that careful selection of patients for laparoscopic fundoplication (LF) based on symptoms, response to medical therapy, and preoperative testing can increase the chances for effective and durable postoperative control of symptoms.
3. A clinical history of GERD mandates preoperative studies for operative planning including pH monitoring, high-resolution esophageal manometry (HRM), upper endoscopy, and esophagram.
4. Understanding the correct construction of a LF is the key to an operation that controls GERD and reduces the risk of postoperative complications.

Introduction

GERD results from incompetency or dysfunction of the lower esophageal sphincter (LES). Depending on the definition, it affects 18%–28% of people in North America, and its prevalence is increasing [1]. The impact and global burden of GERD on healthcare systems is significant.

While proton pump inhibitor (PPI) therapy is the mainstay for treating GERD, it is not effective for the most severe cases. Antireflux surgery is indicated when there is incomplete response to lifestyle modifications and appropriate medical treatment, resulting in poor quality of life or other complications. Fundoplication is the standard surgical treatment for GERD, and since the advent of the laparoscopic approach in 1991 [2], the Nissen fundoplication is the most common antireflux procedure.

Indications and Workup

Patients with a lack of symptom control with medical therapy and/or complications from GERD justify accepting the risk of fundoplication. The spectrum of GERD is broad. Patients with heartburn and regurgitation are usually straightforward to assess, but those with airway/respiratory symptoms and disease (cough, hoarseness, asthma, and interstitial lung diseases) are more complicated.

It is imperative to perform complete diagnostic testing to obtain objective evidence of abnormal gastroesophageal reflux before considering surgical management. According to the ICARUS guidelines [3], pH monitoring and HRM are mandatory prior to referral for antireflux surgery. pH monitoring, done off medical therapy assesses distal esophageal pH over a period of 24–48 h is the gold standard for quantifying GERD. HRM is an important component before any antireflux procedure because it can reveal or rule out a severe motility disorder, such as achalasia, while evaluating the LES [4]. Other helpful tests to understand anatomy are esophagogastroduodenoscopy (EGD) and upper gastrointestinal series (UGI). EGD evaluates for esophageal injury and Barrett's esophagus secondary to GERD while excluding malignant pathology and allows evaluation for the presence of hiatal hernia (HH). UGI provides detailed information about gastroesophageal anatomy and abnormalities such as HH, stricture, diverticula, motility, or tumors [5]. These studies are often complimentary, but an EGD may suffice, especially if performed by the operating surgeon.

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Physiology of Surgical Fundoplication: How Does it Work?

The pathogenesis of GERD involves an incompetent antireflux barrier. Esophageal contraction, gastric cardia sling fibers, diaphragmatic crus, and intra-abdominal position of the LES complex all contribute to proper LES function [5]. Thus, the pathogenesis of GERD is usually defined as a mixture of reduced pressure of the LES, HH, transient relaxation of the LES, and impaired esophageal peristalsis [6]. A fundoplication creates a flap valve mechanism at and around the gastroesophageal junction (GEJ) to improve competency of the LES and reduce reflux. In fact, a proper procedure should place the GEJ and fundoplication below the diaphragm, restore the diaphragmatic pinchcock (with HH repair), and create a grade I Hill valve. Laparoscopic Nissen fundoplication is a 360° fundoplication that plicates the stomach to the esophagus to strengthen the EGJ valve [7]. The partial laparoscopic fundoplication techniques include a 270° posterior (Toupet) fundoplication sutured to the crura and esophagus which creates a flap valve while leaving the anterior esophagus exposed to allow for radial expansion and a 180° anterior (Dor) fundoplication sutured to the esophagus and right crus which restores the angle of His and creates a flap valve mechanism [7].

While it is often assumed that a fundoplication recreates the valve function by increasing LES pressure (LESP), this is not the correct way to think about it even though LESP does go up after fundoplication. In a study by Herbella et al. [8], HRM showed that the LESP increased significantly after the operation, thereby reestablishing an effective barrier to reflux. This, however, does not tell the whole story. It is instructive to look at the LESP profiles of a Nissen and partial fundoplication. Scheffer and colleagues [9] performed HRM studies on GERD patients before and after Nissen fundoplication to evaluate the characteristics of the LES. They found that after the complete fundoplication, the LESP profile was generally longer and higher during transient relaxations, impeding the flow of gastric contents toward the esophagus. Comparing the pressure profiles between Nissen and partial fundoplication, they demonstrated that the LESP was markedly elevated after total fundoplication, but only minimally increased after the partial procedure [10]. Despite the difference in postsurgical LESP, Nissen and partial fundoplication have similar control of GERD (at least in the short term). Conversely, a Nissen causes more dysphagia, bloating, and inability to belch than a partial (again, at least in the short term). Ideally, the intent should be to create a long-term flap valve that maximally prevents reflux with minimal increase in LESP and obstruction.

Brief History of Fundoplication

The concept of gastroesophageal reflux as a functional physiologic disorder due to anatomic abnormalities can be traced to sentinel works by Philip Allison and Norman Barrett in the 1950s. Allison believed that the crural sling acted as a "pinchcock" to prevent gastroesophageal reflux. In 1951, he published his initial case series describing the transthoracic approach to reduction of hernia contents, intra-abdominal gastric fixation, and posterior cruroplasty. Barrett believed in the importance of the cardiophrenic angle of His as the key factor in the prevention of reflux. He suggested that a normal cardiophrenic angle created a mucosal flap valve that was critical to the antireflux mechanism of the gastroesophageal junction. These two principles subsequently provided the basis for the "two-sphincter" understanding of the antireflux mechanism and ushered in the modern era of HH and antireflux surgery [11].

In 1936, Rudolph Nissen treated a patient with a perforated distal esophageal ulcer with a transthoracic distal esophageal resection and primary end-esophagus to side-gastric anastomosis in a Witzel fashion. He later observed that the patients' reflux symptoms resolved. In 1956, Nissen published his seminal paper describing his first two cases of transabdominal "gastroplication" for the treatment of reflux. His procedure included esophageal mobilization and a posterior 360° wrap of the anterior and posterior fundus around the distal esophagus using interrupted sutures over a length of 6 cm [12].

High rates of postoperative dysphagia led to numerous modifications of the Nissen over time. In 1962 Dor described his 180° anterior fundoplication, and in 1963 Toupet published his 270° posterior fundoplication. Rossetti modified the Nissen fundoplication to include only the anterior wall of the gastric fundus. DeMeester and Donahue further modified the Nissen with routine takedown of the short gastric vessels with creation of a "short floppy" Nissen over a length of 1–2 cm, furthering decreasing postoperative dysphagia and gas-bloat symptoms [12].

Technique

Patient's Position

For most surgeons, the patient is placed supine split-leg or modified lithotomy position with care taken to pad the peroneal nerves to prevent compression. Intermittent pneumatic compression boots are placed for deep vein thrombosis prophylaxis. A footboard (supine) or thigh straps (lithotomy/

split leg) should be used to prevent patient movement when placed in steep reverse Trendelenburg position. Foley catheter is generally not necessary. The surgeon stands between the patient's legs, and the assistant stands on the patient's left.

Port Placement

Pneumoperitoneum is obtained with a Veress needle in the left subcostal position (Palmer's point). The first trocar is then inserted in the same location with an 11 mm optical trocar. The camera port is placed 10 cm below the costal margin and 2 cm to the left of midline. A subxiphoid 5 mm port is placed for a Nathanson liver retractor to allow adequate exposure of the esophageal hiatus. Additional 5 mm ports are placed for the surgeon's left hand in the right upper quadrant and the assistant in the left lateral abdomen.

Esophageal Mobilization

The gastrohepatic ligament is incised, and the right crus of the diaphragm is exposed (Fig. 11.1a). The areolar plane between the right crus and hiatal hernia sac or esophagus is identified and entered bluntly (Fig. 11.1b). This plane is opened anteriorly and posteriorly toward the crural decussation. The esophagus is mobilized, and the right pleura and posterior vagus nerve are identified and protected. The phrenoesophageal ligament is divided, and the anterior esophagus is mobilized toward the left crus with care taken to identify and preserve the anterior vagus nerve. The left crus is identified and bluntly separated from hernia sac or esophagus down to the junction with the right crus (Fig. 11.2). Alternatively, the phrenogastric ligament and short gastrics may be divided first, and the hiatus approached from the left. A Penrose drain is then used to encircle the GEJ for retraction. The esophagus is then bluntly mobilized from mediastinal attachments until at least 3 cm of intra-abdominal esophageal length is achieved (Fig. 11.3).

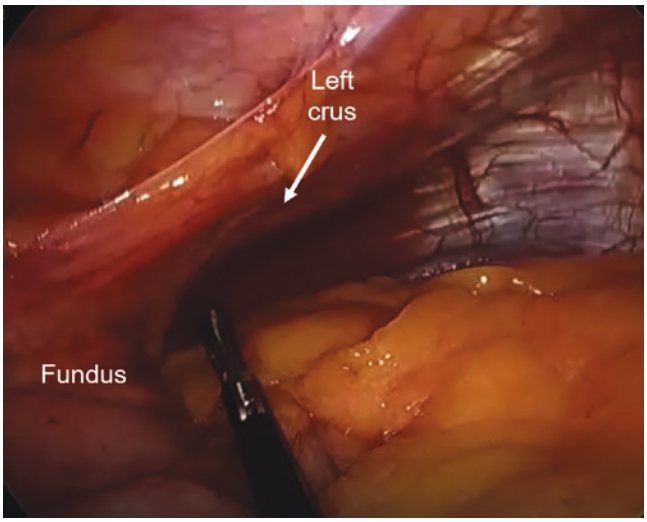

Fig. 11.2 Dissection of the left phrenoesophageal membrane

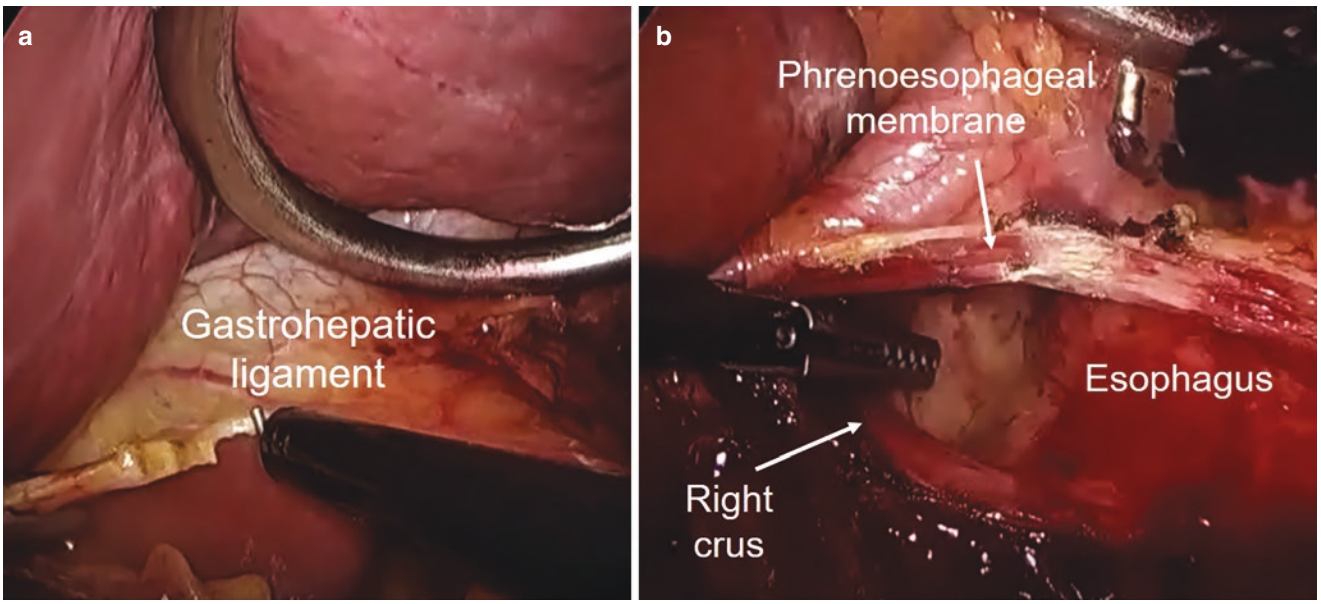

Fig. 11.1 (**a**) Division of the gastrohepatic ligament using the cautery; (**b**) incision of the peritoneal attachments along the right crus

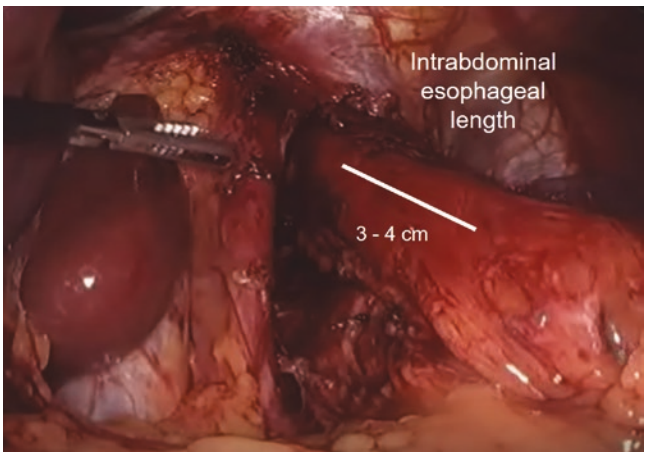

Fig. 11.3 Mobilization of the esophagus to achieve at least 3–4 cm of intra-abdominal esophageal length

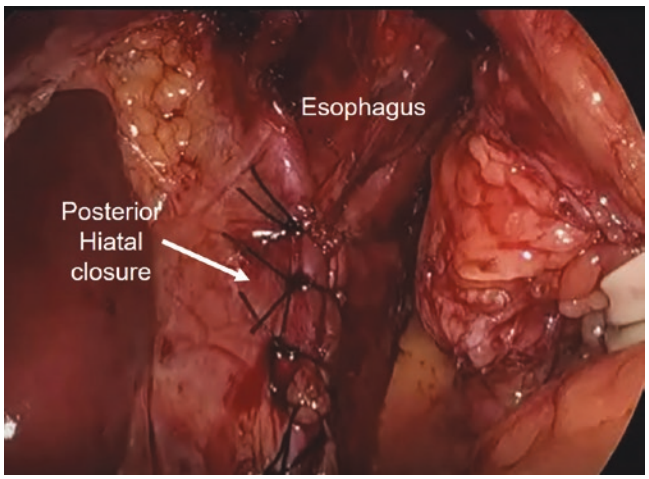

Fig. 11.4 Posterior cruroplasty. The sutures should start at the junction of the right and left crural pillars posteriorly

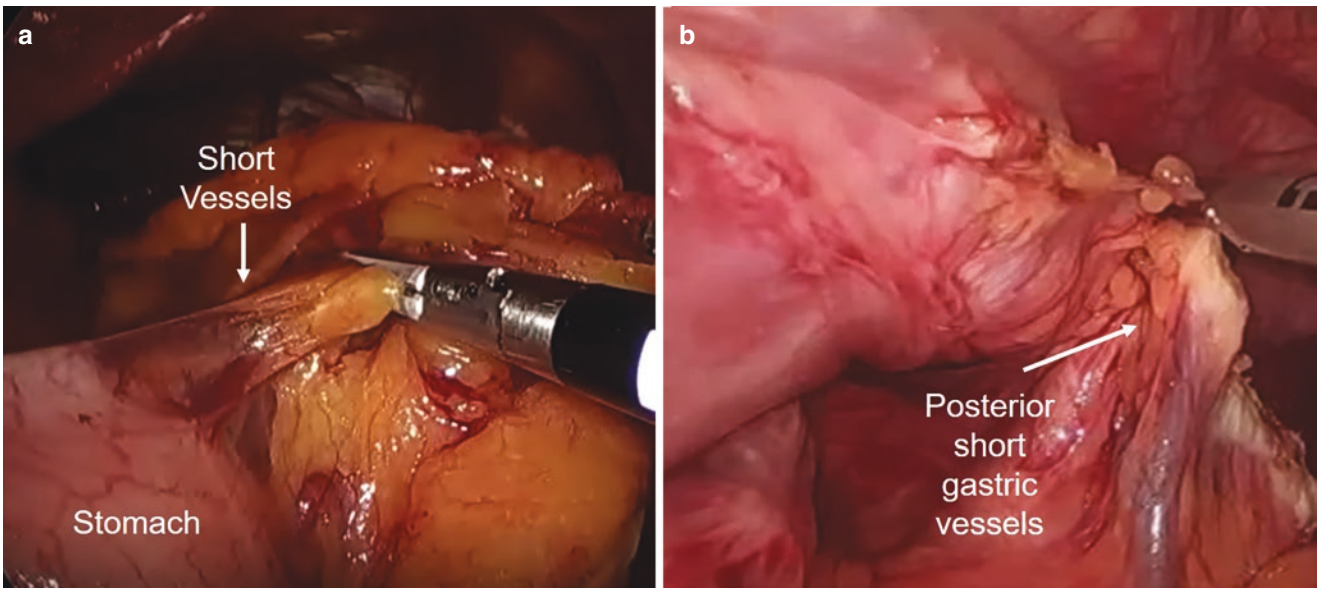

Fig. 11.5 (**a**) Division of the short gastrics close to the greater curvature of the stomach. (**b**) The posterior short gastrics should be divided to free the fundus

Cruroplasty

With the esophagus retracted anteriorly, a posterior cruroplasty is performed with interrupted permanent sutures. The sutures should start at the junction of the right and left crural pillars posteriorly (Fig. 11.4). Care should be taken to include peritoneum in each suture.

Division of Short Gastrics

Whether to divide the short gastrics, as in a traditional Nissen, or leave them intact, as described in the Rossetti Nissen, is controversial.

In a recent systematic review [13], pooled analysis showed no difference in outcomes between patients undergoing division of short gastric vessels versus no division for short- or long-term symptom control, esophageal acid exposure, long-term dysphagia, surgical complications, and rates of endoscopic dilation. Most surgeons perform short gastric vessel division routinely since it allows better visualization of the hiatus and fundus, and routinely achieves a tension-free fundoplication (Fig. 11.5).

Geometry of the Fundoplication

Here we describe and demonstrate the creation and geometry of Nissen and Toupet fundoplication. There are two distinct

geometric patterns. One is to bring the greater curve of the stomach behind the esophagus and suture it to anterior fundus, in a "sling" orientation. The other is to bring the posterior fundus behind the esophagus and suture it to a mirror image (reflected by the greater curve) of the anterior fundus (which is our preference, thus described below).

Laparoscopic Nissen fundoplication (LNF). Our technique begins marking the posterior aspect of the fundus with a suture 3 cm distal to the GEJ and 2 cm off the greater curvature (Fig. 11.6). The posterior fundus is then passed behind the esophagus from the patient's left to right, the anterior fundus on the left side of the esophagus is then grasped 2 cm from the greater curvature and 3 cm from the GEJ, and both portions of the fundus are positioned on the anterior aspect of the esophagus. It is of great importance that the two points at which the fundus is grasped are equidistant from the greater curvature (Fig. 11.7a). One of the most common mistakes is to make the fundoplication too loose or "floppy," thus leaving redundant fundus to herniate should there be any stretching of the hiatal aperture. In the extreme, if the fundus is inappropriately sutured to the body of the stomach, over time the wrap will slip over the cardia and create a two-compartment stomach resulting in dysphagia. Interrupted permanent sutures are used to create a 2–3 cm fundoplication around a bougie (50–60 Fr) to calibrate the geometry and measure the tightness (Fig. 11.7b).

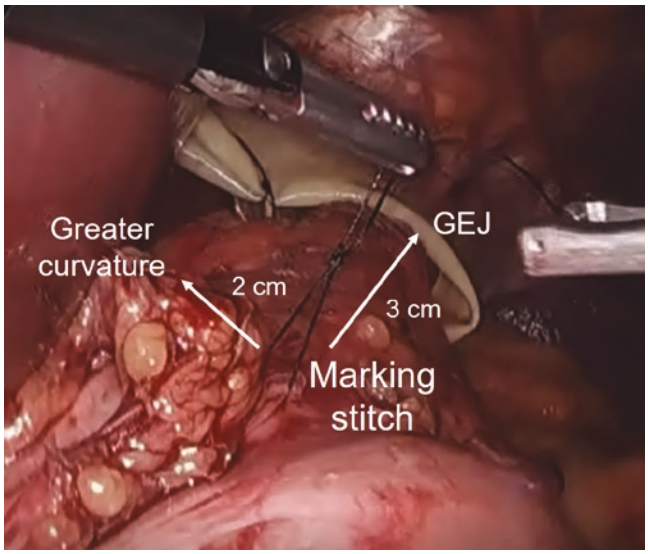

Fig. 11.6 Placement of a marking stitch on the posterior gastric wall 3 cm distal to the GEJ and 2 cm off the greater curvature

Laparoscopic partial fundoplication (LPF). The most commonly performed is the laparoscopic Toupet fundoplication (LTF). In this operation, the gastric and esophageal dissections, as well as the repair of the crura, are the same as for a 360° fundoplication. The geometry of a Nissen and a Toupet should be nearly identical, with the exception of how complete (or close to 360°) it is. On both sides of the esophagus, the most cephalad sutures of the fundoplication incorporate the fundus, crus, and esophagus; the remaining sutures anchor the fundus to either the crura or the esophagus (Fig. 11.8). If an anterior fundoplication is to be performed (Dor), there is no need to disrupt the posterior attachments of the esophagus; the fundus is folded over the anterior aspect of the esophagus and anchored to the hiatus and esophagus.

Fixation

There is debate regarding the need to fix the fundoplication with sutures to the esophagus to prevent slipping of the fundoplication over the body of the stomach or to the diaphragm/abdominal wall to discourage herniation into the mediastinum. We avoid taking bites of the esophagus when creating the Nissen, as we feel it is easy to incorporate the vagus.

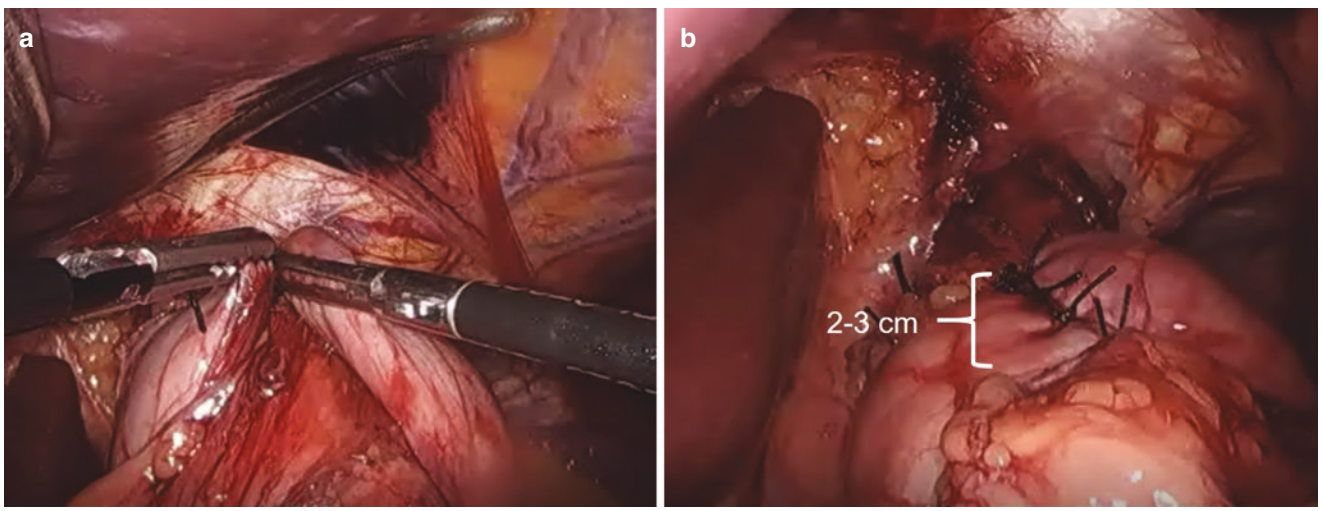

Fig. 11.7 Creation of the fundoplication: (**a**) The two points of the fundus should be equidistant. (**b**) The fundoplication should be 2–3 cm of length

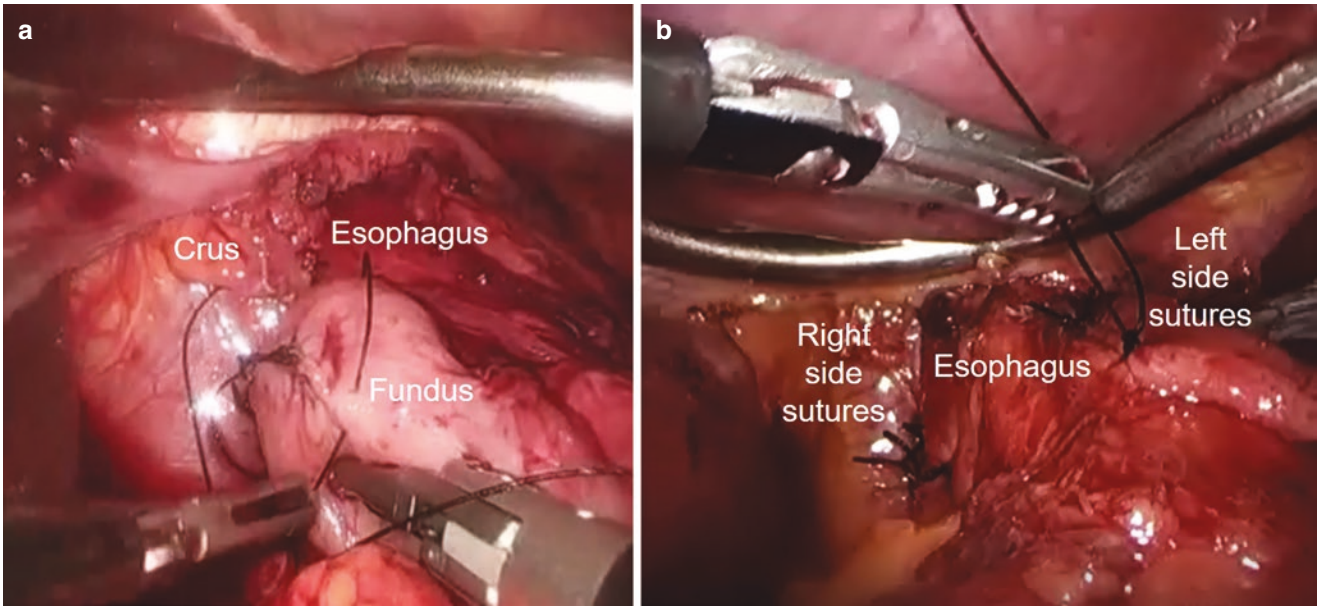

Fig. 11.8 Creation of a Toupet fundoplication: (**a**) The first stitch incorporates the fundus, crus, and esophagus; (**b**) Almost completed Toupet with sutures on both sides; note that the anterior GEJ is free

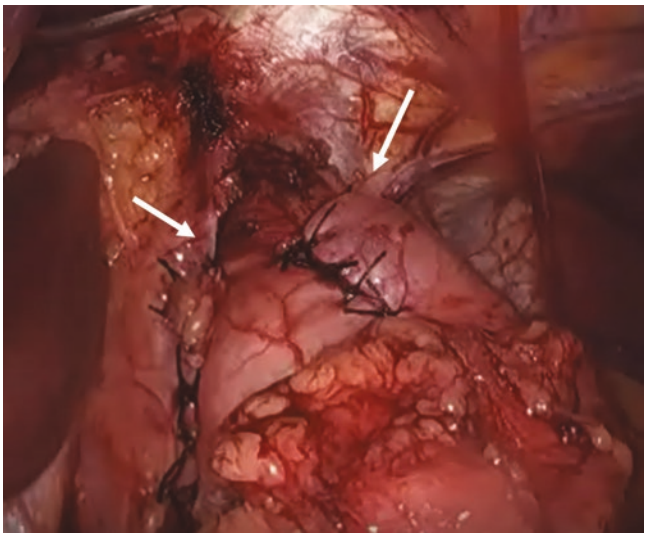

Fig. 11.9 The completed Nissen fundoplication with the fixation sutures to the fundus, esophagus, and crus on the right and left sides (white arrows)

Instead, we take two coronal sutures (fundus, esophagus, and crus) to the right and left side of the esophagus (Fig. 11.9). Others traditionally advocate for a gastropexy to the anterior diaphragm or abdominal wall. We do not think such a "distal" fixation is helpful, and instead place a posterior stitch to the diaphragm/median arcuate ligament.

Other Technical Considerations

Traditionally fundoplication was performed over a large caliber (50–60 Fr) bougie to reduce postoperative dysphagia. Complications of bougie use including a 0.5–1.0% rate of esophageal perforation have led some surgeons to search for alternatives [14]. Numerous studies have shown that complete fundoplication can be performed without routine use of bougie with no increase in postoperative dysphagia, especially if complete mobilization of the fundus is performed [15]. A randomized trial, however, does show slight decrease in both short- and long-term rates of dysphagia with bougie use [16]. More recently, fundoplication performed over a functional lumen imaging probe (FLIP) filled to 30 mmHg showed similar reflux control and decreased rate of esophageal injury, with only slightly increased dysphagia at 6 months without increased need for endoscopic dilation when compared to routine bougie use [17].

Tailoring the Fundoplication

For some years, there has been an attempt to determine which type of fundoplication should be performed based on patients' preoperative esophageal motility and symptoms ("tailored" fundoplication). The choice of wrap has traditionally been based on anatomic considerations and surgeon preference [18]. The surgeon's challenge is choosing the best procedure for each patient based on the severity of disease, presence and size of HH, esophageal function, status of the LES, and mucosal damage in the esophagus, so that there is a balance in outcomes in terms of reflux control, expected longevity of the procedure, and side effects [19]. LNF is considered the gold standard surgical procedure, but in patients with GERD and esophageal dysmotility, it has been suggested that partial fundoplication is a better option because of concern that a LNF leads to greater postoperative dysphagia.

Patti and colleagues [20] compared the tailored approach (in which the kind of wrap was chosen based on preoperative

HRM) with that of doing a total fundoplication regardless of HRM findings. They showed that LPF was less effective than LTF for GERD control and that a total wrap was not followed by more dysphagia, even in patients with weak esophageal peristalsis. Another study by Oleynikov et al. [21] also shown that LNF can be performed in patients with ineffective esophageal motility without an increase in development of dysphagia.

A prospective randomized clinical trial (RCT) that evaluated clinical outcomes after 10 years comparing LNF vs anterior 180° LPF demonstrated that there were no significant differences between the two groups regarding reflux symptoms, dysphagia, abdominal bloating, ability to belch, and overall satisfaction [22]. Hopkins et al. [23] compared the long-term outcomes of LNF with anterior 90° LPF. Both procedures achieved similar success as measured by global satisfaction measures, and patients who had a LNF reported more dysphagia, whereas more heartburn and PPI consumption were reported after anterior 90° fundoplication. A recent systematic review [13] showed that patients undergoing LPF had a lower risk of long-term dysphagia than patients undergoing LTF. There was no difference between the groups in complication rate, rates of endoscopic dilation, reoperation rate, short- or long-term symptom control, short- or long-term quality of life, and postoperative measures of pH normalization.

Analyzing this evidence, the increased incidence of dysphagia and side effects of total fundoplication tend to decline over time and seem to be low or identical for both wraps in long-term outcomes. The results of the analyzed RCTs could not prove a superiority of partial fundoplication over LNF regarding GERD control and quality of life in the long-term follow-up; therefore, the choice of fundoplication should be dictated by the surgeon's expertise and the patient's expectations.

Complications

Laparoscopic fundoplication is a safe procedure with very low rates of morbidity and mortality. Niebisch et al. [24] reported 30-day mortality of 0.19% and morbidity of 3.8% using the National Surgical Quality Improvement Program (NSQIP). The most common side effects of fundoplication are dysphagia, gas-bloat syndrome, increased flatulence, and the inability to belch or vomit. These side effects are usually transient and can be minimized with creation of a short, anatomically correct fundoplication.

Iatrogenic pneumothorax caused by violation of the parietal pleura rarely requires intervention. Transient hypotension or increased peak airway pressures may occur but often normalize with equilibration of pressure between the peritoneal and pleural spaces. Small tears can be suture repaired, and the carbon dioxide will be rapidly reabsorbed. Postoperative chest radiographs are not routinely performed unless the patient is symptomatic.

Esophageal and gastric injuries are rare but potentially devastating complications of antireflux surgery. Excessive manipulation of the stomach and distal esophagus can be avoided by using a Penrose drain for retraction of the GEJ during mediastinal mobilization. Injuries identified during surgery should be repaired. Routine postoperative esophagram is not indicated. Risk of perforation is increased in re-do surgery and can be investigated with on-table endoscopy with air leak test or methylene blue challenge. Routine esophagram is more commonly utilized after reoperations, but surgeons should endeavor to use intraoperative methods to avoid leaving with an iatrogenic injury.

Postoperative Care

The patient is started on a clear liquid diet in the recovery room and advanced to a full liquid diet as tolerated. Adequate oral pain control is achieved, and medications are crushed. Patient is discharged to home on 2 weeks of liquid diet with advancement to soft foods at 2-week follow-up. Patients are instructed to avoid heavy lifting, strenuous exercise, and abdominal exercises for 4–6 weeks to allow adequate healing of the crural repair.

Outcomes: What Can we Expect?

A successful LF is the one that achieves long-term relief of reflux symptoms in the absence of side effects or complications. These can be structural, due to laxity or stenosis of the fundoplication, or functional, leading to bloating and dysphagia. Mild, temporary dysphagia is expected during the first 2–4 weeks postoperatively due to postoperative edema. In most of patients, the dysphagia spontaneously resolves but can persist in 8% of patients in the long term [25]. Late development of dysphagia following LF suggests esophageal obstruction and requires further evaluation. Bloating may be related to the impaired relaxation of the recreated GEJ valve in response to gastric distension and an alteration in receptive gastric relaxation and accommodation [26]. Usually, it can be managed with lifestyle modifications. The approach to complications or side effects of LF should be multidisciplinary and using imaging or functional studies based on patient's surgical history and symptoms.

Compared to medical therapy, LF has proven to be superior for GERD symptomatic control and complications. In the short term, LF leads to relief from GERD symptoms in more than 90% of patients. In a study of a cohort of 288 patients undergoing LF, symptom improvement for heartburn was 90%, and regurgitation was 92% with a median follow-up greater than 5 years [27]. In a subsequent study, it was demonstrated that LF provides effective long-term relief of GERD. Younger patients, men, and those without dysphagia are predictors of superior outcomes [28]. Dallemagne

et al. [29] reported that reflux remained controlled after 10 years in 93% of patients after Nissen and 82% after Toupet fundoplication. Morgenthal and colleagues [30] showed that after a mean follow-up of 11 years, 90% of patients had improvement of heartburn and regurgitation and 70% were off all reflux medications. In another long-term evaluation (15-year) by Csendes et al. [31], LF provided symptom control in 80% of patients, corroborated by endoscopic and histologic examinations, as well as functional studies. Engström et al. [32] published their 20 years of experience with LF. Overall satisfaction rates were approximately 90% for all fundoplication types at late follow-up.

Available evidence proves that laparoscopic fundoplication is an effective and reliable procedure for patients with GERD. Patient satisfaction and quality of life should be the most important outcome measures. The procedure, performed by experienced surgeons at high-volume centers with careful patient selection, has increased durability of symptom improvement with less perioperative complications, shorter length of stay, and more cost-effective healthcare.

Comparison to Other Antireflux Procedures

While fundoplication remains the gold standard for the surgical treatment of gastroesophageal reflux, newer technologies such as magnetic sphincter augmentation (MSA) are increasingly utilized for reflux control [33]. Numerous studies have been published comparing fundoplication to MSA. An early prospective multicenter study comparing fundoplication with MSA at 1-year follow-up showed similar quality of life improvement and PPI cessation. Dysphagia rates were similar, while ability to belch/vomit was well preserved and gas bloat significantly less common in the MSA group [34].

Multiple meta-analyses have also shown efficacy of MSA when compared to fundoplication at short-term follow-up [35, 36]. These studies show similar rates of patient satisfaction, GERD-Health Related Quality of Life Questionnaire (GERD-HRQL), dysphagia requiring dilation, and PPI cessation. Ability to belch/vomit is better preserved, and gas-bloat symptoms are less common after MSA [37].

Ferrari et al. [38] recently published long-term outcomes from 6 to 12 years after MSA. This study showed persistent and significant decreases in GERD-HRQL scores (19.9–4.01) and acid exposure time (9.6%–4.1%), with persistent normalization of esophageal pH in 89% of patients. Complete cessation of PPI was achieved in 79% of patients at a minimum follow-up of 6 years. While no direct comparison to fundoplication was performed, these results are comparable to long-term results for LNF.

Conclusions

LF is the gold standard for the surgical treatment of GERD with effective reflux control, short hospital stay, rapid return to normal activities, and minimal perioperative morbidity. Despite its cost-effectiveness, it can be followed by some side effects, such as dysphagia, gas bloat, and inability to belch. The outcomes of LF are, unfortunately, variable, emphasizing the experience needed to construct an effective fundoplication. Failure of the closure of the crura and an anatomically incorrect wrap are the most common technical errors and the main reasons for failure of antireflux surgery. Several studies have shown that a partial fundoplication is associated with less complications than a full posterior wrap with equal control of reflux, but recent evidence suggests that there is no difference in long-term outcomes. LF can provide excellent durable relief of GERD when patients are appropriately selected, and excellent technique by an experienced surgeon is used.

Questions

1. All of the following are essential diagnostic tests in the evaluation of GERD prior to antireflux surgery, except:
   A. Upper gastrointestinal series
   B. Gastric emptying scintigraphy
   C. Esophageal manometry
   D. Esophagogastroduodenoscopy
   E. pH monitoring

   Answer: B. pH monitoring, UGI, EGD, and HRM are essential to confirm the diagnosis of GERD, the underlying functionality of the LES and esophagus, and investigate any anatomic considerations necessary for successful operative outcomes. A gastric emptying study could be useful in patients with suspected gastroparesis, more as an ancillary test.
2. The most common of anatomic failure with laparoscopic fundoplication is:
   A. Wrap migration or slip
   B. Slipped fundoplication
   C. Wrap or crural stenosis
   D. Hiatal herniation
   E. Fundoplication disruption

   Answer: D. While all are anatomic patterns of fundoplication failure, hiatal hernia is by far the most common.

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Comprehensive Review of the Anti-Reflux Mechanism and Fundoplication

12

Shaun Daly, Michael Tran, Miya Yoshida, David Choi, and Daniel Tseng

Introduction

Through the use of our ever-evolving technology, it has become evident that the anti-reflux barrier is much more sophisticated to be attributed to a single structure's function at the gastroesophageal junction. Consequently, the anti-reflux barrier has become an area of intense research over the past 50 years in gastrointestinal surgery and gastroenterology. The anti-reflux barrier has been identified as multiple anatomic structures that function in coordinated cohesion to halt retrograde progression of gastric contents into the esophagus. Contemporary understanding of the components of this mechanism includes the lower esophageal sphincter, crura, gastroesophageal flap valve, acute angle of His, phrenoesophageal ligament, and sling fibers. It is through these structures and their understood functions that gastroenterologists and surgeons are developing techniques to best augment or recreate the compromised anti-reflux barrier.

Principles of the Anti-Reflux Mechanism

Lower Esophageal Sphincter

The esophagus consists of smooth muscle organized into two muscle layers, the circular (CM) and longitudinal layer (LM). In cadaveric dissections, there is no singular structural difference seen to distinguish the lower esophageal sphincter compared to the rest of the esophagus [1]. However, in vivo studies have demonstrated real-time contractions of the esophagus under ultrasound guidance that showed changes in muscle thickness not evidenced during cadaver dissections [1]. The dynamic change in thickness was correlated further with manometric studies which also showed asymmetric pressure values in the lower 3–4 cm segment of the distal esophagus compared to the body of the esophagus. With manometry, researchers were able to define the lower esophageal sphincter (LES) as the distal 3–4 cm of the esophagus. The pressures from the lower esophageal sphincter appears to be mediated by myogenic, neural, and neural hormonal factors which was further corroborated through various stimulatory and inhibitory studies of the LES that demonstrated changes in manometric values recorded in animal and human models [2–4]. The lower esophageal sphincter's high basal tone compared to the esophageal body maintains closure of the sphincter and prevents any retrograde passage of refluxate as a vital component to the reflux barrier.

Gastric Sling Fibers

Anatomic and manometric studies suggest that LES muscle cells are not oriented in a complete circular pattern. In the lower part of the esophagus, the tissue layers form into incomplete C-shaped fibers from the left and right sides. The left side of the C-shaped fiber intermingles with the gastric sling fibers [4]. Some of the longitudinal muscle fascicles of the esophagus leave the esophagus and enter into the crural diaphragm, and the remainder terminate into the sling fiber of the stomach which may also contribute to the acute angle of His [5]. Several studies on animal and human models show functional differences between the clasp fibers and gastric sling fibers. Whereas the clasp fibers have a high basal tone, the gastric sling fibers have a lower resting basal tone but have a more dynamic and responsive contraction to neurohormonal stimulation [4, 6–8]. The sling fibers are responsible for the asymmetry of the pressure seen at the LES and

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the regional sensitivity to anticholinergic agents and other agents [4, 6–8]. The sling fibers form a noose-like loop around the gastroesophageal junction producing the pressure asymmetry but also help maintain sphincter closure and contribute to the pressure exerted by the LES.

Angle of His

The angle of His is an acute angle between the fundus of the stomach and the esophagus. It is formed from sling fibers and circular muscle fibers around the gastroesophageal junction. It contributes to the anti-reflux barrier by positioning the entry of the esophagus to the stomach at an oblique angle to make use of the gastroesophageal flap valve created from the angle of His [9].

Gastroesophageal Flap Valve

The gastroesophageal flap valve is a 120–180 degree musculomucosal fold opposite to the lesser curvature of the stomach. As the esophagus connects to the stomach, the sling fibers that connect from the gastric cardia form an asymmetric configuration with an acute angle of insertion called the angle of His. This forms a musculomucosal fold called the gastroesophageal (GE) flap valve. As an intraluminal extension of the angle of His, the GE flap valve responds accordingly to the changes in the angle of His during respiration or gastric distension [10]. The GE flap valve contributes to the anti-reflux barrier by providing a physical musculomucosal barrier against refluxate.

Crural Diaphragm

The esophageal hiatus has two components which rests atop the LES to provide an anti-reflux barrier. The esophageal hiatus is formed from two skeletal muscle components: the crural and the costal diaphragm. Moreover, the crural muscle fibers originate from the lumbar vertebrates that cause a vertical or craniocaudal movement as well as a circumferential contraction within the esophageal hiatus to function like a sphincter [11]. The crural diaphragm is unique in that it serves both respiratory and gastrointestinal anti-reflux functions [12]. The crura and LES are connected together by the phrenoesophageal ligament to the abdominal compartment. Thus, the crural diaphragm works in synergy with the LES by contributing an extraluminal pressure to the LES's intraluminal high pressure zone.

Phrenoesophageal Ligament

The phrenoesophageal ligament is an extension of the diaphragmatic fascia that splits into the inferior and superior portions. These portions tether the esophagus to the inferior aspect of the crural diaphragm [13]. Although it has some laxity to allow the esophagus and LES to slide across the esophageal hiatus, the phrenoesophageal ligament in healthy individuals functions to anchor the LES and crura. It anchors the structures within the pressure dynamics of the abdominal compartment rather than the negative pressure dynamics of the thoracic compartment. It allows the crura and LES to be superimposed on each other, thereby function synergistically as components to the anti-reflux barrier.

Mechanism of the Fundoplication

Many factors contribute to the role in the mechanism of anti-reflux surgery. This includes the GE junction flap valve and reconstruction of the angle of His, fundoplication/lower esophageal sphincter augmentation, intra-abdominal length of the esophagus, and the crural repair of the diaphragmatic hiatus [14, 15].

Lower Esophageal Sphincter Augmentation/ Fundoplication

Fundoplication aids in anti-reflux by a variety of mechanisms. The fundamental theory behind this is Laplace's law for a cylindrical structure. It is described as $P = T/R$ where P equals distending pressure, T is wall tension, and R is radius. The smaller the radius of the tube, the greater the pressure that is required to cause distension. The greater the wall tension, the greater pressure is needed to distend [1]. Fundoplication in effect increases the pressure required to open the LES as the wall tension is increased. This is due to mechanical compression with decreased transient lower esophageal relaxation (TLESR) episodes [14, 16–18]. Decreased episodes of TLESR are associated with the anti-reflux effect of fundoplication [14, 16–19]. This effect appears equivalent whether fundoplication is complete or partial [17]. Furthermore, fundoplication often elongates and changes the angle of the flap valve which provides an anti-reflux effect. It also has been suggested that the anti-reflux mechanism of fundoplication is due to reducing LES relaxation by decreasing axial stretch of the LES and thus cranial movement of the LES [20, 21]. This mechanism however has only been observed in rat models [21].

Intra-Abdominal Esophageal Length

During hiatal hernia repair, adequate intra-abdominal esophageal length is important not only for anatomic reasons but also functional. Having adequate length will allow the lower esophageal sphincter to be exposed and subject to higher intra-abdominal pressures, thereby increasing the pressure on the abdominal portion of the esophagus to deter reflux. The increased pressure may provide greater resistance to the pressure required for a reflux event to occur [14–16].

GEJ Flap Valve and Recreation of the Angle of his

Creation of the gastroesophageal flap valve in effect restores the natural angle of His and is an important element for anti-reflux surgery [19]. When the angle is effaced, the esophagus enters straight into the stomach and allows a direct pathway for reflux. Reducing the angle of His, creating the flap valve, and changing the entry of the esophagus to a more oblique angle restores the natural gastroesophageal flap valve and increases the anti-reflux effect. The importance of the angle of His is furthered in the situation of a laparoscopic sleeve gastrectomy where the incidence of reflux is increased. The division of the sling fibers of the cardia as well as close resection to the angle of His increases reflux [22]. The importance of the angle of His in anti-reflux is underscored in a laparoscopic sleeve gastrectomy which divides the sling fibers of the cardia as well as resects tissue proximal to the angle of His which has shown to increase the incidence of reflux events post-procedure.

Crural Repair

During anti-reflux surgery, crural repair is just as important as sphincter augmentation. This is related to the factors of distensibility pressures and radius from Laplace's law that a crural repair provides. Given that increased distensibility pressures in Laplace's law has a direct relationship with reflux events, a crural repair will help decrease the distensibility pressure in a compromised reflux barrier. Distensibility has been shown to be increased in reflux patients and decreased in those that have undergone fundoplication [15]. Crural repair also contributes to lower esophageal sphincter resting pressures [17]. The effect of crural repair was evaluated using EndoFLIP technology evaluating cross-sectional area (and thus the radius of a cylinder) as well as distensibility. Crural repair and re-approximation contributes to a 79% reduction in distensibility as well as reduction in 82% of cross-sectional area. Sphincter augmentation/fundoplication contributes 21% and 18%, respectively [15]. Crural repair appears to provide a greater contribution to reducing distensibility and thus improving reflux control [15].

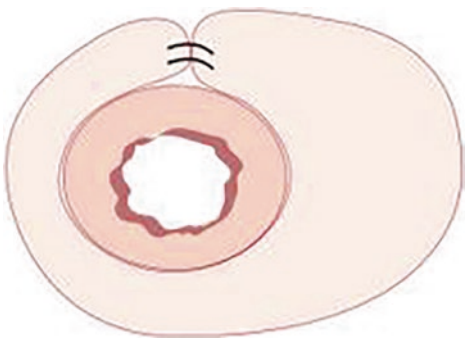
Creation of the Fundoplication

Nissen Fundoplication

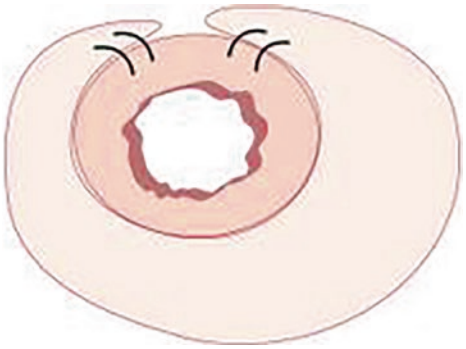
The original Nissen fundoplication was performed thru an open incision though laparoscopy is now the standard approach for the procedure. The original Nissen fundoplication was performed via open incision, but laparoscopic approach is now the more commonly practiced approach for the Nissen. Circumferential dissection of the distal esophagus and gastroesophageal junction (GEJ) is performed. After reduction of any concomitant hiatal hernia and adequate intra-abdominal esophagus is obtained, the fundus of the stomach is wrapped posteriorly to the esophagus to create a 2 cm, 360° posterior wrap. Sutures are placed medial and lateral to the esophagus from one fold of fundus to the other, thus creating a tunnel of stomach over the distal esophagus. Sutures are commonly placed through the anterior esophagus during creation to secure the fundoplication to the esophagus (Picture 12.1).

Nissen-Rossetti Fundoplication

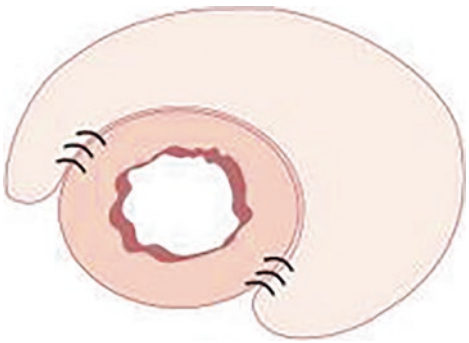
The Nissen-Rossetti fundoplication was developed by Dr. Nissen and his mentee Dr. Mario Rossetti. This modified technique involves using only the anterior wall of the fundus to create the wrap. After circumferential dissection around



Picture 12.1 Nissen fundoplication—360-degree posterior wrap



Picture 12.2 Toupet fundoplication—270-degree posterior wrap



Picture 12.3 Dor fundoplication—180-degree anterolateral wrap

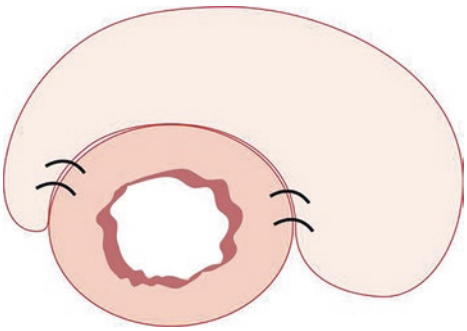
the esophagus and mediastinal mobilization to gain satisfactory intra-abdominal length, the anterior fundus is brought posterior and around the esophagus. A floppy 360° wrap measuring about 2 cm is then created in the manner described by the Nissen fundoplication.

Toupet Fundoplication

One of most commonly performed partial fundoplications, the Toupet involves grasping a portion of the anterior wall of the fundus and pulling it posteriorly to the esophagus to create a 270° posterior wrap. The edge of fundus on either side of the fundoplication is then anchored to the crus and to the esophagus to generate a 3 cm wrap (Picture 12.2).

Dor Fundoplication

The Dor fundoplication was designed specifically as an anti-reflux procedure for patients undergoing Heller myotomy for achalasia. Once the esophagus is dissected free and enough intra-abdominal esophagus is obtained, the anterior wall of the gastric fundus is brought anteriorly to create the 180° wrap. The wrap should be approximately 3 cm and able to easily reach the right crura. A variable number of sutures are placed to anchor the fundus to the hiatus (Picture 12.3).



Picture 12.4 Watson fundoplication—180-degree anterior wrap

Watson Fundoplication

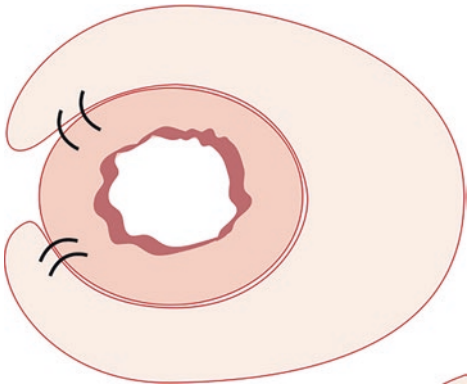
In 1991, an anterior partial fundoplication was described by Dr. Watson which involves mobilizing the gastric fundus anteriorly toward the patient's right and recreating the angle of His by tacking fundus to the left crus. The esophagus and fundus are then anchored to the anterior right crus, thus leaving the right side of the esophagus bare. This produces a 180° anterolateral fundoplication (Picture 12.4).

Belsey-Mark IV Fundoplication

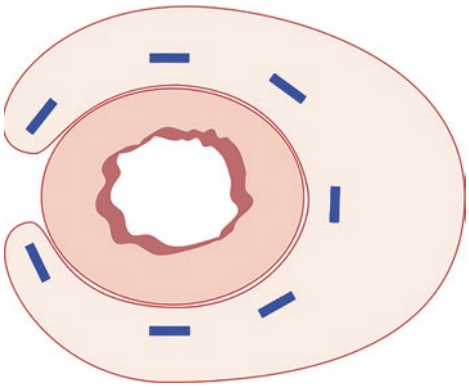
Unlike the previous described fundoplication, the Belsey Mark IV is performed via a thoracic approach to produce a 240–270° anterior wrap. A left posterolateral thoracotomy is utilized to enter the chest and the pleura over the esophagus is opened. If present, the hiatal hernia is dissected off the esophagus and the phrenoesophageal ligament is incised. The fundus is then mobilized and the hiatal closure sutures are placed but left untied. The fundoplication is performed with three horizontal mattress sutures on the fundus 2 cm distal to the GEJ. A second row of horizontal mattress sutures is then placed approximately 2 cm more proximally to the first row, incorporating the stomach, diaphragm, and esophagus. The crural sutures are then tied.

Lind Fundoplication

In 1965, Lind began carrying out modifications to Belsey's fundoplication technique. Through an intra-abdominal approach, the fundus is wrapped posteriorly to the esophagus and then sutured to the lateral esophagus on both sides. In addition, a portion of the fundus is brought anteriorly and sutured to the esophagus, leaving a small window of bare esophagus, which produces a 300° posterior fundoplication. The superior portion of the wrap is typically anchored to the hiatus as well (Picture 12.5).



Picture 12.5 Lind fundoplication—300-degree posterior fundoplication



Picture 12.6 Transoral incisionless fundoplication—full-thickness fasteners

Transoral Incisionless Fundoplication (TIF)

A transoral incisionless fundoplication (TIF) is performed with the EsophyX device (EndoGastric Solutions, Redmond, Washington, USA) and has gained popularity over the last decade as an endoscopic alternative for the treatment of reflux. The EsophyX device creates a 270° anterior fundoplication by deploying polypropylene fasteners to plicate and rotate the fundus circumferentially around the esophagus. An area along the lesser curvature is left open and allows for an "omega"-shaped gastroesophageal valve that is 2–3 cm in length (Picture 12.6).

Fundoplication Outcomes

The history of anti-reflux procedures dates to the original Nissen fundoplication in 1955 and the Belsey Mark IV in 1952. The current standard to which all anti-reflux procedures are compared to remains the laparoscopic Nissen fundoplication. While Nissen's fundoplication provides excellent relief from acid exposure, it may be associated with side effects that can impact quality of life for patients. Development of alternatives to Nissen fundoplication has focused on reduction of side effects without compromising long-term reflux control. Improved understanding of the mechanism of reflux disease has provided different iterations of anti-reflux surgery with variable outcomes. To study these outcomes, some metrics used to evaluate the adequacy of each procedure include symptom control, proton pump inhibitor usage, long-term dysphagia rates (>5 years), endoscopic dilation, quality of life, and reoperation [23]. These metrics are critical when evaluating the breadth of anti-reflux procedures available with emphasis on both the subjective and objective benefits while minimizing side effects and risks of each procedure. The ideal anti-reflux operation remains controversial; however, there has been an increasing trend toward partial fundoplication rather than total fundoplication as demonstrated by the most recent SAGES guidelines [23].

Watson Fundoplication

Since the anterior 90-degree fundoplication was first developed in pigs in 2000 by Yau et al., several human studies have suggested very good results for the procedure [24]. Initial short-term studies suggested fewer adverse side effects with 90-degree anterior fundoplication, but the benefit disappeared with long-term results. Five-year data in two randomized controlled trials suggest a trend toward higher rates of recurrent heartburn and PPI use with 90-degree anterior fundoplication but fewer side effects [25, 26]. These patients were followed for a total of 10 years [27] (Table 12.1). Conclusion to this study supports a 90-degree fundoplication is an effective anti-reflux procedure with high levels of patient satisfaction but may not be as durable a barrier as the Nissen fundoplication.

Dor Fundoplication

One of the most popular partial fundoplication techniques is the 180-degree anterior (Dor) approach. Several mid-term trials have demonstrated similar results between the two procedures [28, 29]. Long-term trials and well-performed meta-analysis have confirmed the similarity between the two procedures (Table 12.2). The longest randomized control trial

Table 12.1 Watson vs. Nissen. 10-year follow-up

	Nissen	Watson	*P*-value
Heartburn analogue score	1.9	2.83	0.035
PPI	22%	39%	NS
Dysphagia analogue score (solids)	3.18	2.03	0.037
Bloating	26%	41%	NS
Satisfaction	84%	86%	NS
Reoperation	11%	12%	NS

Table 12.2 Meta-analysis comparing Nissen vs. Dor in published trials over 5-year follow-up

Meta-analysis	Nissen	Dor	*P*-value
Heartburn	13%	16%	NS
PPI	14%	18%	NS
Dysphagia	40%	26%	0.009
Bloating	48%	36%	NS
Belching	64%	81%	0.001
Satisfaction	96%	93%	NS
Would do again	89%	93%	NS
Dilation	5.7%	2.5%	NS
Reoperation	7.4%	11%	NS

Table 12.3 12-year follow-up of RCT Nissen vs. Dor [30]

12-year follow-up	Nissen ($n = 52$)	Dor ($n = 38$)	*P*-value
Heartburn (VAS)	0	1	NS
PPI	8%	29%	<0.008
Dysphagia (Dakkak score)	4	2.5	NS
Bloating	40%	53%	NS
Belching	79%	79%	NS
Satisfaction (VAS)	10	10	NS
Would do again	90%	82%	NS
Reoperation	8%	16%	NS

Table 12.4 Outcome data from meta-analysis of randomized controlled trials

	Nissen	Toupet	*P*-value
Overall satisfaction	89%	85%	NS
Dysphagia	12%	5%	<0.01
Bloating	31%	24%	0.02
Belching	85%	92%	0.03
Heartburn	14%	12%	NS
Regurgitation	3.4%	10%	NS
PPI use	13%	11%	NS
Reoperation	5%	7%	NS

Table 12.5 Nissen versus Lind 12-month follow-up results

	Nissen	Lind	*P*-value
Heartburn	2.9%	13%	NS
Regurgitation	3%	0%	NS
Dysphagia	15%	2.6%	NS
Bloating	6%	0%	NS
Belching	100%	100%	NS
Satisfaction	91%	100%	NS
Reoperation	5%	7%	NS
Post-op pH < 4	80%	90%	NS

published 12-year data that demonstrates that rates of heartburn, dysphagia, bloating, patient satisfaction, and reoperation were equivalent between the two procedures. However, reinstitution of antacid therapy was higher in the Dor fundoplication group than the Nissen patients [31] (Table 12.3).

Toupet Fundoplication

Alternative to the anteriorly placed Dor fundoplication, posterior 270-degree fundoplication has been developed with the same goals of preventing troublesome side effects of Nissen fundoplication. Multiple randomized control trials have been published with a recent meta-analysis of these data compiled in 2015 [32]. The evaluation comprised 13 randomized controlled trials; a total of 814 patients underwent laparoscopic Nissen fundoplication compared to 750 patients who underwent laparoscopic Toupet fundoplication. Both types of fundoplication were found to be adequate in preventing reflux, but Toupet was associated with fewer side effects (Table 12.4).

These data were confirmed by an additional meta-analysis in 2016 and have been represented in the most recent guidelines produced by SAGES [23, 33].

Belsey Mark IV Fundoplication

To date there are no randomized controlled trials comparing Belsey versus Nissen fundoplication. Case-control trials between the two procedures are scattered throughout the anti-reflux surgery literature. Uncontrolled comparison studies demonstrate good results with each procedure with 85–90% of patients achieving good-to-excellent results, failure rates 7–10%, inability to vomit or belch 7–10%, and 73–82% of patients satisfied with the results [34, 35]. However, these findings are controversial with several studies suggest higher rates of esophageal injury and recurrence rates with the Belsey procedure [36, 37]. This procedure has mostly fallen out of favor due to performance via a thoracic approach rather than abdominal in many circumstances.

Lind Fundoplication

There is a paucity of data regarding the results of Lind fundoplication. The largest case series consisted of 320 patients with a mean follow-up of 31 months [38]. 91% of patients had significant improvement in heartburn scores, while recurrent symptoms occurred in only 7%. Of the 22 patients reporting recurrent reflux, pH testing revealed that only 1 patient had abnormal results. The only published prospective randomized trial that compared laparoscopic Nissen fundoplication to laparoscopic Lind fundoplication analyzed 12-month follow-up data comparing 61 Nissen and 60 Lind fundoplication patients [39]. Short-term results are comparable between the two procedures. Excellent results can be demonstrated with both (Table 12.5).

A non-randomized case-control series of a total of 52 patients comparing Nissen versus Lind with mean follow-up of 13 months demonstrated that dysphagia occurred in 31%

of Nissen vs. 23% in Lind group [40]. Gas bloat was similar between both procedures at 38%.

Transoral Incisionless Fundoplication

The TEMPO Trial was a randomized, multicenter, open-label study with a crossover arm which was carried out at seven community-based programs in the United States of America and enrolled 63 eligible patients. Forty patients were randomized to the TIF arm and 23 patients were randomized to the PPI arm. Forty-four patients completed 5-year follow-up. Elimination of troublesome regurgitation was achieved in 86% of patients, and elimination of atypical symptoms occurred in 80% of patients. Thirty-four percent of patients remained on daily PPI at 5-year follow-up, while 46% of patients completely stopped their PPI medications. Reoperation rate of 5% was comparable to the reoperation rate of laparoscopic Nissen fundoplication [41].

Conclusion

After decades of study in the variations of anti-reflux operations, it remains evident that there is no one-size-fits-all procedure. What has become increasingly evident is that partial fundoplication whether anterior, posterior, 90 degree, or 300 degree can have satisfactory results with excellent control of reflux. Further understanding of the pressure dynamics with each fundoplication, underlying esophageal motility issues as related to long-standing reflux changes, and more accurate esophageal testing may help guide future direction in creation of a tailored anti-reflux valve mechnism for each patient.

Questions

1. Which of the following does not contribute to the anti-reflux mechanism?
   A. Lower esophageal sphincter
   B. Crural diaphragm
   C. Longitudinal muscles of esophagus
   D. Gastroesophageal flap valve

Answer: C. The lower Esophageal Sphincter, Crural Diaphragm, Gastroesophageal Flap Valve, Gastric Sling Fibers, Angle of His and Phrenoesophageal Ligament all have been shown to contribute to the anti-reflux mechanism.

2. Which of the following are not considered partial a fundoplication?
   A. Nissen fundoplication
   B. Dor fundoplication
   C. Toupet fundoplication
   D. Transoral incisionless fundoplication (TIF)

Answer: A. The Nissen fundoplication is classified as a complete fundoplication.

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Laparoscopic Magnetic Sphincter Augmentation

13

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Introduction

For many years the binary options of antisecretory medications and antireflux surgery in the form of fundoplication have been the mainstays of treatment for GERD. Laparoscopic Nissen fundoplication has been the standard operation yet remains unpopular due to bothersome postoperative symptoms, including dysphagia, an inability to vomit, and gas bloat syndrome. The benefit of an alternative to Nissen fundoplication providing similar efficacy in reflux control without the adverse symptoms and easy technical reproducibility led to the concept of an implantable magnetic sphincter augmentation (MSA) device, the LINX Reflux Management System (Torax Medical/Ethicon/J and J, Shoreview, MN). In this chapter we will review the conceptual development and mechanism of MSA, indications, preoperative evaluation, implantation technique, postoperative management, complications, and reported clinical outcomes.

Device and Mechanism

The implantable magnetic sphincter device is composed of 13–17 rare earth magnets hermetically sealed inside 5.85 mm titanium cases which are interlinked together by individual titanium struts to create an expandable bracelet. A "Roman arch" configuration avoids complete magnetic apposition and collapse of the bracelet. Placed circumferentially and clasped around the esophagus at the gastroesophageal junction (GEJ), the device non-compressively augments the opening pressure of the lower esophageal sphincter (LES). The device will almost double its circumference when fully expanded (Fig. 13.1) [1].

In the resting or closed position, the magnetic force of the device is highest and prevents the LES from opening until intraluminal pressure exceeds ~30 mmHg [1]. During a normal swallow, the average pressure generated of ≥35 mmHg will separate the magnets transiently allowing food to pass into the stomach. Most reflux occurs during spontaneous shortening or opening of the LES, with an abdomino-thoracic pressure gradient of 10–15 mmHg, which is insufficient to open the augmented LES with the MSA placed around the gastroesophageal junction [2, 3] (Fig. 13.2).

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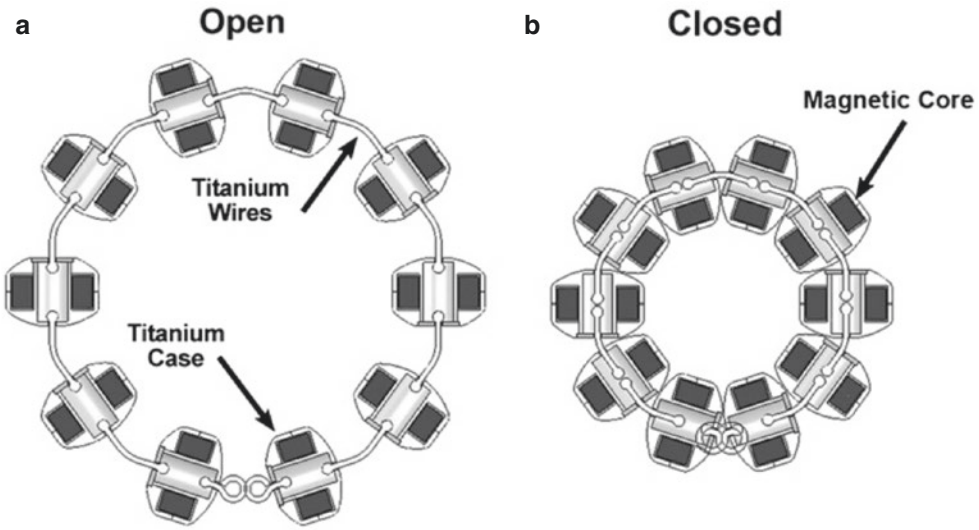

Fig. 13.1 LINX in open (**a**) and closed (**b**) position. schematic

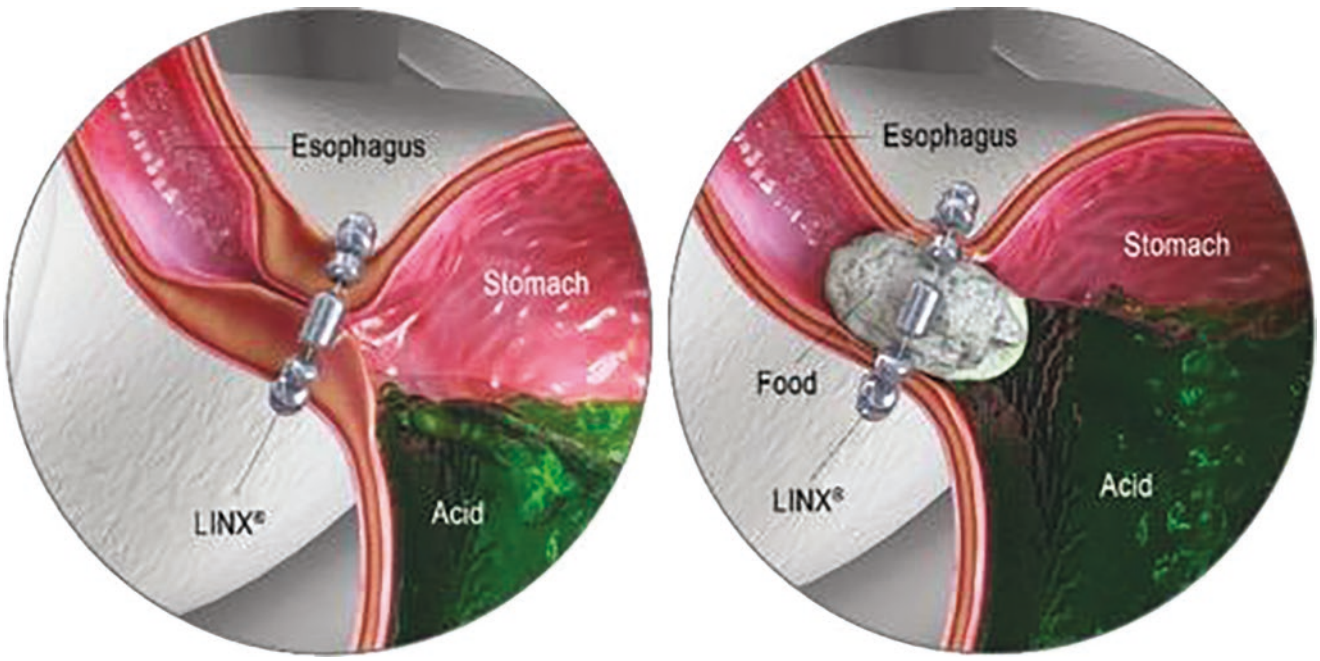

Fig. 13.2 LINX position and function

Concept Development and Early Trials

Initial ex vivo studies determined that magnetic separation forces resulted in augmented LES pressures determined by manometry. Subsequent in vivo animal studies involved pigs, whose peristaltic pressures are similar to humans. Normal eating patterns were noted postoperatively with no changes to eating behavior or weight gain. Average LES pressure increased from 22.9 to 35.6 mmHg post implantation [1].

Human trials with MSA began with 38 patients undergoing implantation between February 2007 and October 2008. Short term, 1–2 years, 4 years, and 5 years of follow-up have been reported [4–7]. The results in these patients demonstrated improvements in symptom control and objectively measured distal esophageal acid exposure, with 80–85% of patients free from daily PPI use and were sustained in the 1–2-year, 4-year, and 5-year marks. A subsequent 14-center trial with 3-year follow-up demonstrated a ≥50% reduction in quality-of-life scores, and a 50% reduction in the dose of PPIs were achieved in 92% and 93% of patients, respectively. The median DeMeester pH score improved from 36.6 to 13.5 at 1 year, at 3 years 64% of patients achieved a ≥ 50% reduction in the percent time, and esophageal pH was <4

compared to baseline; 58% of patients fully normalized their esophageal acid exposure [8].

Indications and Patient Selection

Patients being considered for magnetic sphincter augmentation require an objective diagnosis of GERD. *Patients considered for MSA should also demonstrate sufficient distal esophageal contraction to enable a swallowed bolus to overcome the magnetically augmented sphincter, generally over 30 mmHg*. Contraindications to implantation are an allergy to titanium, stainless steel, nickel or other ferrous materials, the presence of esophageal cancer, and the need for an MRI >1.5 Tesla. (Of note, the LINX device itself does not contain nickel; the sizer however does.) Expert opinion would not recommend placing the LINX device in a patient with absent esophageal peristalsis (e.g. achalasia, scleroderma).

Patient selection for MSA implantation has evolved over the last decade. Some initial precautions have been evaluated and support use of MSA in patients with hiatal hernias >3 cm, ineffective esophageal motility, select patients with Barrett's esophagus, obesity, and prior esophageal or gastric surgery is emerging. The precaution related to hernia size >3 cm has been removed by the FDA.

Severe disease including recurring strictures, long-segment Barrett's, a defective and patulous lower esophageal sphincter, and life-threatening aspiration are probably better served by a complete fundoplication. Additional considerations include type of symptom, degree of preoperative dysphagia, ability to follow a postoperative diet, disease severity, response to acid-suppressive medication, and patient expectations. Patients with regurgitation-predominant refractory GERD are excellent candidates for MSA [9]. Patients with bothersome preoperative dysphagia are more prone to postoperative dysphagia from any antireflux procedure; this may be more pronounced following MSA than partial fundoplication. Intuiting a patient's ability to follow the post-MSA diet is key as this relates to the patient's understanding and the surgeon's ability to set/establish patient expectations.

The historic goal of completely replacing acid-suppressive medication dependence by an antireflux procedure may need resetting as more patients are seeking a balance between medical and surgical therapies. Going forward, taking a patient uncontrolled on medication to controlled on medication or to controlled with on-demand medication or a substantial reduction in medication should be considered therapeutic victories particularly if GEJ physiology can be maintained.

Preoperative Evaluation

The preoperative evaluation of a potential patient for MSA implantation is the same as for any other antireflux procedure. Key components of the evaluation are pH testing off medical therapy to objectively diagnose GERD and assessment of esophageal body function by manometry or specific video esophagram protocol to evaluate esophageal body function beyond ruling out achalasia.

Technical Considerations

The surgical technique for implantation has evolved since MSA was introduced into the United States in 2012. Initial implantations were completed using a "minimal dissection technique," hoping to leave as much of the native structure of the antireflux barrier intact as possible. Over time it has been understood that some of the core surgical principles of traditional antireflux surgery must be maintained. Specifically, hiatal closure and restoration of intra-abdominal esophageal length are required in order to restore reflux barrier possible, and to ensure the device is reliably secured around the distal esophagus just above the endoscopic GEJ.

Surgical Technique

The surgical technique for MSA implantation has been described in detail elsewhere [4, 10]. The approach is similar to patients undergoing laparoscopic or robotic fundoplication. The authors favor complete esophageal dissection regardless of presence or absence of a hiatal hernia. Precise closure of the hiatus around an empty esophagus restores the crural component of the high-pressure zone, improves reflux

Fig. 13.3 Precise crural repair

control [11], and may decrease potential for intrathoracic migration of the less-bulky MSA [12] (Fig. 13.3). The device is implanted at the level of the insertion of the angle of His over top of the anterior vagal nerve and within a tunnel underneath the posterior vagal nerve.

Device Sizing and Implantation

Determining the appropriate size of the device requires use of the manufacturer's sizing device. This consists of a rigid tubular shaft from which a curved flexible plastic catheter with magnetic tip is deployed, looping around the esophagus and attaching to the ferrous end of the tubular shaft (Fig. 13.4). Numbers on the handle of the device indicate the number of beads corresponding to the diameter of the loop created.

The device is inserted from the patient's right side and follows the path planned for the MSA device (Fig. 13.5).

The authors use several steps in succession to determine a size that is non-compressive on the esophagus. First, simple visual inspection for the first evidence of compression during closure of the device and noting the device size. Second, rotating the device shaft back and forth at each size while looking for movement of the white loop up-down the esophagus until there is no movement. Third, close the sizer until the magnetic tip pops off and note the size. It is critical in steps (1) and (2) that the sizing device is in a neutral position with the part of the sizing ring that goes behind the esophagus is just in contact with the esophagus and not pushing the esophagus anterior or another direction. After steps 1 and 2, the ultimate size is determined by adding one bead to the observed size. In step 3, the device size is chosen by adding two or three beads to the size which the sizing device disengages. The limit to the pop-off method is that popping off measures the compressibility of the esophagus and that compressibility can vary between patients.

Drs. Bell and Woodworth favor size selection after steps 1 and 2 and find that the pop-off method most commonly correlates with three above the pop-off size, whereas Dr. Louie often finds that steps 1 and 2 match with step 3 when two beads are added to the pop-off. Drs. Bell and Woodworth prefer to have the MSA device lie slightly obliquely on the esophagus, whereas Dr. Louie prefers it to sit on the esophagus without a tilt (Figs. 13.6, 13.7, 13.8 and 13.9).

When the sizes between the three do no correlate, a decision is made to select the device that best matches the size of the esophagus without compression, with the mantra that if in doubt, go bigger. Once the device is connected, it should lay at the level of the insertion point of the angle of His. Some surgeons will confirm placement of the device endoscopically at the top of the rugal folds.

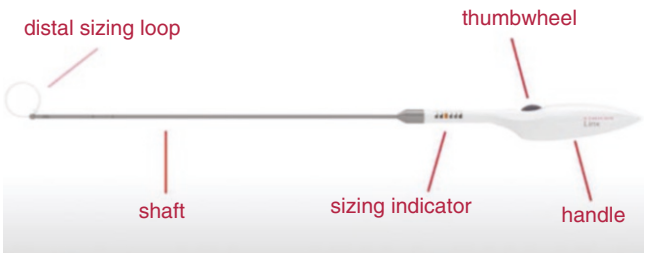

Fig. 13.4 LINX sizing tool

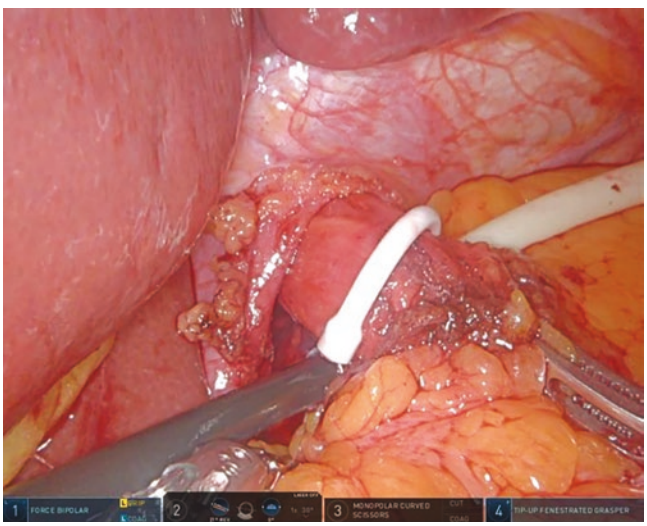

Fig. 13.5 Sizing device in place around the distal esophagus

Postoperative Management

Discharge the day of implantation is anticipated with postoperative pain managed primarily with nonnarcotic medications supplemented with narcotics and antinauseants. A postoperative CXR is often helpful to establish the baseline position of the device for future reference.

Postoperative diet instructions are different from those of fundoplication and are one significant element in decreasing long-term dysphagia. Patients are instructed to eat small portions of food that fit into the patient's palm, every hour while awake for up to 2 months after implantation. They must chew food thoroughly but not so much to create a paste and to not swallow large chunks. This actuates or "exercises" the device and minimizes the rigidity of the postimplantation scar/encapsulation that leads to dysphagia. Swallowing difficulties may peak 1–3 weeks after surgery and subsequently improve. Steroids (40–80 mg of prednisone daily × 5 days) are prescribed in problematic cases. Dilation is avoided as much as possible for the first 3 months.

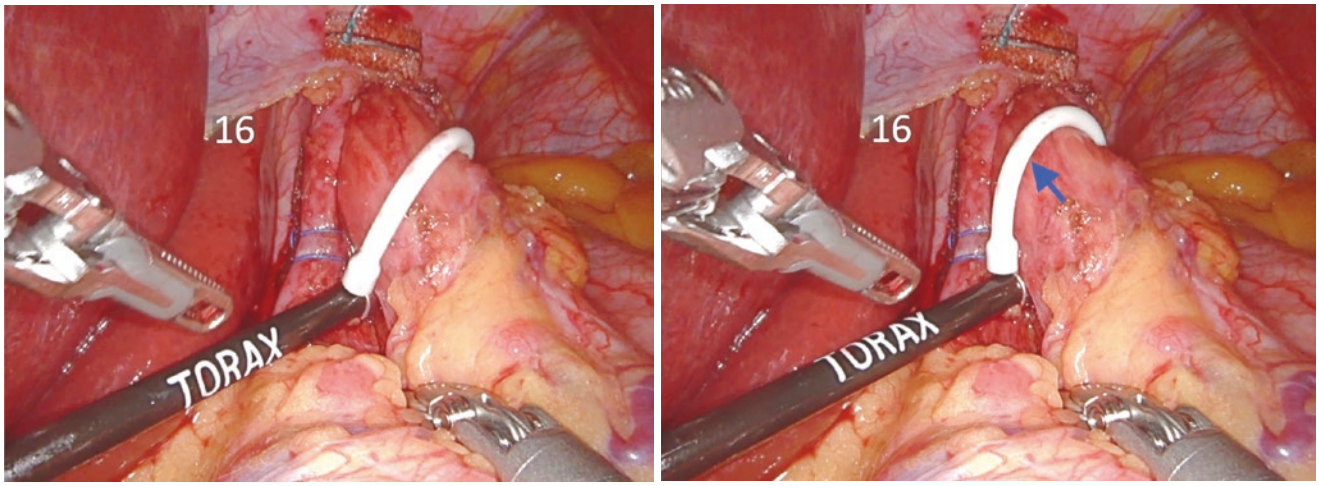

Fig. 13.6 Sizer around distal esophagus with white band at right angle to esophagus (left, Dr Louie technique), or allowing obliquity (right, blue arrow, Drs. Bell and Woodworth technique)

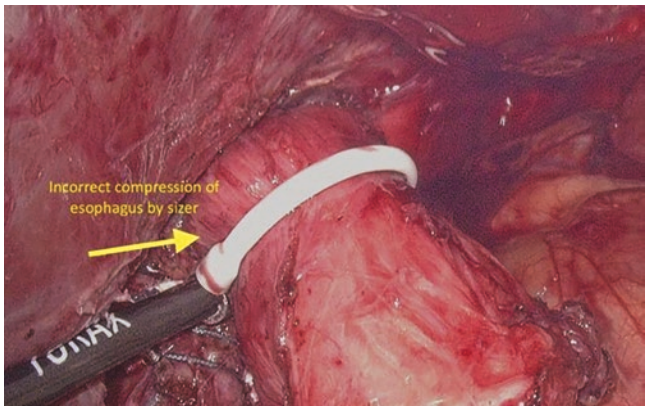

Fig. 13.7 Incorrect sizing, visible compression of the esophagus

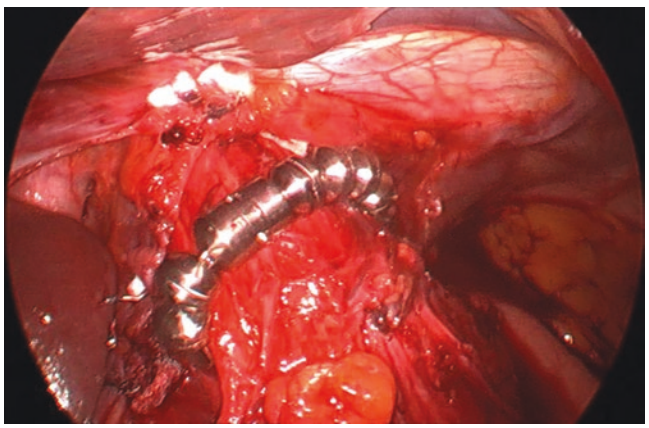

Fig. 13.9 MSA in position, at right angles to the esophagus (Louie technique)

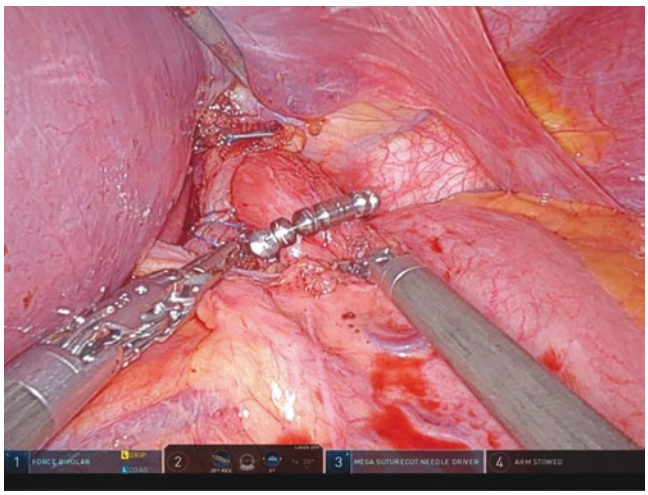

Fig. 13.8 MSA in position, slightly oblique to the esophagus (Bell, Woodworth technique)

Complications

Intra- and Perioperative Complications

Intraoperative and perioperative complications are reported to occur in 0.1% of cases [13]. The range is similar to that with Nissen fundoplication and is generally related to performance of the laparoscopy.

Postoperative Dysphagia

Dysphagia is the most common side effect after MSA and is defined as symptoms that are bothersome every day and taken from the patient-reported outcomes using the GERD-

HRQL questionnaire questions 7 and 8 [14]. There are three distinct patterns of dysphagia: early, persistent, and late.

Early dysphagia, within the first 3 months of surgery, is reported in up to 30% of patients [15]. It is common to begin 10–14 days and be most intense 6 weeks after implantation, when capsular fibrosis is most exuberant [16]. Postoperative diet instructions on regular swallowing help most patients through this; occasionally steroids are needed. Dilation is avoided whenever possible as it may worsen the dysphagia; rarely explantation is needed.

For persistent dysphagia extending beyond 3 months, when reinitiating postoperative dietary instructions does not work, endoscopic dilation can be considered with balloon size appropriate for the size of the MSA device. Often a single dilation will resolve the dysphagia with a small number of patients requiring an additional dilation or larger size. If three dilations are unsuccessful, device explantation is an appropriate option [15].

Late, new-onset dysphagia after a period of normal swallowing can develop months to years postoperatively. Late dysphagia is often associated with more significant symptoms, including repeated vomiting, severe chest pain, and food impaction. Hernia recurrence, progressive dysmotility, device migration onto the proximal stomach, or device erosion may be causal and warrant further investigation by upper endoscopy, barium swallow, or manometry. Dilations may be successful at this stage; severe and refractory dysphagia may be managed with device removal (without needing conversion to fundoplication) [16, 17].

Explantation and Migration

Explantation of the device has been reported between 3 and 7% of patients with roughly half of the removals performed for refractory dysphagia and half for refractory GERD. Removal for erosion or device discontinuity occurs in less than 0.3% of patients [17]. Explantation in preparation for MRI is infrequent with the current 1.5 Tesla FDA MRI Conditional device. Patients undergoing elective explanation may to be converted to Nissen or partial fundoplication if GERD is the dominant reason, with or without partial fundoplication if dysphagia is the reason. Both endoscopic (for erosion) and laparoscopic explantation techniques have been described [17].

Recurrent hernia, in which a correctly positioned device is located above the diaphragm, may present with new-onset dysphagia and/or recurrent GERD symptoms. Typically gastric herniation to some extent accompanies this. A barium swallow may be required if an AP chest X-ray does not demonstrate a supradiaphragmatic MSA. Barium swallow may be more sensitive to device herniation, whereas careful endoscopy is more sensitive for fundoplication herniation; however, 1–2 cm of rugal folds above the diaphragm with a subdiaphragmatic MSA can be a normal finding, especially in patients with a dilated distal esophagus. This is not related to the device, but to failure of the hernia repair as is also seen following fundoplication. Revisional surgery with repair of the hiatal hernia with device preservation, device replacement, or device removal and creation of a fundoplication are options. No data clearly supports one option over the other.

Erosion

Device erosion remains a rare event with a current rate of <0.28% at 7 years. The smaller device sizes (11 or 12 beads) have been discontinued due to erosion (and dysphagia) rates. The most recent data regarding the 13 bead or larger devices found the 7-year erosion risk 0.28% [18].

All known device erosions have been successfully removed endoscopically and/or laparoscopically, preferring first an attempt at endoscopic removal [17]. The current 1.5 T devices require either an ERCP mechanical lithotripter device (Olympus Medical Systems, Center Valley, PA, USA) or the OVESCO DC Clip Cutter to cut the titanium wire ring linking the magnetic beads with [19, 20]. The string of beads are then pulled into the stomach and extracted through the mouth, or a few of the beads cut out and the remainder removed laparoscopically weeks later after the eroded mucosa has healed.

Outcomes

Prospective Single-Arm Studies

Multiple single-arm prospective studies of MSA have routinely evaluated quality of life, freedom from daily PPI use, and in some cases objective outcomes. In each of these outcomes, the 1-year results have been consistent with patient-reported symptom control using the GERD-HRQL questionnaire ranging from 75 to 89%, freedom from any PPI use 75%–87%, and ambulatory pH normalization with current implantation techniques ranging from 76 to 90% of patients (Table 13.1).

Two early clinical studies of MSA with 5-year follow-up demonstrated consistent improvement in patient-reported outcomes using the GERD-HRQL improving from 27 at baseline to 4 post-surgery, with 75% free from PPIs and healing of esophagitis in 75% [7, 21].

Ferrari reported on 124 patients 6–12 years post MSA, finding persistent improvement in GERD-HRQL scores from 19.9 to 4.01, complete PPI discontinuation in 79% of patients, and mean time with pH <4 off PPI reduced from

Table 13.1 Single-arm prospective studies of MSA

Author	*n*	Follow-up (months)	Median GERD-HRQL	PPI cessation % (n)	pH testing (DeMeester score)	Dysphagia/need for dilation	Esophagitis/intestinal metaplasia (IM)	Regurgitation	Reoperation/ explantation (%)
Ganz, et al. [21]	100	60 (85/100 patients)	Preop – 27 off PPI; 11 on PPI Postop 4	84.7% 9.4% PRN use only	–	Preop 5% Postop 6%	Esophagitis preop, healed at 5y – 76.5% No esophagitis preop, still absent at 5y – 90%	1 patient with persistent symptoms	7 reoperations: 4 for dysphagia 1 for chest pain 1 for vomiting 1 for persistent reflux 3/7 converted to Nissen
Ferrari, et al. [22]	124	72–144	Preop 19.9 Postop 4	100% off – 79% ≥50% off – 89.5%	Preop 40.7 Postop 16.3	Dilations 2.4%	Postop esophagitis 4.7% Incomplete intestinal metaplasia 2.8%	Preop 59.6% Postop 9.6%	9.2% explantation
Saino [7]	44	60	Preop 25.7 Postop 2.9	87.8% off 93.9% – ≥50% dose reduction	Preop 42.3 Postop 16.1 $P < 0.01$ Total % time pH < 4 Preop 11.9% Postop 4.6% $p < 0.01$	–	–	–	–
Bonavina et al. [23]	100	36	Preop 24 Postop 2	85%	Preop 3.01 Postop 11.2 $p < 0.001$ Total % time pH < 4 Preop 8% Postop 3.2% $p < 0.001$	–	–	–	–
Louie, Smith [24]	200	12	Preop 26 Postop 4	87.4% (91.4% including PRN use)	Preop 33.4 Postop 12	36.6% 13/30 patients dilated	–	Moderate to severe Preop 61.5% Postop 5.4%	2.5% (5/200 patients)

9.7% to 4.2%. Less than 10% of patients underwent reoperation by 12-year follow-up [22].

Comparison with Proton Pump Inhibitors

An RCT compared patients with moderate to severe regurgitation on 20 mg omeprazole daily found that 96% of patients randomized to MSA had relief of regurgitation, compared to 19% of patients randomized to an increased dose 20 mg omeprazole bid. The MSA group had similar outcomes to the observational single-arm trials with esophageal acid exposure time decreased from 10.7% to 1.3%; DeMeester scores reduced from 40.5 to 5.3, with 70% of patients showing total normalization. In this patient population, baseline degree of response to PPIs (partial or none) had no bearing on improvement in heartburn or regurgitation post MSA [9, 14].

Comparison with Fundoplication

Single-center comparative studies of MSA to Nissen or Toupet fundoplication with up to 5-year follow-up have found that MSA results in similar improvements in GERD-HRQL and freedom from PPIs [25–30]. A lower incidence of postoperative gas bloat, greater ability to belch and vomit, and a similar incidence of postoperative dysphagia following MSA compared to Nissen was found in most studies. Warren reported that MSA patients achieved significant improvement in ambulatory pH exposure, though pH normalization was more reliably attained after Nissen fundoplication [31] (Table 13.2).

In a multi-institutional study, MSA resulted in equivalent symptom control, improved quality of life with fewer adverse effects, but lower rate of freedom from PPI when compared to fundoplication at minimum 12-month follow-up. Patients with MSA had more physiologic venting capabilities. Ninety-six percent of MSA patients could belch and 95% could vomit, compared to 69% and 43% of Nissen patients. There was also less gas bloat reported in the MSA group [32].

MSA in Patients with Hiatal Hernias Greater than 3 Cm

The initial FDA precaution regarding MSA in hernias >3 cm was removed in 2018. Two single-arm, observational studies have reported outcomes in hernias larger than 3 cm with favorable improvements in GERD-HRQL, postoperative dysphagia, need for dilation, freedom from PPIs, or need for reoperation. Buckley et al. reported on 200 patients undergoing MSA with hernias >3 cm, including 156 with an axial hernia ≥5 cm or large paraesophageal component. 78% patients were followed a median of 8.6 months. GERD-HRQL scores improved from 26 at baseline to 2 postoperatively, and PPI independence was achieved in 94% (147 of 156). Video esophagram in 51 patients at median 11 months found 3 asymptomatic hernias, all ≤2 cm in axial dimension. One symptomatic patient underwent successful repair of the hernia without MSA manipulation [10]. Dunn reported median 3-year follow-up on 79 patients with a hiatal hernia ≥3 cm undergoing MSA. Median DeMeester scores decreased from 42.45 to 9.10 (3.05–24.30). Severity of esophagitis significantly improved as did GERD-HRQL scores (from 21 to 2). Five (6.3%) hiatal hernia recurrences occurred, and one required reoperation [33].

Obesity

A potential concern about the use of MSA in obese patients relates to the increased EGJ pressure gradient in obese patients compared to normal individuals. This gradient ranges from 2 to 5 mmHg at expiration from 10 to 15 mmHg at inspiration in patients with a Body Mass Index (BMI) >30 and changes minimally with higher BMIs [34, 35]. Recalling that the intraluminal force required to overcome the magnetic attraction of the MSA beads is ~28 mmHg, it seems obesity inherently should not result in an increased failure rate in obese patients. Initial studies of MSA excluded patients with a BMI ≤35 kg/m^2. James evaluated relative outcomes of 361 patients undergoing MSA with regard to BMI and found no difference in outcomes in patients grouped by BMIs of <25, 25–25.9, 30–34.9, or >35 kg/m^2 [36].

Motility Disorders

Initial series of MSA included patients with normal motility defined as >70% peristalsis and distal amplitudes >35 mm Hg. However, GERD patients often have dysmotility with ineffective esophageal motility (IEM) found in 20%–30% of chronic GERD patients during esophageal manometry. A recent multicenter case-control study which compared the outcomes of 105 IEM patients undergoing MSA with matching controls reported similar improvements in GERD-HRQL but lower rates of GERD control based on the post-MSA DeMeester score and the percent pH normalization. Rates of new-onset dysphagia and the need for dilation were higher in patients with IEM, but this was not statistically significant. Explantation rates were similar between the groups at 9%; IEM patients were more commonly explanted for dysphagia. Percent intact swallow was more predictive of need for dilation than was DCI, and the authors suggest that 40% or more intact swallows would be reasonable for MSA implantation with a cutoff of 20% intact swallows and a DCI of <200 [37].

Table 13.2 Studies with comparative outcomes of MSA and fundoplication

Author	Procedure	n	Follow-up (months)	Median GERD-HRQL	PPI cessation % (n)	pH testing	Dysphagia/ need for dilation	Gas-related symptoms	Ability to belch and vomit % (n)	Reoperation (%)
Reynolds, et al. [28]	MSA	50	12	4.2	83% (39/47)	–	10.6%[a] (5/47) Dilation 16% (8/50)	Overall 27.7% (13/47) Severe 0%	Belch 91.5% (43/47) Vomit 95.7% (45/47)	0
	LNF	50	12	4.3 $p = 0.88$	91.5% (43/47) $p = 0.355$	–	12.8% (6/47) $p = 0.766$ Dilation 10% (5/50) $p = 0.554$	Overall 38.3% (18/47) $p = 0.067$ Severe 10.6% (5/47) $p = 0.022$		0
Louie, et al. [25].	MSA	34	6	5	100% (24/24)	DeMeester score – 14.2% time pH <4–4.6	40.2[b] Dilation 4.2% (1/24)	1.32[c]	67% (16/24) $p = 0.0001$	0
	LNF	32	10	5.1 $p = 0.93$	96.9% (31/32)	DeMeester score – 5.1 $P = 0.0001$% time pH <4–1.1 $p = 0.0001$	36.9 Dilation 0% $p = 0.24$	2.36 $p = 0.059$	0%	0
Riegler, et al. [26]	MSA	202	12	3	81.8%	–	7% Dilation p = ns	10%	Belch – 98.4% Vomit 91.3%	4%
	LNF/LTF	47	12	3.5 $p = 0.18$	63% $p = 0.009$	–	10.6% $p = 0.373$ Dilation p = ns	31.9% $P < 0.001$	Belch 88.9% $p = 0.007$ Vomit 44.4% $p < 0.001$	6.4%
Sheu, et al. [27]	MSA	12	7	–	–	–	83% Dilation 50%	0%	–	–
	LNF	12	7	–	–	–	58% $p = 0.37$ Dilation 0% p = 0.014	33% $p = 0.21$	–	–
Asti, et al. [30]	MSA	135	44	0	p = ns	–	p = ns	p = ns	–	p = ns
	LTF	103	42	2 p = ns		–			–	
O'Neill, et al. [30]	MSA	20	68	9	60% off Daily use 30%	–	25%	Bloating score 1.5/5	–	20% (5/20) 1 hiatal hernia repair 4 device removal
	LNF	36	65	7.5	66% off Daily use 14%	–	36%	Bloating score 3/5	–	7%

[a]Values in % (n). Corresponds to moderate/severe dysphagia: symptoms more than once a week, regurgitation of undigested food, vomiting, or requiring dietary modifications
[b]Measured by dysphagia score (ranges 0–45; 0 being most severe dysphagia and 45 being no dysphagia)
[c]Values extrapolated from the GERD-HRQL scores. Lowest values indicate less symptoms

Barrett's Esophagus

Two studies from a single institution have investigated the impact of MSA on Barrett's esophagus. At 1-year of follow-up post MSA, regression was more often seen in patients with ≤1 cm (83%) compared to patients with short-segment Barrett's esophagus (SSBE) (1–3 cm) (73%) and long-segment Barrett's esophagus (LSBE) (25%). A statistically significant inverse relationship was identified between preoperative DeMeester score and regression of intestinal metaplasia [38]. At 2-year follow-up, 60% showed complete regression of intestinal metaplasia, and 9.5% had a reduction in their Barrett's category (e.g., long to short) The DeMeester pH score improved from 34 to 13.7 and nearly 30% of patients remained on PPI therapy [39].

Post Bariatric Surgery

Persistent or de novo GERD after bariatric surgery is a recognized and increasingly prevalent entity. Sleeve gastrectomy is most commonly associated with the potential for de novo GERD. Although Roux-en-Y gastric bypass (RYGB) has been proposed as an effective treatment for GERD, persistent or de novo GERD has been reported in patients post RYGB as well. In this situation, traditional fundoplication is technically difficult if not impossible due to separation or elimination of the gastric fundus from the downsized stomach. A recent meta-analysis of MSA for persistent GERD after bariatric surgery found only 3 of 22 studies totaling 33 patients met inclusion criteria. A significant improvement in GERD-HRQL score of 17.5 (CI -22.88 to −12.20) was observed [40]. In a small series of 10 patients, Kuckelman found that post-bariatric patients required a larger size MSA device (16 bead) compared to non-bariatric patients (14 bead) [41], which the authors agree and noted that occasionally the post sleeve esophagus is too big even for the largest MSA device. The results of a multicenter prospective study of MSA in 30 patients after sleeve gastrectomy are expected to be reported this year.

Conclusion

Laparoscopic magnetic sphincter augmentation with the LINX device has offered patients and surgeons an alternative to laparoscopic fundoplication, with the benefits of greater ability for gastric venting and no manipulation of normal gastric anatomy. Long-term symptomatic outcomes are similar to laparoscopic Nissen fundoplication, whereas objective pH control is probably less. Refinement in technique has pushed recognition of the importance of the crural diaphragm as an adjunct to sphincter augmentation in surgical technique. Postoperative dysphagia has been lessened by slight increase in sizing practice and postoperative dietary instructions. It has a clear place in the surgical treatment of GERD, as recognized in the 2021/2022 American College of Gastroenterology and American Gastroenterology Association guidelines for the management of GERD [42, 43].

Questions

1. The *best* patient for magnetic sphincter augmentation would be:
   A. No hernia, burning in throat, severe dysmotility, pH test at upper limit of normal, no response to acid-suppressive medications.
   B. Severe regurgitation improved on medication, heartburn resolved on medication, abnormal pH test (DeMeester 35, total time pH< 4 of 10%), normal esophageal body peristalsis, 3 cm hiatal hernia, no dysphagia.
   C. Long-segment Barrett's with low-grade dysplasia, history of strictures, 5 cm fixed hiatal hernia, mild IEM.

Answer: Patient B. Patient A is a poor candidate for any antireflux procedure based on symptoms, pH, motility, and response to medication. Patient C has severe reflux disease which may better respond to a complete fundoplication than MSA.

2. Safety of MSA demonstrates
   A. A risk of erosion is less than 0.3% at 7 years, with ability to remove an eroded with minimal serious complications.
   B. Early dysphagia is the most common postoperative side effect and resolves in the majority of patients.
   C. Device explanation for recurrent reflux or dysphagia occurs in 3%–7% of reported series.
   D. All of the above.
   E. None of the above.

Answer: D, all of the above.

3. Early techniques favoring minimal dissection with selective hernia repair have been superseded by routine hiatal dissection with hiatal repair to restore the crural sphincter. Concomitantly, sizing has trended to be larger, with 12 and 13 bead (the smallest devices) implants having been eliminated or infrequently used.
   A. True
   B. False

Answer: True. Although no prospective studies have evaluated these changes, retrospective studies have shown benefit to routine hiatal dissection and repair. As the hiatus has become more "snug," many surgeons have sized the MSA larger (e.g., 3 above "pop" vs. 2 above "pop" as the technique has evolved).

4. Comparative studies between MSA and fundoplication have found:
   A. Similar durability.
   B. Similar control of reflux symptoms and use of continued acid suppression.
   C. Similar if rates of reoperation.
   D. Fewer gas-related symptoms and increased ability to belch and vomit with MSA compared to complete fundoplication
   E. All of above.
   F. None of above.

Answer: E, All of the above. Though few gas-related symptoms and abilities to belch and vomit have not been seen in all comparative studies, the trend has been in this direction.

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Diagnosis and Management of Paraesophageal Hiatal Hernia

14

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Objective

1. This chapter will review the history, pathophysiology, classification, diagnosis, and surgical management of a paraesophageal hiatal hernia. The chapter will also briefly review the pros and cons of mesh use in repair of hiatal hernias.

Introduction, Definition, Incidence, and Prevalence

Hiatal hernia is a common disorder. It is characterized by a protrusion of any abdominal structure other than the esophagus into the thoracic cavity through a widening of the hiatus of the diaphragm. Prevalence of hiatal hernia in the literature varies from 10% to 60%, but it is hard to estimate the true prevalence of hiatal hernias since many patients may remain asymptomatic and diagnostic criteria are variable. More than 95% of all hiatal hernias are sliding hiatal hernias, while the remaining 5% account for paraesophageal hernias. Hiatal hernias are infrequent in younger adults (before 50 years of age); late-middle-aged and older individuals are more affected by large hiatal hernias. As the population progressively becomes older in the West, the need for PEH surgery will continue to rise.

History of Paraesophageal Hernia

Paraesophageal hiatal hernia (PEH) derives its name from being "alongside" the esophagus. Initially, this was first recognized in an 1853 paper by Bowditch in which he described three cases of what we would now classify as type II PEH. However, it was only with the advent of radiology in the late nineteenth century that the prevalence hiatal hernia was better elucidated. In 1926, Akerund, a radiologist, first coined the term "hiatus hernia" and proposed three types. It was in the early twentieth century that Winkelstein proposed a relationship between the presence of hiatal hernia and gastroesophageal reflux disease (GERD). It was not until 1952 that Nicholson classified hiatal hernias into type I, the sliding hiatal hernia where the gastroesophageal junction displaces cranially into the posterior mediastinum in an axial direction, and type II, the paraesophageal hernia, where the stomach is displaced into the mediastinum juxtaposed to the esophagus. Adson and McVay describe these PEHs as "rolling" hernias, in that the phrenoesophageal ligament is intact, but the peritoneum balloons through the enlarged hiatus anterior to the esophagus. This was the definition of PEH, i.e., the gastroesophageal junction fixed inferior to the hiatus with the stomach rolling into the mediastinum, until the "mixed" type was recognized as distinct type of PEH, the type III, and, later, type IV which includes other organs were added, in the latter half of the twentieth century.

Early surgical correction focused on reducing the hiatal hernia with suture closure of the hiatus to restore "normal" anatomy. Following Soresi's initial operative report in 1919, the Mayo Clinic published their experience in treating 27 patients in 1928 with a similar transabdominal approach. These were followed by the first transthoracic technique by Sweet at the Massachusetts General Hospital in 1950. Although Allison is credited with initiating the modern era of anti-reflux surgery in his 1951 description of the altered physiology at the cardia leading to regurgitation symptoms, his focus was on the treatment of GERD, not necessarily treating the consequences of PEH. Medical treatments for GERD in the mid-twentieth century were rudimentary at best; therefore, the sequelae of GERD were more severe. Ulceration, stricturing, and fibrosis were more common leading to the "short esophagus." Collis, in 1957, addressed

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this problem by developing the esophageal-lengthening gastroplasty which now bears his name. However, it was in 1967 that Skinner reported the high risk of mortality in patients with PEHs and the dictum that all PEHs need repair prior to catastrophic gastric incarceration and strangulation was set forth. It was not until the 2002 publication of Stylopoulos, Gazelle, and Rattner that this dictum was challenged and observation become acceptable for asymptomatic patients.

Open operations were the norm, until Dellamagne's publication of the first laparoscopic Nissen fundoplication. Shortly thereafter in 1992, Congreve described the first laparoscopic paraesophageal hernia repair. After years of debate, this now has become the accepted first-line approach. Although still controversial, mesh reinforcement was first reported in 1993 by Kuster and Gilroy.

This history has brought us to our present-day approach to PEH.

Classification

Paraesophageal hernias are classified into four types according to the degree of the intrathoracic prolapse of the GEJ and its relationship to the herniated stomach. See Table 14.1 for more details about the different types of paraesophageal hernia. Imaging of the different types are also shown in Fig. 14.1.

Table 14.1 Classifications of paraesophageal hiatal hernia

Type	Characteristic	GEJ location	Anatomic findings
Type I (sliding hiatal hernia)	Most common type and represents more than 95% of all cases	Intrathoracic	Laxity of phrenoesophageal ligament, with the contextual creation of a peritoneal sac These hernias can be observed in cases of increased intra-abdominal pressure (obese, pregnant patients, and patients with constipation)
Type II	Rarest of all hiatal hernias	Intra-abdominal	The GEJ is below the hiatus, likely held in place by residual intact portion of the phrenoesophageal ligament Form due to a local defect of the phrenoesophageal membrane, usually in the left posterior aspect. A true hernia sac forms through this defect, with intrathoracic herniation of the gastric fundus
Type III	Most common type of paraesophageal hernias	Intrathoracic	Represent a combination of sliding hernias and type II hernias As the size of the hernia sac continues to enlarge with relative fixation of the terminal esophagus to the prevertebral fascia, the greater curvature slides up, flipping over in the form of both organoaxial and mesoaxial rotation This results in a twisted upside-down stomach in which the pylorus may be higher than the GEJ and the greater curvature is to the right of the esophagus
Type IV		Intrathoracic	This is the result of an increased intra-abdominal pressure in the presence of a large hiatal defect and abnormal laxity of the gastrosplenic and gastrocolic ligaments Type IV PEH occurs when another abdominal organ, such as the spleen, the small intestine, or, more frequently, the colon herniates and joins the stomach in the intrathoracic sac

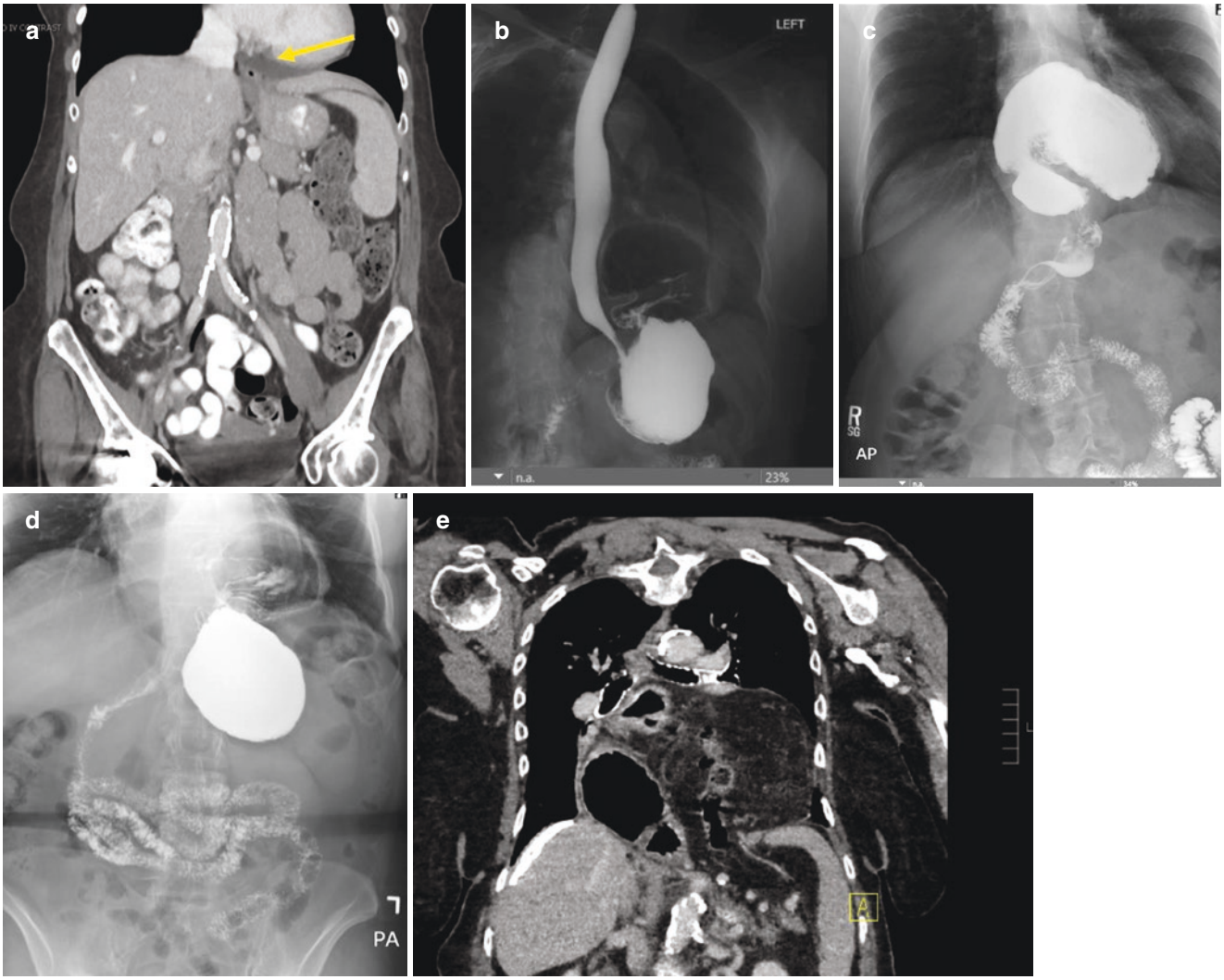

Fig. 14.1 (**a**) Type 1 (sliding) hiatal hernia on CT scan. (**b**) Type 2 hiatal hernia on upper GI series. (**c**) Large type 3 hiatal hernia on upper GI series. (**d**) Type 3 hiatal hernia with organoaxial rotation on upper GI series. (**e**) Type 4 hiatal hernia with stomach and bowel herniation on CT scan

Indications for Surgery

Most surgeons will agree that symptomatic hernias require surgical repair. Type I sliding hiatal hernias have been thought to be almost inconsequential and not warranting surgical repair except when accompanied by GERD. On the contrary, the management of asymptomatic patients remains controversial. Analysis of five studies suggested that routine elective repair of asymptomatic paraesophageal hernias is not indicated. They concluded that the risk of elective repair exceeds any benefit in otherwise asymptomatic patients aged 65 years or older. At the same time, the results of emergent surgery for acute paraesophageal hernia have improved through the years. Patients with hiatal hernia who present with strangulation of the stomach because of acute gastric volvulus should undergo emergent reduction of the stomach and limited gastric resection in cases of gastric necrosis. In general, patients often adjust their diet or eating habits to avoid symptoms so a detailed history should be obtained (Table 14.2).

Table 14.2 Diagnostic modalities for paraesophageal hernia

Imaging	Uses	Diagnosis	
Contrast studies	Determine the anatomy, size of the hernia, and orientation of the stomach – Helpful to gauge the reducibility of the hiatal hernia – Precisely localize the gastroesophageal junction in relation to the esophageal hiatus – May detect short esophagus in some cases	Sliding hiatus hernia: Greater than 2-cm separation between the mucosal B ring at the site of the squamocolumnar junction and the diaphragmatic hiatus. If a B ring is not evident on barium swallow, the demonstration of at least three rugal folds traversing the diaphragm is diagnostic of a sliding hiatus hernia	
Esophagogastroduodenoscopy	– Allows visual assessment of the mucosa of the esophagus, stomach, and duodenum – Determine the size and type of hernia – Evaluate gastric viability among patients undergoing emergency surgery for incarcerated hernias	– Inability to reach the duodenum in the presence of a large hiatal hernia is diagnostic of a volvulized paraesophageal hernia – Retroflexed view on upper endoscopy shows a portion of the stomach herniating upward through the diaphragm adjacent to the endoscope – Sliding hiatus hernia is diagnosed when there is greater than 2-cm separation between the squamocolumnar junction and the diaphragmatic impression	
Esophageal manometry	Demonstrate the level of the diaphragmatic crura, the respiratory inversion point, and the location of the lower esophageal sphincter	– Hiatus hernia is characterized by the separation of the crural diaphragm from the lower esophageal sphincter (LES) by a pressure trough – Small sliding hiatus hernias (<2 cm) often reduce spontaneously during manometry and can only be diagnosed with certainty during surgery	
pH testing	Identify the presence of increased esophageal acid	Confirmation of abnormal gastroesophageal reflux by demonstration of increased esophageal acid exposure is necessary before considering operative intervention in patients with a sliding hiatal hernia	
Computed tomography (CT) scan	In urgent situations for patients with suspected volvulized paraesophageal hernia	If intestinal obstruction and strangulation occur, dilated intestinal segments will be visualized with air-fluid levels within the chest cavity and abdomen	
Chest radiograph	Identify soft tissue opacity with or without an air-fluid level within the chest	Retrocardiac air-fluid level is pathognomonic for a paraesophageal hiatal hernia	

Surgical Anatomy

It should be noted that in clinical parlance, what is often referred to as the right crus of the diaphragm is technically speaking the anatomic right bundle of the right crus. Similarly, the left crus is technically the anatomic left bundle of the right crus (see Fig. 14.2). The true left crus travels to the left of the aorta. In this chapter, we will adopt the clinical nomenclature since this work is being written for clinicians.

The diaphragmatic crura tether the diaphragm to the vertebral column. These "legs" of the diaphragm split from the central tendon and extend around the esophagus to create the hiatus.

The area where the legs cross inferiorly to the esophagus and across the aorta is known as the crural decussation and median arcuate ligament. The right crus is typically straight at the hiatus, while the left crus tends to bow out toward the left. This has implications when closing the crural defect in hiatal hernia repair as one often must travel farther on the left crus than the right for a symmetric closure when the closure is started inferiorly and proceeds cephalad. The anterior part of the crura is more tendinous, and although anterior crural repair is technically easier and may seem a good choice, this technique leads to kinking of the esophagus that may cause dysphagia.

In the course of surgical repair, particular attention must be paid to avoiding compromise of crural integrity during sac dissection, in order to prevent recurrences. When performing surgical procedures on the esophageal hiatus, it is imperative to recognize and preserve the contiguous structures, which could be accidentally injured. The aorta can be very close to the right and left crus, particularly in thin patients. Care must be exercised when initially developing the plane between the right crus and esophagus to not go too far posterior and encounter the aorta. Similarly, when mobilizing the left side of the esophagus, it is critical to have the aorta in sight as the tissues between the esophagus and left crus are separated. The posterior vagus nerve will often remain on the base of the right crus with anterior retraction of the esophagus. Care must be taken to make sure that all tissue in front of the decussation is mobilized with the gastroesophageal junction (GEJ) to avoid injury to the posterior vagus nerve during mobilization of the GEJ. The anterior vagus nerve is typically more embedded into the esophageal wall located at the 12–1 o'clock position at the hiatus. Injury can be avoided with gentle downward traction of the anterior fat pad and careful dissection of this area.

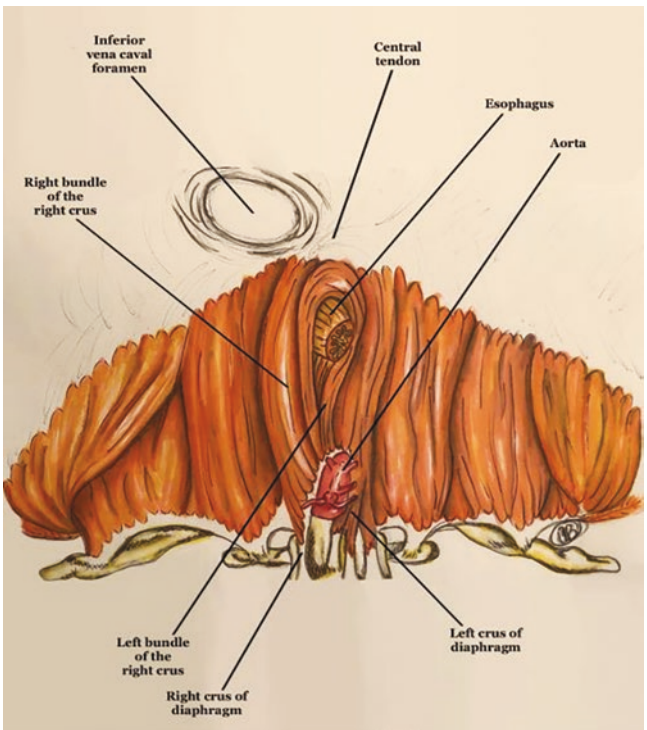

Fig. 14.2 Anatomy of the inferior diaphragm showing the relationship of the crura and the esophagus and the aorta

During the mediastinal dissection, the pleura may be encountered crossing the midline from either side or may be adherent to the esophagus in cases of long-standing disease. No structure above the hiatus should be transected without first full visualization and identification of the critical anatomic structures in the region.

The anterior and posterior vagal trunks cross the hiatus along the esophagus, together with the esophageal branches of the left gastric artery and vein, and some lymphatic vessels. Although the IVC is generally not encountered during routine anti-reflux surgery, it can be remarkably close to the margin of the right crus during paraesophageal hernia repair. It is imperative that the surgeon avoids wide swings of motion which may injure the inferior vena cava medially or the spleen laterally, especially while suturing and tying in this relatively confined anatomic space.

The thoracic duct, the celiac ganglia, the phrenic artery and vein, the mediastinal pleura, and an inconstant aberrant left hepatic artery lie close to the hiatus and should all be preserved.

The phrenoesophageal ligament, or Laimer's membrane, is an extension of the inferior diaphragmatic fascia and attaches to the esophagus at the gastroesophageal junction. The phrenoesophageal ligament serves to seal the esophageal hiatus to maintain separation between the chest and abdominal cavities. An anterior weakness in Laimer's membrane, together with a contextual weakening of the pleuroperitoneal membrane and the enlargement of the esophageal diaphragmatic hiatus, may permit the herniation of the fundus and the body of the stomach into the thorax, alongside the esophagus.

There is usually a fat pad surrounding the GEJ, which should be dissected carefully during the course of a PEH

repair to enhance visualization and mobilization. One of the anatomic structures that maintains the location of the GEJ is the meso-esophagus, a dense fibrous cellular tissue, included in the posterior gap between the peritoneal leaflets interposed between the esophagus, the aorta, and the diaphragmatic pillars. The meso-esophagus is prolonged inferiorly by the gastrophrenic ligament, whose dissection is necessary when the gastric fundus is mobilized to strengthen the fundoplication.

Technical Considerations

Open Vs Laparoscopic Vs Robotic

Laparoscopic approach has come to be considered the standard of care today for repair of elective paraesophageal hernias as a result of the superior short-term outcomes displayed in many studies. Figure 14.3 illustrates the typical laparoscopic view on entering the abdomen. The laparoscopic approach has the advantage of ensuring decreased perioperative morbidity and mortality compared to open transthoracic repair. For emergency cases where there is peritoneal contamination or in cases of contraindications to pneumoperitoneum, the transabdominal open approach is still considered the most appropriate.

Robotic-assisted surgery represents a novel approach to PEH repair that could be advantageous for the surgeon, especially during the most challenging cases. Despite the evolution of laparoscopic surgery as the accepted standard in the surgical management of PEH because of lower morbidity than open repair, concerns remain regarding long-term recurrence rates. Robotic surgery has been increasingly applied to PEH repair as in other areas of surgery. There is a growing body of literature supporting the feasibility and safety of robotic PEH repair. Early retrospective studies have suggested similar short-term outcomes including length of stay, operative time, and morbidity. However, there have been no randomized trials comparing robotic PEH repair to laparoscopic repair. Concerns regarding cost and long-term outcome remain.

Dissection of the Hiatus

Most paraesophageal hernia surgeries begin with gaining exposure to the esophageal hiatus. A proper hernia repair requires complete dissection of the hiatus rather than reduction of the hernia contents from the sac (see Fig. 14.4a). We begin by gentle reduction of the stomach and any other organs from the hernia sac. Many authors describe starting their hiatal dissection at the right crus and proceeding posteriorly to the left crus. While this approach is routinely done for laparoscopic fundoplication, this may not be the safest approach especially for large paraesophageal hiatal hernia repairs. We frequently find that the left gastric vessels have migrated into the chest, thus making dissection along the right crus more challenging. Therefore, we prefer to approach the hiatal dissection with initial sac dissection starting at the left crus. We begin our dissection with the short gastric vessels in the left upper quadrant, the dissection of the fundus and display of the left crus. We recommend staying above the level of the middle of the spleen to avoid the splenic artery. Dividing the short gastric vessels will increase mobilization of the stomach, facilitate a fundoplication, and improve exposure of the operative site. The dissection is taken anteriorly dissecting the sac while traction on it is directed caudad. Anteriorly, this dissection is taken to a point across the midline (12 o' clock position of the hiatus). Posteriorly, the phrenoesophageal membrane is gently dissected till the confluence with the right crus begins to be seen. Attention is then directed to the right side. This dissection is started at the *pars flaccida*; then, the gastrohepatic ligament is divided leaving sizable accessory or replaced left hepatic arteries along with the hepatic branch of the vagus nerve intact.

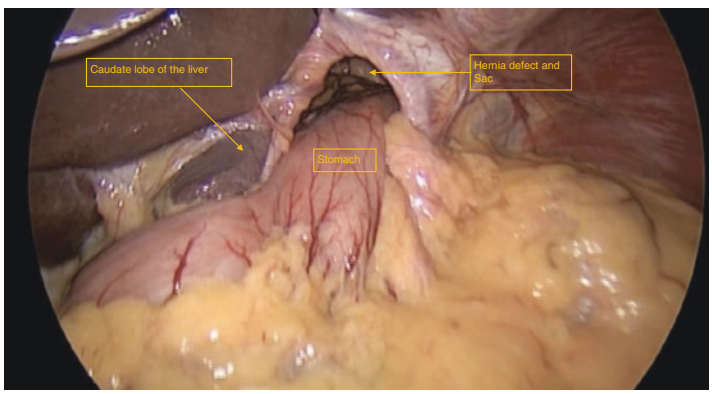

Fig. 14.3 Typical anatomic findings in a paraesophageal hiatal hernia

The left gastric artery should always be identified and avoided. In large PEHs this vessel may be displaced cephalad even into the mediastinum and could potentially be injured. The surgeon should also be cognizant of the possibility of other anomalous arterial architecture. The repositioned left hepatic artery originating from the left gastric artery is often encountered. The left gastric artery may also originate directly off the aorta instead of the celiac trunk and could be at risk for iatrogenic injury. Adroit technical skill is required in dissecting in what is a relatively confined space.

After traversing the phrenoesophageal membrane posteriorly from the right side, a Penrose drain or umbilical tape is placed around the esophagus to facilitate the dissection of the posterior portion of the hernia sac and the mediastinal

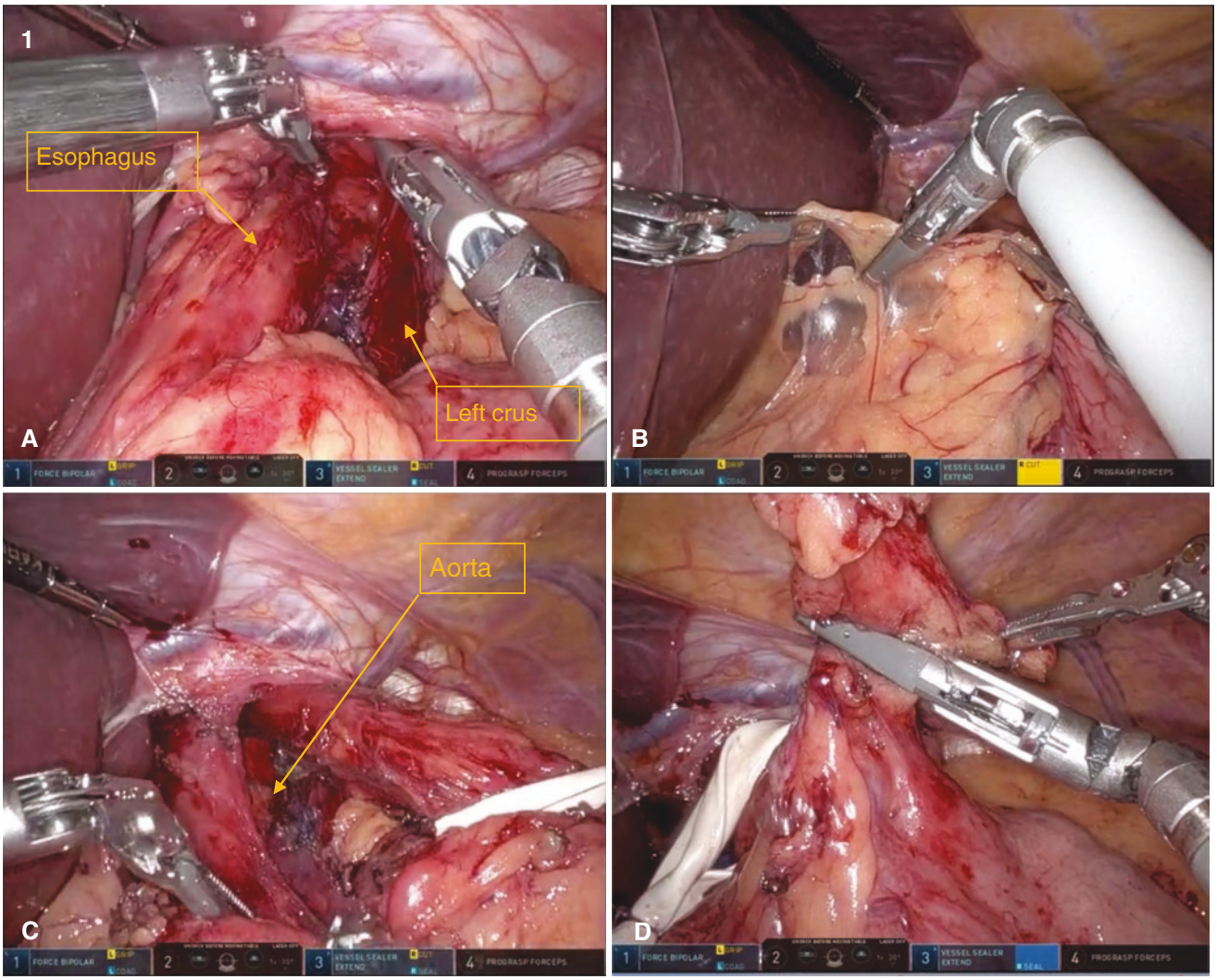

Fig. 14.4 Operative technique: (1.) dissection of the hiatus—(A) Dissection of the left crus and mobilization of the sac (**B**) Dissection of the gastrohepatic ligament starting at the pars flaccida provides access to the right crus (**C**) completed hiatal dissection (**D**) Excision of fat pad and sac.

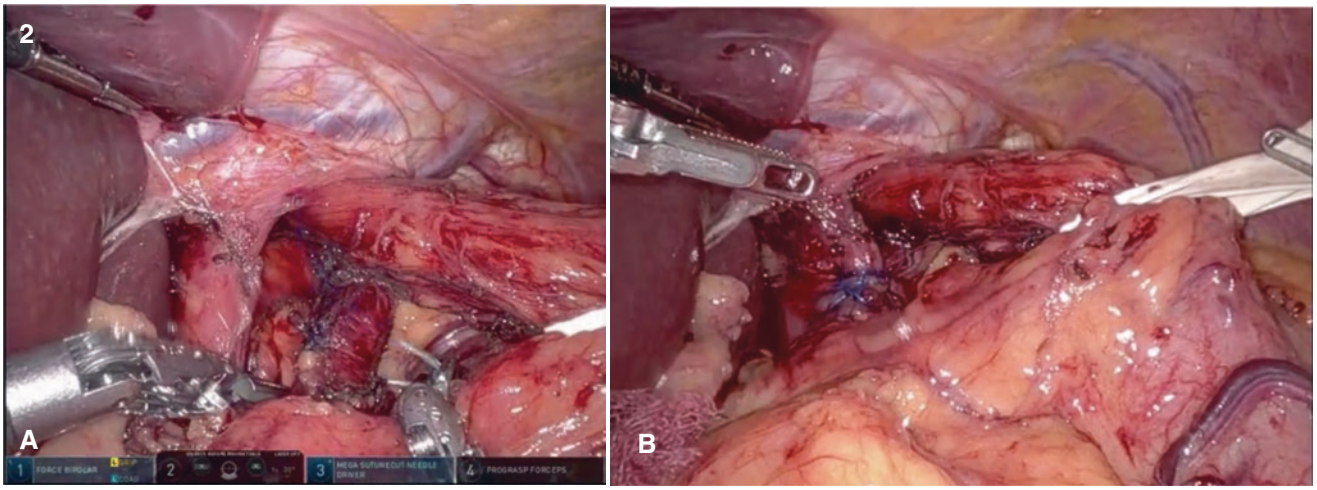

Fig. 14.4 **Operative technique: (2.) crural repair—(A)** Placement of initial suture. *Note proximity of the aorta as it courses under the lowest portion of the left crus.* **(B)** Completed crural repair, in this case with permanent monofilament barbed suture

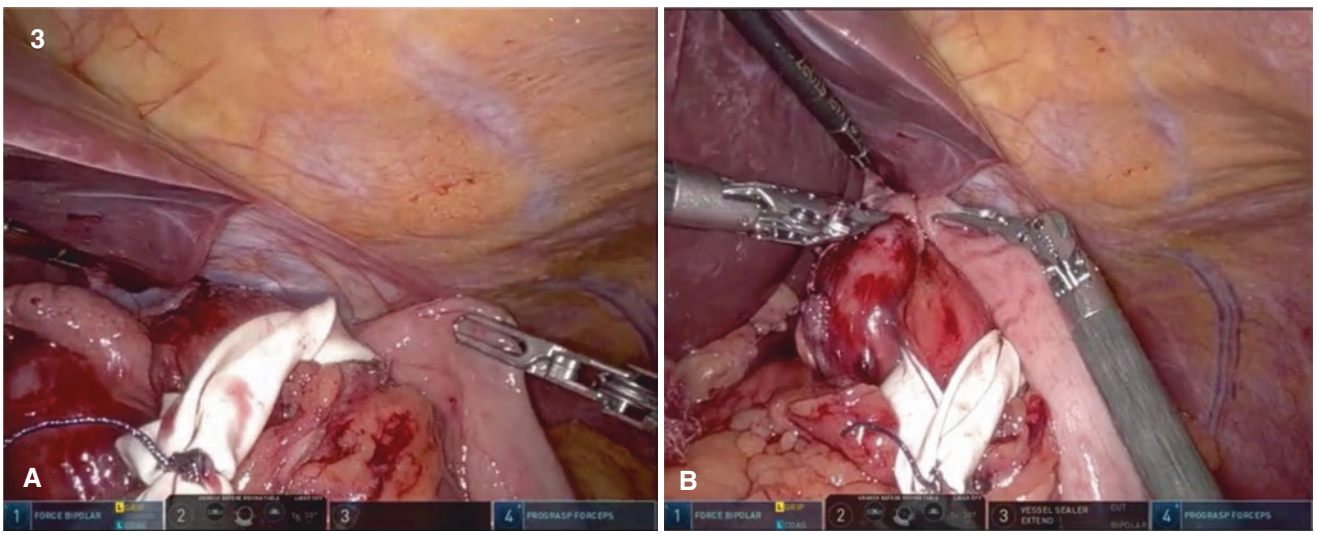

Fig. 14.4 **Operative technique: (3.) assessing floppiness of the wrap. (A)** "Shoe shine" maneuver **(B)** Ensuring adequacy of the fundoplication over the size 58Fr bougie

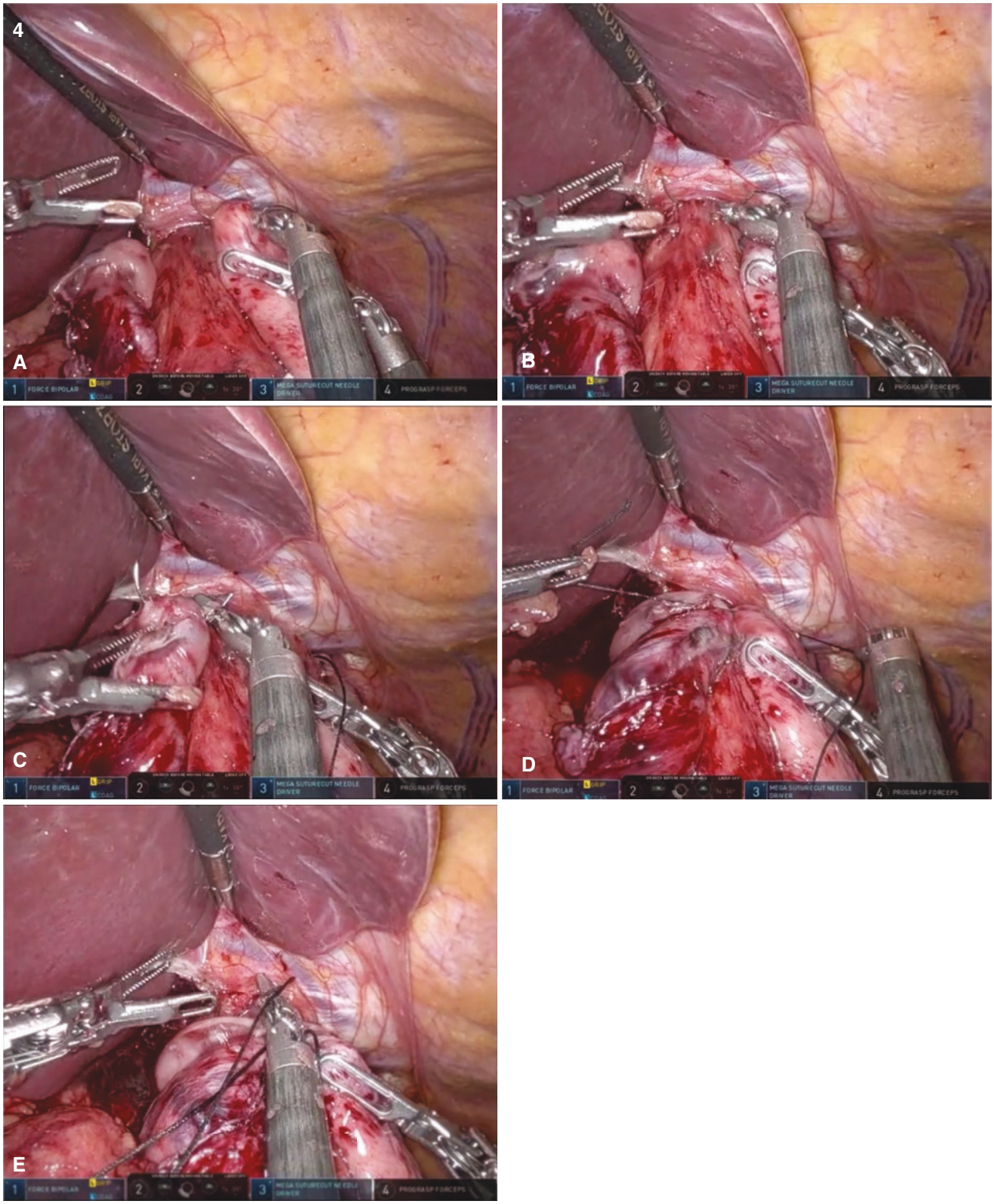

Fig. 14.4 Operative Technique: (4.) Nissen Fundoplication. The first suture is placed through the left side of the fundus (**A**), through the esophagus (**B**) then through the right side of the fundus (**C**). This suture is tied (**D**) then the same strand used to anchor the wrap to the superior aspect of the right crus (**E**)

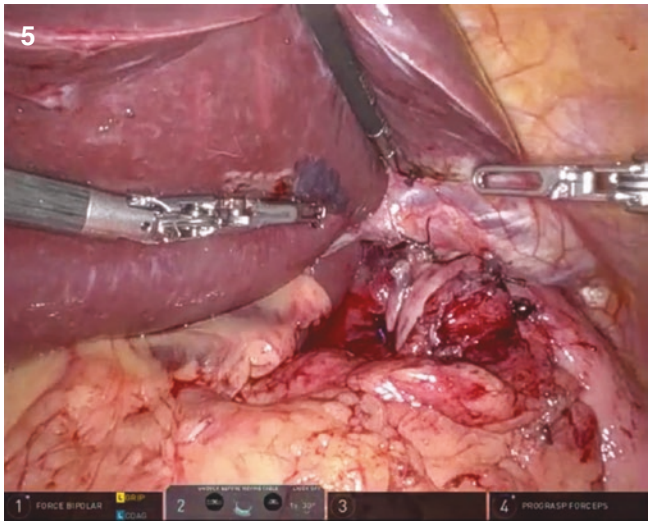

Fig. 14.4 Operative Technique: (5.) Completed repair. Additional sutures have been placed incorporating fundus to fundus. The wrap has also been anchored to the left crus and the crura posteriorly on the right side

dissection. Using gentle anterior and caudad traction on the Penrose drain, the dissection of the hiatus is continued. Injury or transection of the vagal nerves should be avoided to reduce the risk of delayed gastric emptying.

Excision of the Hernia Sac

Several studies found that sac dissection and excision are essential key steps in paraesophageal hiatal hernia repair. Sac dissection help release the tethering of the esophagus, facilitate intraoperative reduction of the hernia, and decrease early recurrence, as well as protecting the esophagus from iatrogenic damage. After reducing the hernia contents, traction should be placed on the hernia sac and not on the stomach, in order to prevent inadvertent injury. As previously mentioned, a Penrose drain or umbilical tape can be used around the esophagus for traction to facilitate the dissection. The sac dissection is carried out in the avascular plane to avoid injury to nearby critical structures. The hernia sac should be dissected completely off the mediastinum to allow complete reduction of the herniated organs. Subsequent excision of the peritoneal hernia sac is performed routinely, yet the evidence to support this practice is not enough. Although we think that sac dissection and excision should be an essential part of the procedure, no strong evidence from the literature exist.

A special consideration is for large hiatal hernias where sac excision often is very challenging and hazardous. For large hiatal hernias, sac excision might predispose to vagal nerve injury. Therefore, some experts advocate that disconnection of the sac from the crura and sac dissection only with partial sac excision is enough. Partial sac dissection is important to allow fundoplication to be performed without excess bulk by a large residual sac.

Esophageal Mobilization

Several technical factors can reduce hiatal hernia recurrence. One of the very important technical issues that is wildly (widely?) agreed upon is to bring the gastroesophageal junction at least 2–3 cm into the abdomen without tension. Extensive mediastinal esophageal mobilization and high mediastinal dissection help bring the gastroesophageal junction into the abdomen. If mobilization fails to bring the gastroesophageal junction into the abdomen, an esophageal lengthening procedure should be performed. Rathore et al. and others suggested the addition of an esophageal lengthening procedure such as Collis gastroplasty when esophagus can't be mobilized. In the retrospective reviews where Collis gastroplasty was utilized, the recurrence rates was very low. Although enough evidence from many studies ensure that performing a Collis gastroplasty is safe, it may carry a higher complication rate.

Repairing the Hiatus

The closure of the hiatal defect is considered one of the most critical steps in repair of PEH (see Fig. 14.4b). We usually perform the closure inferior and posterior to the esophagus using nonabsorbable 0 stitches. When the crus can't be approximated because of a large hiatal defect, crural relaxing incision is made to allow primary crural closure. We have abandoned the use of permanent synthetic mesh owing to the risk of erosion into the esophagus. Pledgettes of Dacron or other material may be used to reinforce the suture repair of the crural defect.

Mesh Vs No Mesh

Until the late 1990s, the use of mesh for reinforcement of hiatal hernia repair was rare. Many reports in the early 2000s suggested an extremely high recurrence rates after paraesophageal hernia repair without mesh. This has prompted many experts to advocate the use of a mesh to reinforce the primary repair without strong evidence from the literature. The most common technique described in the literature is the on-lay technique where the mesh is placed as an on-lay to buttress the underlying suture after primary crural closure.

Several trials examined the question of whether the mesh repair is beneficial. Oelschlager concluded that the benefit of

biologic prosthesis reduced the risk of severe hernias leading to fewer reoperations, but it did not reduce the rate of hiatal hernia recurrence on the long term. In summary, these trials indicate that mesh use reduces risk of recurrence on the short term, but this benefit has not been borne out with longer-term results.

Many different types of mesh have been used for paraesophageal hernia repair, but there is no consensus about which is the best. The characteristics of an ideal mesh include the following: rapid tissue integration, minimal shrinkage, lack of adherence to hollow viscera, and secure attachment.

Mesh Complications

Mesh erosion remains one of the most feared complications. Mesh erosion into the esophageal lumen leads to progressive stenosis and consequent dysphagia, esophageal obstruction, fistulization, or perforation which usually require drastic measures like esophagogastrectomy and esophagectomy. Some authors suggested that synthetic mesh when placed as a bridge is more likely to have direct contact with the esophagus and therefore might cause erosion. Biological meshes are not usually associated with erosions, but they have been associated with dysphagia. Biological meshes are thought to avoid erosion due to their capability of being progressively colonized and replaced by autologous tissue. In addition, animal studies show that biological meshes ensure adequate tensile strength and, at the same time, form minimal adhesions. Furthermore, they are more resistant to infections and induce less fibrosis compared with synthetic meshes. All these factors combined lead many authors to abandon the use of nonabsorbable mesh.

Fundoplication

Although there is no high-level evidence to support routine fundoplication during PEH repair, many reports of paraesophageal hiatal hernia repair in the recent literature describe the performance of a fundoplication as part of the repair. The choice of whether to add an anti-reflux procedure to the repair of paraesophageal hernia represents another controversial surgical decision. Most surgeons recommend an anti-reflux procedure for patients with reflux symptoms. Please see Fig. 14.4c, d. For the asymptomatic patients, the literature is split between those who advocate for the addition of this procedure in the absence of such symptoms and those who argue against that. Those who always choose to perform a fundoplication advocate that it aids in prevention of postoperative reflux, especially given that the extensive hiatal dissection during the repair might potentiate reflux. Adding an anti-reflux procedure was also found to buttress the repair to prevent recurrence. Moreover, Fuller et al. found that most patients with paraesophageal hernias have an incompetent lower esophageal sphincter and might therefore benefit from routine fundoplication.

Preoperative evaluation of esophageal peristalsis (barium swallow or esophageal manometry) helps the surgeon decide about the use of partial fundoplication versus complete wrap as in the Nissen fundoplication. If preoperative studies revealed impaired peristalsis, then partial wrap is preferred to a complete wrap. Partial fundoplication carries a lower risk of postoperative dysphagia especially with preexisting motility problems but is less effective against reflux symptoms.

Gastropexy

Ponsky et al. were one of the first groups to promote an anterior gastropexy to reduce the recurrence rate after laparoscopic hiatal hernia repair. In their prospective series, no recurrences were reported in up to 2 years of follow-up evaluation. Ponce et al. support the previous findings in their study, where 89 patients with large hiatal hernias underwent laparoscopic repair. They concluded that the addition of an anterior gastropexy significantly reduced recurrent hernias. On the contrary, Diaz and colleagues did not find any significant difference in recurrence with and without gastropexy. Yet, in patients who are too frail to undergo formal paraesophageal hernia repair, some authors have described hernia reduction and gastropexy alone without cruroplasty or sac excision. Some use a gastrostomy tube as the means of gastropexy to the abdominal wall while the stomach may also be anchored to the abdominal wall with interrupted or continuous sutures without tube placement.

Postoperative Consideration

Puri et al. recommended maintaining all patients on antiemetics for the first 24 h postoperatively to minimize this risk of postoperative nausea or vomiting, which might disrupt the hernia repair. In high-risk patients, we advise the performance of barium swallow on postoperative day one to evaluate for delayed gastric emptying and motility and to assess for esophageal leak and early hernia recurrence. It's not uncommon to find delayed gastric emptying postoperatively especially in patients with a long-standing paraesophageal hernia. This delayed gastric emptying might be mediated by possible mechanisms of an atrophic gastric musculature or vagal neurapraxia from the dissection or excessive traction during surgery. If the barium swallow

study shows an adequate repair, patients are started on a clear liquid diet and advanced to soft solids as tolerated. A full liquid diet is recommended for some period of time up to 2 weeks postoperatively. We also discourage a diet containing steak or tough meats for the first 3 months after surgery.

Healthcare Costs

Very few studies in the literature discuss the cost of paraesophageal hernia or the difference in cost between repair with and without mesh. The cost difference reported in hiatal hernia repair using different types of mesh was incurred by the cost of mesh alone.

Although biological mesh decreases the rate of early reoperations and therefore could decrease the cost of readmission and reoperation, this benefit dissipates over time. With the widespread implementation of pay-for-performance incentives to improve patient outcome, the focus on short-term outcomes has become important. Specifically, "readmissions" have become a major metric by which the performance of hospitals is ranked. Adding to that, readmissions usually represent an adverse event for the patient, and it directly affects quality of care and medical costs. Although biological mesh has not been proven to decrease long-term recurrence, many authors agree that it decreases recurrence and reoperations on the short term.

Although the synthetic nonabsorbable meshes are the least expensive, we advise against their use because of the reported erosions that usually require drastic measures. None of the biological meshes had been deemed superior to any other type. Therefore, choosing the least expensive mesh provides the best cost-benefit ratio. While surgeon and hospital preference play an important role in choosing the type of mesh used, knowledge of the individual mesh cost and outcomes will help surgeons make more informed decisions in the future.

Questions

1. A 79-year-old female is brought to the office by her daughter with complaints of severe heartburn, voice changes, and early satiety. She suffers from obesity and hypertension. She has been using a proton-pump inhibitor for several years. Her internist had obtained an upper GI barium study prior to the visit and this is shown above (Fig. 14.5). The patient has a:
   A. Type 1 hiatal hernia
   B. Type 2 hiatal hernia
   C. Type 3 hiatal hernia
   D. Type 4 hiatal hernia

Answer C. The patient has a type 3 hiatal hernia. The various types are shown in Table 14.1. In type 1 hernias, there is laxity of the phrenoesophageal ligament and the gastroesophageal junction migrates above the diaphragm into the posterior mediastinum. In type 2 hernias, the junction is intact but the funds migrates alongside the junction. Type 4 hernias involve herniation of other organs, e.g., colon, pancreas, or spleen.

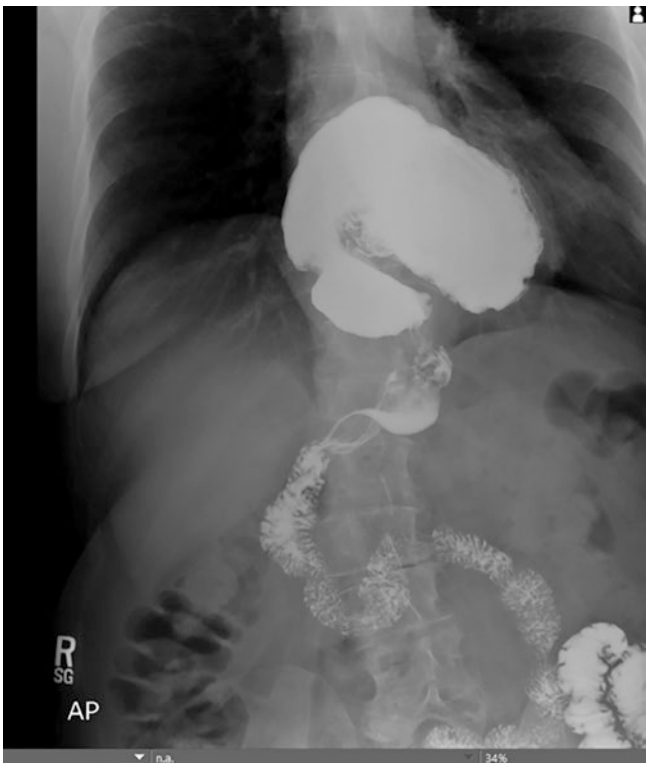

Fig. 14.5 Upper GI study showing hiatal hernia

2. The patient's internist had apparently been encouraging lifestyle modification, weight loss, and proton-pump inhibitor (PPI) for several years without success. An endoscopy is performed revealing no esophageal or gastric dysplasia. Esophageal manometry shows normal motility. Her medical comorbid conditions are optimized. The best next step in treatment is:
   A. Open hiatal hernia repair and Nissen fundoplication
   B. Laparoscopic hiatal hernia repair and Nissen fundoplication with permanent mesh
   C. Laparoscopic hiatal hernia repair and Nissen fundoplication with absorbable mesh
   D. Laparoscopic hiatal hernia repair without fundoplication

Answer C. Open hiatal hernia repairs have been replaced by the laparoscopic approach since the evolution of laparoscopy in the 1990s.

The use of permanent mesh in the repair of hiatal hernias is associated with an increased risk of erosion into the esophagus, stenosis, and dysphagia. For these reasons, this practice is not recommended. The data on biologic or absorbable

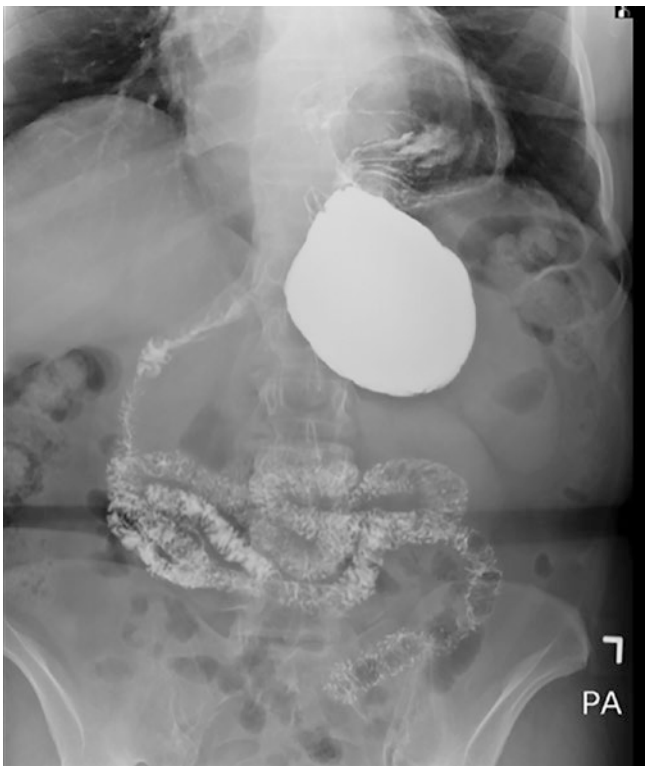

Fig. 14.6 Upper GI study showing hiatal hernia

mesh use showed short-term improvement in recurrence rates after one year; however this did not persist over longer term. However, of the choices listed it is the best next step.

The patient is symptomatic from her reflux. The patient suffers with obesity and was appropriately treated in the past with lifestyle modification, weightless, and PPI by her internist. She has clearly failed at this and surgery is appropriate.

3. A 75-year-old female is seen in the emergency room with complaints of chest pain. Bloodwork shows that she is significantly anemic. On evaluation, she is found to have sustained an acute myocardial infarction (MI). She is admitted to the medical service. Her MI is appropriately treated; however, as part of her work-up an Upper Gastrointestinal Series (UGI) with barium is obtained. A representative image is shown below (Fig. 14.6). The finding on UGI series has no bearing on her current condition:
   A. True
   B. False

Answer B. The image depicts a large type 3 hiatal hernia with some organoaxial rotation. Two common complications of paraesophageal hiatal hernias are chronic blood loss anemia and gastric volvulus. The anemia is caused by ulcers on the gastric mucosa in the area of the herniated stomach. It is not uncommon for patients to present with an acute MI related to the anemia and burden on the heart of an elderly patient. The finding on UGI series clearly could be related to her chest pain and MI from the standpoint of either the anemia or from reflux symptoms.

4. Which of the following statements is true:
   A. In performing a repair for the problem noted on UGI, closure of the defect is not necessary as long as a 360-degree wrap is performed.
   B. The use of permanent mesh is required as this is a very large defect.
   C. The sac should be left in place to avoid early recurrence.
   D. Postoperative delayed gastric emptying may occur in patients who have had this as a longstanding condition.
   E. A Collis gastroplasty should be avoided in this situation.

Answer D. In performing a paraesophageal hiatal hernia repair, closure of the defect is a critical aspect of the operation to reduce the risk of early recurrence. This is independent of whether a fundoplication is performed.

Although some surgeons may use mesh reinforcement in a large defect, permanent mesh is not recommended due to the potential catastrophic consequences of erosion, stenosis, and severe dysphagia.

Dissection and excision of the sac is actually associated with a reduction in early recurrence.

Delayed gastric emptying may occur in patients who have longstanding large hiatal hernia defects. This may be mediated by possible mechanisms of an atrophic gastric musculature or vagal neuropraxia from the dissection or excessive traction during surgery.

In patients with large or longstanding paraesophageal hiatal hernias, esophageal shortening may be present. A Collis gastroplasty may actually be useful in preventing early recurrence. The surgeon must be sensitive to this and be prepared to perform this procedure in these situations as opposed to avoiding it.

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Reoperative Anti-Reflux Surgery

15

Sumeet Mittal, Paul Kim, and Adrian Park

Objectives

1. Define anti-reflux surgery failure and understand the various mechanisms of failure
2. Understand how to work up and identify the cause and mechanism of possible failure.
3. Describe various surgical approaches for anti-reflux surgery failure

Introduction

Gastroesophageal reflux disease (GERD) is a common disorder affecting millions of patients worldwide resulting in a high healthcare burden and economic toll. Most patients are adequately treated and maintained on medical therapy, but anti-reflux surgeries (ARS) remain an important part of GERD management. Currently, there are many options available, led by the time-tested open and laparoscopic fundoplication as well as numerous endoluminal therapies and minimally invasive surgical devices which are being utilized with variable efficacy and supported by inconsistent outcome data. Unfortunately, most of the data behind the endoluminal therapies and surgical devices are observational in nature and are further limited by small sample sizes and lack of long-term data and durability. At this point in time, it is unclear where they fit within the treatment algorithm of GERD.

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Thus, fundoplication remains the gold standard with good long-term data. There is some variation within the literature, but most patients following the procedure remain off medications with good long-term outcomes. Nevertheless, reported fundoplication failure rate can range from 3 to 30%. This wide variability is due to the lack of a standardized definition of anti-reflux surgery failure as well as differences in preoperative patient selection and operative techniques. Failures are variably defined by subjective return of symptoms; persistent need for medications; patient dissatisfaction from side effects; and recurrent pathologic reflux objectively measured from various studies including EGD, pH study, and imaging studies.

The risks of failure and reoperation are multifactorial including patient and operative/technical factors. Patient risk factors include obesity; noncompliance with postoperative dietary habits; atypical symptoms including cough, globus sensation, and hoarseness; poor preoperative esophageal motility; and large hiatal hernia. Hence, patient selection, preoperative preparation, and patient engagement are critical to a successful outcome of the operation. Patients who are non-adherent to their postoperative diet and/or gain weight especially tend to have worse outcomes. Operative technical factors that may contribute to failed anti-reflux surgery include inadequate hiatal closure; insufficient intra-abdominal esophageal length; and misplaced or malconstructed wrap. Combinations of these patient and technical elements can then lead to fundoplication failure.

Regardless of the risk factors, patients who undergo reoperative anti-reflux surgery are driven ultimately by their symptoms. The most prevalent presenting symptom in these patients is recurrent heartburn. Other common symptoms include dysphagia and recurrent regurgitation. These ailments then prompt further workup that can elucidate various causes and mechanisms of failure. Hiatal hernia, either sliding or paraesophageal in nature, is the most commonly reported mechanism of failure in over 70% of the cases. Other causes include partial or complete disruption of the fundoplication in 15–20% of the cases and slipped or malpo-

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sitioned wrap in 10–12% of the cases. Once the mechanism is identified, the failure can be addressed in a variety of ways, most commonly via redo fundoplication or Roux-en-Y (RNY) reconstruction as guided by the preoperative workup and intraoperative findings.

Preoperative Evaluation and Workup

Clinical evaluation and workup of a failed ARS patient can be time-consuming but needs to be thorough. It starts with a detailed history of symptoms prior to ARS including response to acid suppression medications and workup prior to surgery. A complete understanding of the indication for surgery and preoperative physiology/anatomy is essential. Operative details such as use of any mesh at the hiatus, division of short gastric arteries, and type of fundoplication performed need to be ascertained. It is also important to elucidate the postoperative course—patients may have some degree of dysphagia and bloating for the first 6–12 weeks but is usually self-limiting. Persistent dysphagia beyond 3 months may require assessment and intervention. It is also important to inquire about resolution of reflux symptoms. It is very unusual for primary reflux-related symptoms to not respond after ARS at least for some duration. If there is no improvement of primary symptom, the initial diagnostic assessment must be questioned. This is especially true for extra-esophageal symptoms such as hoarseness, cough, etc. This process needs to be repeated for each previous ARS procedure if the patient has had more than one prior surgery.

The patient's current symptoms should then be thoroughly explored. Workup should include complete anatomical and physiological assessment of the esophagus and stomach. This should include an upper endoscopy (preferably by the operating surgeon), a video barium esophagram, and a manometry. If predominant symptoms are recurrent reflux, then pursuing objective evidence of reflux with pH monitoring off acid-suppressive therapy is essential to document recurrent reflux. Gastric emptying study is helpful if the patient has significant bloating. These tests help objectively determine presence of recurrent reflux and the current anatomy of the region.

As mentioned previously, there is no consensus classification of failed ARS, but it can be classified based on patient symptoms or anatomical status of the fundoplication and recurrence of hiatal hernia. Types of anatomical failures are more likely to be associated with certain symptoms. These symptoms can be due to obstruction of passage of food bolus from the esophagus into the stomach, abnormal backflow of gastric contents into the esophagus, or delayed gastric emptying. One should always be aware that more than one of these can occur in the same patient at presentation. Reoperative surgery should only be undertaken if symptoms cannot be controlled with medical therapy or endoscopic intervention and anatomical/physiological findings are consistent with patient-reported symptoms.

Operative Approaches

Any revisional surgeries are fraught with increased technical difficulty and potential complications, especially considering the cramped, "high priced real estate" such as the hiatus and the mediastinum in which foregut revisional surgery is undertaken. Thus, reoperative foregut surgery should be approached with caution and only by those with thorough understanding of esophagogastric physiology and expertise in foregut procedures. Experienced, skilled surgeons should be able to complete the majority of these procedures minimally invasively with conversion rates as low as 1–7%. Nevertheless, redo ARS carry an increased risk of intraoperative hollow viscus perforation, vagal injury, or need for esophagogastric resection. Additionally, there are progressively diminishing return of improvements in patient-centered outcomes associated with multiple previous procedures. Use of mesh in previous surgeries is also associated with increased need for esophagogastric resections for redo ARS.

Several patient-related factors play a critical role in decision-making of redo ARS. Morbidly obese patients are better steered toward a RNY gastric bypass as an anti-reflux procedure. Giant recurrent PEH with a hostile abdomen may be easier to approach from a transthoracic route compared to transabdominal approach. While moderate degrees of delayed gastric emptying may warrant a pyloric drainage procedure, severe or persistent delayed gastric emptying may warrant a RNY conversion. Severely impaired esophageal motility such as a dilated aperistaltic esophagus, undilatable strictures, or damage to gastroesophageal junction (GEJ) or fundus may warrant limited or subtotal esophageal resection with reconstruction. Short esophagus, if present, needs to be addressed. Figure 15.1 gives a brief schema as to our approach to surgical intervention for failed ARS.

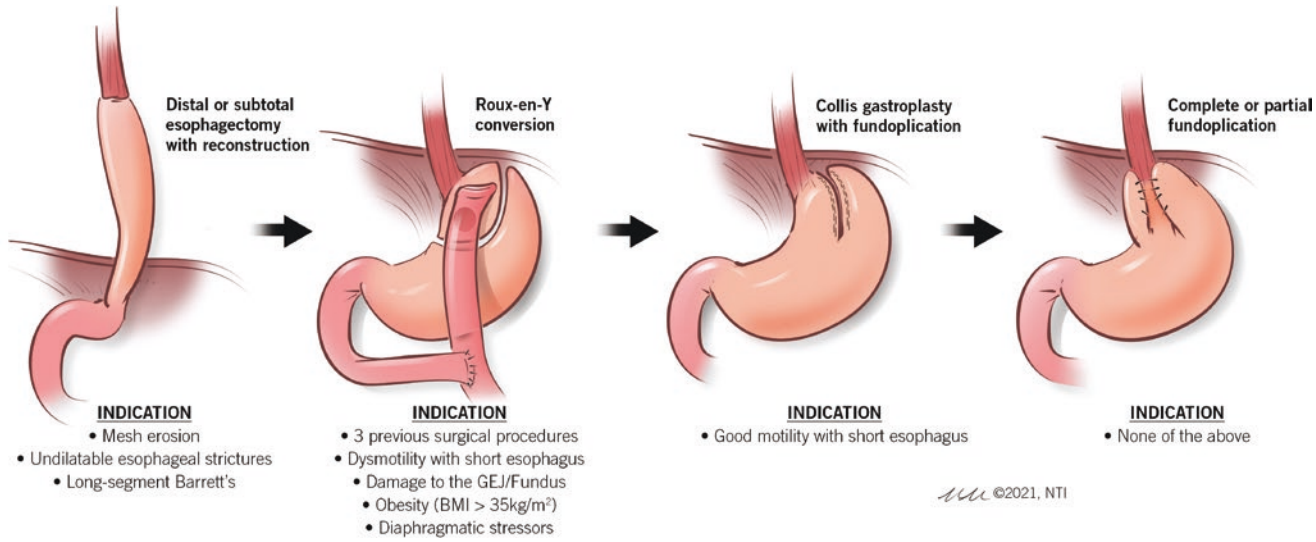

Fig. 15.1 Options for re-operative intervention after failed anti-reflux surgery

Redo Hiatal Hernia Repair and Fundoplication

For patients with good esophageal and gastric motility and intact gastric tissue that would accommodate another fundoplication, laparoscopic redo hiatal hernia repair with fundoplication should be the operation of choice. The general steps and concepts of the procedure will be detailed below, but the approach and dissection will differ in each case depending on how the initial procedure was performed.

The patient is positioned in lithotomy or split-leg position and placed in steep reverse Trendelenburg position. Pneumoperitoneum and intra-abdominal access are achieved per surgeon's preference. A total of four 5 mm ports are placed in the epigastrium, right upper quadrant, left mid quadrant, and left subcostal region. The abdomen is inspected and adhesiolysis is performed. Often, the liver needs to be carefully separated from the stomach via sharp and blunt dissection. Once that is accomplished, a liver retractor is positioned.

Unfortunately, there is great variability in fundoplication and hiatal closure techniques. If the prior surgeon used pledgets or mesh, this could render the posterior dissection more tenuous. Therefore, it is critical to approach the dissection cautiously with meticulous technique, seeking and identifying key anatomic structures such as the crura, GEJ, caudate lobe, and spleen to always ensure safe planes of dissection. The stomach is carefully mobilized dividing all the adhesions, slowly working toward the hiatus. Minor injuries to the stomach and liver may occur but are generally easily managed. Obviously however, injuries to the vena cava, aorta, esophagus, or spleen can be disastrous and must be avoided at all costs. Once the crural pillars are identified, circumferential dissection of the hiatus is performed. If hiatal hernia is present, complete dissection and reduction of the hernia sac and the stomach is performed. The vagus nerves, if preserved during the initial operation, are at great risk of injury during this phase of the dissection, and great care must be taken to identify and preserve them. Again, most of these dissections can be safely completed minimally invasively, but if there are significant adhesions that prevent safe dissection, conversion to either open transabdominal or thoracic approach may be needed.

Once the stomach is returned to its anatomic position, the fundoplication is evaluated. If the wrap is intact and in good position and a recurrent hiatal hernia was found and corrected, revision of the fundoplication may not be needed. Otherwise, and more commonly, the fundoplication must be taken down. In most cases, a plane between the wrap can be identified and developed. An adequate 2–3 cm length of intra-abdominal esophagus must be secured. If additional length is needed, Collis gastroplasty can be performed using an endoscopic linear stapler over a bougie. The fundus is then evaluated to ensure there is enough healthy stomach left to perform a redo fundoplication. In the setting of an inadequate or attenuated fundus, Collis gastroplasty can also be very useful to create a neo-fundus for the fundoplication. Cruroplasty is performed posteriorly in a standard fashion with nonabsorbable sutures with the bougie in place. Depending on the integrity of the crura, the hiatal closure can be reenforced with patient's autologous tissue such as the triangular ligament or falciform ligament flap. If there is no suitable tissue, a biosynthetic absorbable mesh can also be used for buttressing. Finally, either a full or partial fundoplication is performed according to the preoperatively determined esophageal motility.

Multiple studies have shown that redo fundoplication is safe, feasible, and effective with perioperative complication

rate of 14% but with a reported range of 0–44%. The most common complications are pneumothorax or capnothorax and gastrointestinal perforation either stomach or esophagus. Overall reported conversion rates for minimally invasive approaches are low at around 7%. It is important to reiterate the long-held laparoscopic conventional wisdom that it is not a failure to convert to an open approach for safe completion of the procedure. In certain cases, knowing when to desist surgically rather than proceeding until the patient is subject to irreparable damage demonstrates sound surgical judgment. Overall success rates of revisional anti-reflux surgery vary from 57 to 94% depending on the series, but on average, 80% of the patients have relief of their symptoms long term. Unfortunately, 5–10% of the patients end up requiring further revision, which unfortunately carries a lower success rate.

Roux-en-Y Reconstruction

The term Roux-en-Y has become sine qua non for a gastric bypass and bariatric surgery, but the term implies a Roux limb gastrojejunostomy. This can be done either with a gastric bypass leaving distal stomach in situ or with a distal gastrectomy. RNY reconstruction intuitively makes sense for definitive management of pathological reflux as it eliminates the gastric reservoir diminishing gastroesophageal reflux. The size of proximal gastric pouch determines the degree of reflux—larger pouch allows for greater food intake and possible addition of fundoplication but results in larger acid-producing reservoir. A RNY reconstruction also effectively eliminates bile reflux and improves gastric emptying.

Traditionally, outcomes of fundoplication have been reported to be poor in obese patients. With increasing experience of RNY gastric bypass for bariatric surgery, the salutary effect of the procedure on elimination of GERD in this population became apparent. The exact BMI cutoff as to when to proceed with RNY over fundoplication, >35 versus >40, has been debated. In fact, a study showed that patients with BMI greater than 32 have significantly worse outcomes with redo fundoplication. In addition to amelioration of GERD, a RNY reconstruction can have additional benefit of weight loss depending on size of gastric pouch and length of biliary and alimentary limbs.

Besides the obese patients, RNY reconstruction is preferred in the following subset of patients who are likely to have poor outcomes after redo fundoplication.

Multiple Previous Fundoplications

Previous anti-reflux surgery increases the likelihood of visceral and vagal injury during reoperative procedure. The risk rises significantly with increase in number or prior procedures. This holds true both in the open era and in the laparoscopic era with two or more prior surgeries being associated with significant risk of vagal injury and poor outcomes. Perhaps, it is wiser to strongly consider a RNY reconstruction after two or more prior surgeries.

Short Esophagus

An adequate intra-abdominal esophageal length is a requisite for tension-free fundoplication. There is a greater prevalence of short esophagus in patients undergoing redo anti-reflux procedures. While Collis gastroplasty and fundoplication are options in these patients, one study showed that RNY reconstruction fared better in these patients. Additionally, a RNY reconstruction may be the most viable alternative in patients who already have had a prior Collis-fundoplication procedure.

Esophageal Dysmotility

The concern in patients with esophageal dysmotility is whether there is ample distal esophageal peristaltic vigor to propel the food across the fundoplication. Unfortunately, esophageal dysmotility is quite frequent in patients undergoing reoperative anti-reflux surgery. A redo partial fundoplication is an option depending on the degree of severity of the dysmotility. However, RNY reconstruction has also been shown to be an effective alternative for reflux control in this subset of patients especially for those with moderate to severe esophageal dysmotility.

Damaged Gastroesophageal Junction or Fundus

Perhaps the most definitive indication to use RNY reconstruction is a damaged GEJ or fundus which precludes creation of a redo fundoplication. Reoperative anti-reflux surgery almost always requires full takedown of previous fundoplication and restoration of normal anatomy prior to redo fundoplication. Use of mesh at previous surgery has been associated with increased visceral and/or vagal injury at the time of re-operative surgery. Similarly, an increasing number of previous procedures increase the chance of surgical injury and/or devitalized tissue. Redo fundoplication is not a safe or viable option in these patients, and RNY reconstruction is the only alternative. Operative findings may even warrant a RNY esophagojejunostomy if GEJ is not salvageable. More commonly, a small gastric pouch can be preserved for GJ anastomosis. Sometimes, a long narrower pouch is needed as the proximal most part of lesser curvature

has been devascularized either during the prior surgery or during the takedown of a slipped fundoplication limb.

Delayed Gastric Emptying

Delayed gastric emptying is not infrequently present in patients undergoing reoperative anti-reflux surgery. It is either due to preexisting unidentified delayed gastric emptying or secondary to vagal injury during the prior procedure. Unfortunately, nuclear medicine gastric emptying study does not correlate very well with patient-reported symptoms, which may be a manifestation of other underlying GI disorders such as IBS. However, objective evidence of delayed gastric emptying, either delayed gastric emptying study or finding of food/bezoar in the stomach, should prompt some additional procedure to improve gastric emptying. While pyloric drainage procedures can be used, a RNY reconstruction is the most definitive treatment. In patients with underlying severely delayed gastric emptying along with bile gastritis, an antrectomy with RNY is an excellent definitive procedure, and a redo fundoplication can still be created if esophageal motility and GEJ anatomy so allow.

Overall, RNY conversion is an excellent alternative redo fundoplication in a subset of patients with challenging anatomy (short esophagus/damaged GEJ) and/or physiology (poor motility, delayed gastric emptying, obesity). Some concerns raised with RNY reconstruction include increased operative morbidity and potential weight loss and nutritional deficiencies. However, one study showed that while overweight patients lose weight, most underweight patients actually gain weight after their severely debilitating symptoms are ameliorated. More recently, another study has shown that in experienced hands, the morbidity of a RNY conversion is similar to redo fundoplication and advocated for earlier adoption in properly selected patients. Over the last 15 years, it has gained increasing recognition as a definitive and better intervention for failed anti-reflux surgery – it has gone from being dismissed and to be kept as last nuclear option to a viable definitive option in properly selected patients.

Non-tissue Redo ARS

As mentioned previously, there are numerous endoluminal therapies and minimally invasive surgical devices which are being utilized, but the data remains inconsistent even when used in procedure-naïve patients. While there may be some anecdotal uses of endoscopic ARS or LINX procedure as a redo anti-reflux procedure, there is no literature or data to support the use in patients with failed previous ARS and should not be used.

If the patient is presenting after a failed endoluminal therapy or minimally invasive surgical device placement, the same thorough workup and principles apply. Intraoperatively, any previously placed surgical devices should be removed, and careful dissection must be carried out to restore "normal" anatomy. Depending on tissue quality or damage to the GEJ/fundus, either a fundoplication or Roux-en-Y reconstruction can be performed.

Conclusion

Failure of anti-reflux procedure, most commonly defined by recurrence of symptoms, must be worked up thoroughly with studies such as barium esophagram, EGD, pH study, manometry, and gastric emptying study to elucidate the cause of the failure. Redo ARS can be performed minimally invasively with good outcomes, but the approach and the type of redo ARS should be determined and handled carefully by surgeons with appropriate foregut experience and expertise.

Questions

1. While doing a laparoscopic redo hiatal hernia repair and fundoplication for failed previous Nissen fundoplication, you notice that although the fundus appears healthy, you do not have enough fundus to bring retro-esophageally. What is the next best course of action?
   A. Do not perform a fundoplication.
   B. Attempt a partial fundoplication.
   C. Collis gastroplasty, Nissen fundoplication.
   D. Gastrectomy with esophagojejunostomy.

Answer: C. Collis gastroplasty can be used to create a neofundus which can then be used to perform a Nissen fundoplication.

2. Patient presents to your office for possible redo anti-reflux surgery following failure of a previous laparoscopic Nissen fundoplication. Workup has revealed a recurrent pathologic reflux with severe esophageal dysmotility. Intraoperatively, the patient was also found to have a shortened esophagus. What would be the best procedure for this patient?
   A. Collis gastroplasty
   B. Partial fundoplication
   C. Partial fundoplication, gastropexy (PEG)
   D. Roux-en-Y reconstruction

Answer: D. Given the severe esophageal dysmotility with shortened esophagus, Roux-en-Y gastric bypass would be the most optimal procedure. Collis gastroplasty with partial fundoplication may be a potential option, but it is not part of the answer choices.

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Part III

Barrett's Esophagus and Esophageal Neoplasm

Screening for Barrett's Esophagus

16

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Introduction

Screening looks for a condition that predisposes to disease, and it may be applied either to preselected individuals who are considered at high risk or to a whole population. The people who are screened may not exhibit any signs or symptoms (asymptomatic), or they might exhibit a few nonspecific symptoms (oligo-symptomatic). Screening is expected to identify conditions that may turn into a disease in the future, thereby allowing earlier intervention aimed to reduce disease morbidity and mortality.

Barrett's esophagus (BE) is defined as columnar metaplasia of the esophagus in which the squamous epithelium of the esophagus is replaced by columnar epithelium in patients with reflux disease. Chronic exposure of the esophageal mucosa to gastric refluxate causes the squamous epithelium to undergo—as an adaptive response—replacement by gastric refluxate-resistant intestinalized columnar epithelium [1]. This leads to a disease spectrum that begins with gastroesophageal reflux disease (GERD), over time progressing to BE and in turn further progression to esophageal adenocarcinoma (EAC). Esophageal cancer constitutes 1% of all cancers and has a very poor prognosis, affecting 19,260 people and leading to 15,530 deaths annually in the United States [2]. BE is the only known precursor of EAC [1]. With strong data on the potential of endoscopic treatment of dysplasia to prevent progression to EAC, screening for BE and treatment of dysplasia may prevent EAC [3]. This chapter discusses the rationale, indications, methods, and outcomes of screening for BE.

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Why Screen for BE?

EAC incidence has increased exponentially over the past 3–4 decades, making it the predominant type of esophageal cancer in the United States [4]. EAC is associated with a dismal 10–20% 5-year survival rate, owing to paucity of symptoms until advanced stages are reached and propensity for early extraesophageal metastasis given the tumor access to lymphatic drainage in the esophageal submucosa. BE is categorized endoscopically according to its length using the Prague classification and histologically as containing no-dysplasia (ND), low-grade dysplasia (LGD), or high-grade dysplasia (HGD), each with respective but increasing risks of invasive esophageal adenocarcinoma (EAC) [5]. The progression of BE to EAC is thought to happen in a step-wise manner, transitioning from nondysplastic BE (NBDE) to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to intramucosal EAC and, finally, invasive EAC. EAC is 30–125 times more likely to occur in persons with BE than in the general population. BE itself has no specific signs or symptoms and has a prevalence of 1–2% in the general population and 5–10% in people with chronic GERD [6–8].

The recognition and management of BE have two objectives: (1) the treatment of underlying GERD and (2) elimination of morbidity and mortality associated with incident EAC. The latter objective involves (1) eradication of dysplasia and surrounding metaplasia to reduce EAC incidence, and (2) surveillance to detect incident cancer at an early stage, aiming to reduce the probability of cancer-related death.

Over the past decade, literature has consistently demonstrated that endoscopic eradication therapy of dysplasia in

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BE can reduce progression to EAC [9–12]. Additionally, chemoprevention with proton pump inhibitors and aspirin in patients with BE may lower all-cause mortality [13]. Early-stage EAC (T1a) found during surveillance can be treated endoscopically with excellent long-term prognosis [7]. A systematic review and meta-analysis demonstrated that regular surveillance was associated with diagnosis of EAC at earlier stages and lower EAC-related and all-cause mortality [14]. Hence, a significant proportion of the population is at risk of developing a cancer with a poor prognosis that may benefit from screening for its precursor.

Whom to Screen?

Screening for BE should be performed only in individuals who are at increased risk for BE and as a result EAC. Screening of the general population is not recommended at this time.

Risk Factors for BE

The odds of developing BE in a patient with GERD is 6–8 times higher than in a patient without GERD, making reflux disease the strongest risk factor for BE. If present, the duration of symptoms is particularly important since experiencing GERD for more than 5 years appears to substantially increase the risk of BE. However, reflux symptoms alone cannot be used as a reliable predictor of BE since studies have demonstrated a substantial prevalence of BE in patients without reflux symptoms. Indeed, 40–50% of patients with BE and EAC do not report chronic reflux symptoms.

Obesity and, more specifically, visceral adiposity are other independent risk factors for BE. The incidence of BE and EAC has increased in parallel with the incidence of obesity in the past few years. A body mass index (BMI) of >30 is associated with greater odds of developing BE; however, the waist–hip ratio (WHR >0.9), a reflection of central obesity, may be a better predictor of BE compared with BMI. Increasing age, Caucasian ethnicity, and male gender are also well-established risk factors for BE. Obstructive sleep apnea or a history of BE or EAC in a first-degree relative is also associated with an increased risk, as is the presence of a hiatal hernia (especially if longer than 2 cm). A recent systematic review and meta-analysis showed that the greater the number of risk factors present, the higher the prevalence of BE, with each risk factor increasing the prevalence of BE by approximately 1.2% [15] (Table 16.1).

Table 16.1 Risk factors associated with Barrett's esophagus

Clinical variable	Studies	Design	*N*	Results
Age	Eloubeidi and Provenzale (2001) [16] Johansson et al. (2007) [17] Edelstein et al. (2009) [18]	Case–control Case–control Case–control	211 764 615	Age >/ 40 independent predictor, $p < 0.008$ OR = 1.11, 95% CI 1.02–1.21 OR per decade for BE 1.3 [1.1–1.5]
Male gender	Cook et al. (2005) [19]	Meta-analysis	19 studies	M:F = 2.13
Ethnicity	Balasubramanian et al. (2012) [20] Abrams et al. (2008) [21]	Cohort Cross-sectional	1058 2100	Caucasian OR, 2.40 (95% CI 1.42–4.03) Prevalence of BE in Caucasians 6.1% vs. 1.7% –African Americans, 1.6% – Hispanics
GERD symptoms	Taylor et al. [22]	Meta-analysis	26 studies	OR 2.9 (4.5 in 12 studies with GERD for at least 2 weeks)
Central adiposity Obesity	Singh et al. (2013) [23] Kamat et al. (2009) [24]	Meta-analysis Meta-analysis	11 studies 9 studies	aOR 2.04; 95% CI 1.44–2.90 (independent of GERD) OR = 1.35 [1.15–1.59]
Tobacco use	Andrici et al. (2013) [25] Andrici et al. (2013) [25]	Meta-analysis	10 studies 4 studies	OR = 1.42 [1.15–1.76], ever smoked vs. population control OR = 1.96 [1.41–2.73], adjusted for confounders
Family history	Chak et al. (2002) [26]	Case–control	1 study	OR = 12, adjusted for age, sex, obesity
OSA	Leggett et al. (2014) [27]	Case–control	*N* = 262	OR = 1.8 [1.1–3.2]
Hiatal hernia	Andrici et al. (2013) [28]	Meta-analysis	33 studies	OR = 3.94 [3.02–5.13]

BE Risk Assessment Tools

Several risk assessment tools have been developed using demographics, anthropometric variables, GERD symptoms, and other parameters (Table 16.2) to assess BE risk. These are summarized in Table 16.2. They also show that the addition of variables other than reflux symptoms improves BE risk assessment. While they have been validated in several populations, they have not yet been implemented in clinical practice since the risk threshold where confirmatory BE screening is recommended has not been defined.

The current screening recommendations from different GI societies are summarized in Table 16.3.

Special Populations

Patients receiving per-oral endoscopic myotomy or Heller's myotomy for achalasia are exposed to increased gastro-

Table 16.2 BE risk assessment tools

Model	Variables	AUROC
Brisbane model [29]	Sex, age, tobacco use, BMI, highest level of education, and frequency of acid suppressant use	0.61 (validation cohort) 0.7 (development cohort)
Palo Alto model [30]	Sex, age, race, and severity of seven symptoms	0.72
Mayo Clinic Rochester model [31]	Sex, age, five-page questionnaire regarding GER symptoms, acid suppressant use, and one-page questionnaire on somatization symptoms	0.76
Michigan prediction tool [32]	Age, WHR, weekly GER symptoms, and pack-year smoking history	0.72
Houston model [33]	Age, duration of GER symptoms, sex, WHR, *H. pylori* status, and multiple serum biomarkers (IL 12p70, IL6, IL8, IL10, and leptin)	0.85
Olmsted County model [34]	Sex, age, GERD symptoms, central obesity, Caucasian ethnicity, smoking history, excess alcohol use (men: >2 alcoholic drinks per day; women: 1 alcoholic drink per day), and family history of BE or EAC	0.72

AUROC Area under the receiver–operator curve.

Table 16.3 Recommendations for BE screening from GI societies

GI society name	Year	Recommendations	Level and strength of recommendation
ACG [35]	2016	Screening for BE may be considered if the following criteria were met: Male gender AND with GERD symptoms – (a) greater than 5 years OR (b) frequency of symptoms weekly or greater AND presence of two or more other risk factors – Age >50 years, waist circumference >102 cm or WHR >0.9, Caucasian ethnicity, active or history of smoking, first-degree relative with BE/EAC	Strong recommendation, moderate level of evidence
AGA [36]	2011	Screening for BE is suggested in patients with multiple risk factors associated with EAC (age > 50 years, male sex, white race, chronic GERD, hiatal hernia, elevated BMI, intra-abdominal distribution of body fat)	Weak recommendation, moderate quality evidence
ESGE [37]	2017	Endoscopic screening for BE is not recommended; however, screening can be considered in patients with GERD symptoms >5 years and multiple risk factors (age >50 years, white race, male sex, obesity, first-degree relative with BE or EAC)	
BSG [38]	2014	Patients with GERD and at least three risk factors; age >50 years, Caucasian race, male sex, obesity; threshold to be lowered in presence of family history of BE or EAC	Low-quality evidence, grade C recommendation
ASGE [39]	2019	Screening for BE is suggested in an at-risk population At-risk population is defined as those with a family history of EAC or BE (high risk) OR those with GERD plus at least one other risk factor (moderate risk)	Low-quality evidence and low strength of recommendation

ACG American College of Gastroenterology, *AGA* American Gastroenterological Association, *ESGE* European Society of Gastroenterology, BSG British Society of Gastroenterology, *ASGE* American Society of Gastroenterology

esophageal reflux and should undergo screening EGD to look for esophageal mucosal damage and evidence of BE/EAC in the postprocedure setting.

In patients undergoing a sleeve gastrectomy (SG), the presence of esophagitis or BE should be considered a contraindication for this procedure due to the high prevalence of postoperative GERD, with RYGB being the preferred approach [40].

When to Stop Screening?

The decision about when to stop screening should be individualized based on a shared decision-making and taking into account the patient's risk, prior screening, personal preferences, and whether the patient's comorbidity and life expectancy justify the risks and inconveniences of continued screening. Most continue to screen through age 75 years for average-risk patients as long as their life expectancy is 10 years or greater. Screening should be supported by a program that assures prompt follow-up of abnormal findings as well as ongoing screening.

How to Screen?

Endoscopic Screening

Conventional Esophagogastroduodenoscopy (cEGD)

High-definition EGD is the gold standard and the most commonly used modality for BE screening. BE is diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending >/ 1 cm proximal to the gastroesophageal junction with biopsy confirmation of intestinal metaplasia. In cases of suspected BE, at least eight random biopsies should be obtained unless the patient has short segments of BE where at least four biopsies per cm of circumferential BE and one biopsy per cm in tongues/islands of BE should be obtained. Biopsy should not be performed in the presence of a normal Z line or a Z line with <1 cm variability. To report the BE extent, the endoscopic Prague grading classification has been generally accepted and it measures the distance of various landmarks from the incisors during endoscope withdrawal. Using this grading, the *circumferential extent (C value)* measures the depth of endoscope insertion from the circumferential extent of the suspected columnar epithelium while the *maximum extent (M value)* measures the depth of endoscope insertion from the maximal extent of columnar epithelium. The Prague criteria have good interobserver reliability for BE involving >1 cm of the distal esophagus, but they do not account for metaplastic islands, such as those encountered either at baseline or, more importantly, after ablation [35].

If initial endoscopic evaluation is negative for BE, repeating EGD for BE is not recommended. However, in the presence of LA grade C or D esophagitis, repeat EGD is recommended after 8–12 weeks of PPI therapy to confirm healing and exclude underlying BE. However, EGD is an expensive and invasive procedure with a sensitivity and specificity of 82% and 81% for a BE diagnosis and is less accurate in those with short-segment BE (<3 cm) (50 vs. 25%) [42]. Although minimal, there are risks of bleeding, perforation, adverse effects of sedation, and associated cardiopulmonary risks. It also is associated with operator dependence and risk of sampling error, leading to false-negative results on histopathological examination (HPE).

Unsedated Transnasal Endoscopy

Unsedated transnasal endoscopy (uTNE) has emerged as an alternative screening modality for BE. It involves an ultrathin endoscope (<6 mm diameter), passed through the nares for mucosal visualization of the upper GI tract (Fig. 16.1c, e, f). It does require the use of pediatric biopsy forceps for sampling, resulting in smaller biopsy specimens.

EndoSheath is a novel uTNE system utilizing a disposable silicone sheath covering the scope that precludes any disinfection and has a more compact processing system allowing for easy portability. It was evaluated in a prospective randomized population-based study and was shown to have comparable effectiveness compared to cEGD (Fig. 16.1e, f) [43].

EG scan (Intromedic, Seoul, South Korea) is a disposable transnasal capsule imaging probe for visualizing the esophagus, with a reusable handle. Its compact and portable design makes it usable in the community setting. Sensitivity and specificity of EG scan (Fig. 16.1c) for BE diagnosis in an international multicenter case–control study was found to be 89.4% (95% CI 83.3–95.6) and 90.3% (95% CI 84–96.7), respectively, compared with cEGD [44]. uTNE has been compared against cEGD on multiple factors, and the results are summarized in Table 16.4.

Hence, uTNE is an alternative to cEGD for BE screening. Unfortunately, the utilization and adoption of uTNE for this indication have been poor.

Fig. 16.1 Alternatives to conventional sedated oral endoscopy for BE screening: (**a**) tethered capsule endomicroscopy, (**b**) Cytosponge, (**c**) transnasal EG scan system, (**d**) E-nose device, and (**e**, **f**) transnasal EndoSheath system [44]

Table 16.4 Comparison of uTNE and cEGD

Factors	uTNE vs. cEGD
Technical success	No significant difference in technical success rates [45]
Tolerability	Higher patient acceptability and preference for uTNE [46]
Recovery times	Shorter recovery times for uTNE [43]
Cost	Lower direct and indirect costs for uTNE [47]
Specificity and specificity (compared to cEGD)	98% and 100% [48]
Safety	No sedation-related AEs, better safety profile [49] Epistaxis occurred in a small proportion of patients
Limitations	10–11% inability to intubate nares, need for endoscopy suites, specifically trained healthcare provider [50]

Swallowable Imaging Capsules

Esophageal capsule endoscopy (ECE) technique allows visualization of the esophagus but does not have the capabilities of biopsy sampling. It is a safe, noninvasive technique not requiring sedation. The capsule can also be made reusable with the help of a string attached to the end of the capsule. The accuracy of ECE was studied in a meta-analysis of nine studies, which reported a pooled sensitivity and specificity of 78% and 73%, respectively, for the diagnosis of BE in patients with GERD [51]. Given that ECE has suboptimal accuracy, it is currently not recommended for BE screening [44].

Video Capsule Endomicroscopy

Video capsule endomicroscopy (VCE) utilizes a resonant fiber-optic laser scanner in conjunction with an optical fiber and imaging software to produce high-definition, wide-field color images of the esophageal epithelium. This technology is condensed into a 12.8 mm × 24.8 mm capsule, which can be swallowed and withdrawn with real-time imaging (Fig. 16.1a). Findings like include irregular luminal surface, heterogenous backscattering, and intramucosal glands are consistent with BE and can be identified by looking at the differences in image characteristics of normal squamous and BE epithelium. In its initial studies with 38 patients, VCE could effectively image the extent of BE when compared to cEGD with a high correlation ($r = 0.77–0.78$, $p < 0.01$) [14].

Swallowable Cell Sampling Devices Combined with Biomarkers

A number of nonendoscopic swallowable esophageal cell collection devices have been studied for use in BE screening (Fig. 16.2). These consist of either a compressed 25–30 mm spherical piece of compressible polyurethane foam enclosed in a vegetable or gelatin capsule, attached to a cord or a string. The capsule is swallowed by the patient, with a few sips of water. In 5–8 min, the capsule dissolves in the stomach and the expanded piece of foam is withdrawn orally with the string. This samples the entire esophagus and provides a rich cytology sample. Two such devices – Cytosponge (Medtronic, Minneapolis, MN) and EsophaCap (Capnostics, Concord, NC) – are commercially available and FDA cleared. Another device, the EsoChek (Pavmed, New York, NY), is an inflatable and swallowable silicone balloon. The device is swallowed with sips of water, then inflated with 5 cc air to about 18 mm diameter and pulled back to 5 cm proximal to GEJ. The inflated balloon samples the distal esophageal epithelium. Then, the balloon is deflated by inverting the balloon into the outer capsule and pulled out to prevent sampling the rest of the squamous epithelium. These devices are well tolerated, safe, and do not require sedation. They can be performed by a nurse in the office setting (Figs. 16.3 and 16.4).

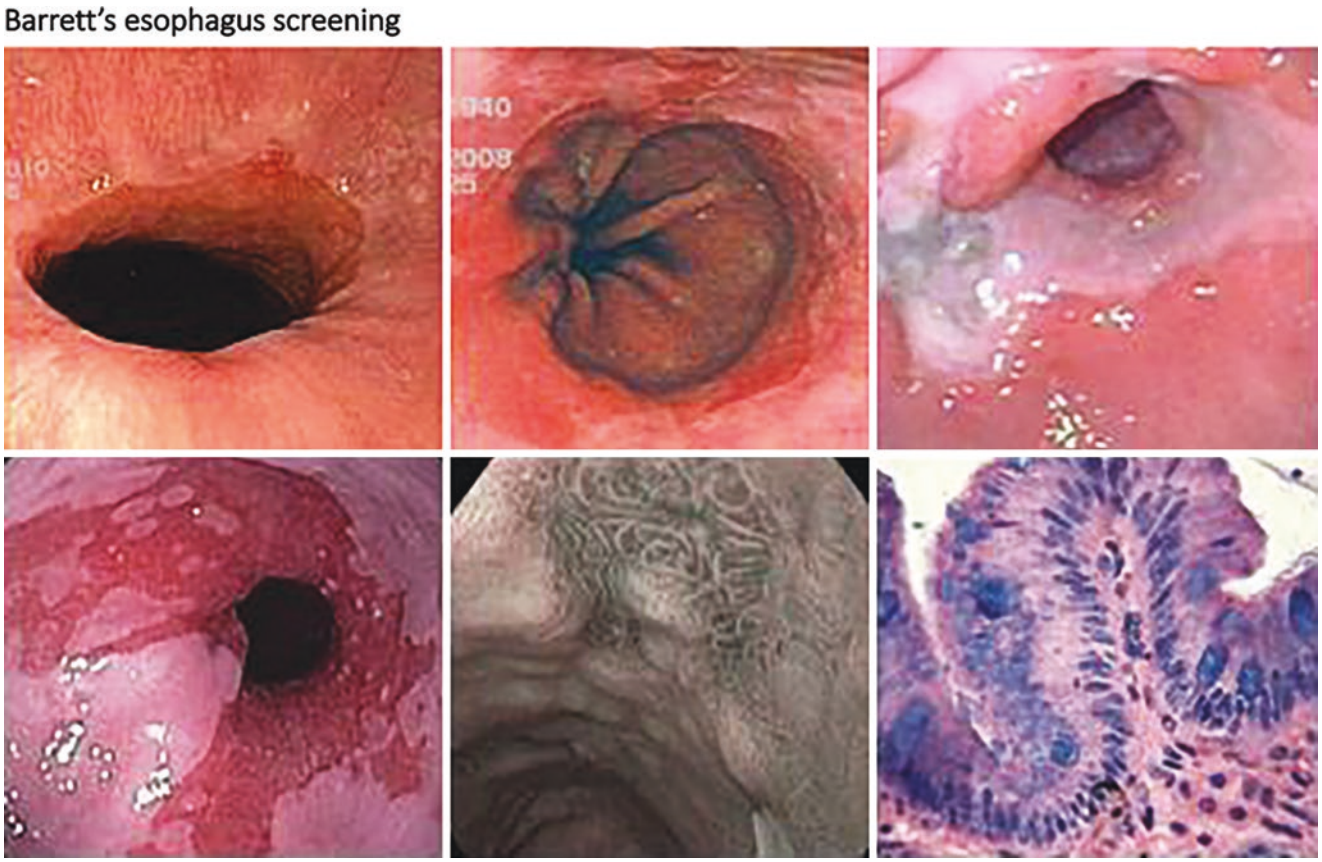

Fig. 16.2 Representative examples of what may be found during Barrett's esophagus screening. *Top left*: laxity of the EGJ is frequently found in patients with GERD. *Top middle*: sliding hiatal hernia with irregular EGJ. Current guidelines do not recommend biopsies in this setting. *Top right*: Los Angeles classification grade D esophagitis. A repeat endoscopic screening is indicated after at least a 2-month course of proton pump inhibition therapy in order to expose any underlying Barrett's mucosa with or without dysplasia. *Bottom left*: classical appearance of circumferential Barrett's esophagus interspersed with squamous islands. This will require formal endoscopic assessment using the Prague C&M classification. *Bottom middle*: narrow band imaging identifying an area of dysplasia. *Bottom right*: histology revealing low-grade dysplasia in the context of intestinal metaplasia

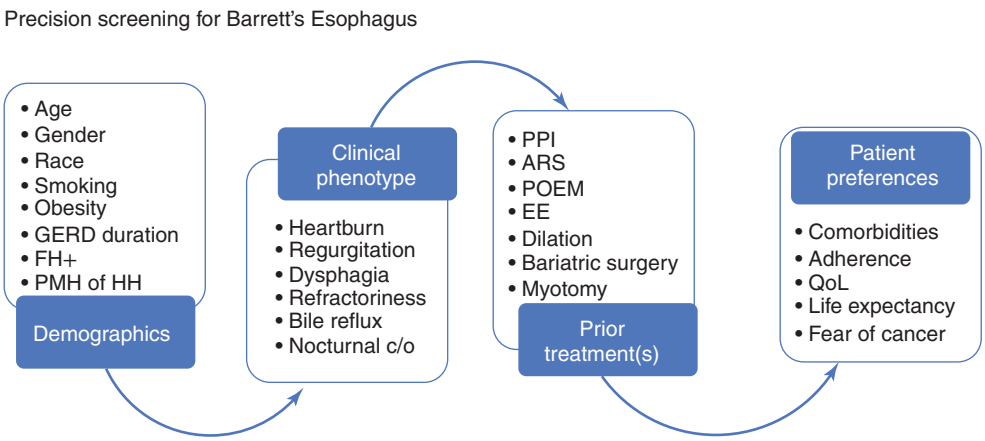

Fig. 16.3 Precision screening for Barrett's esophagus that incorporates patients' demographics, clinical phenotype, prior treatments for GERD symptoms, and preferences. In contrast to the conventional screening assessments, mostly taking into consideration the epidemiology and cost-effectiveness of the disease, precision screening adds multiple layers of additional considerations that have not yet been accounted for [41]

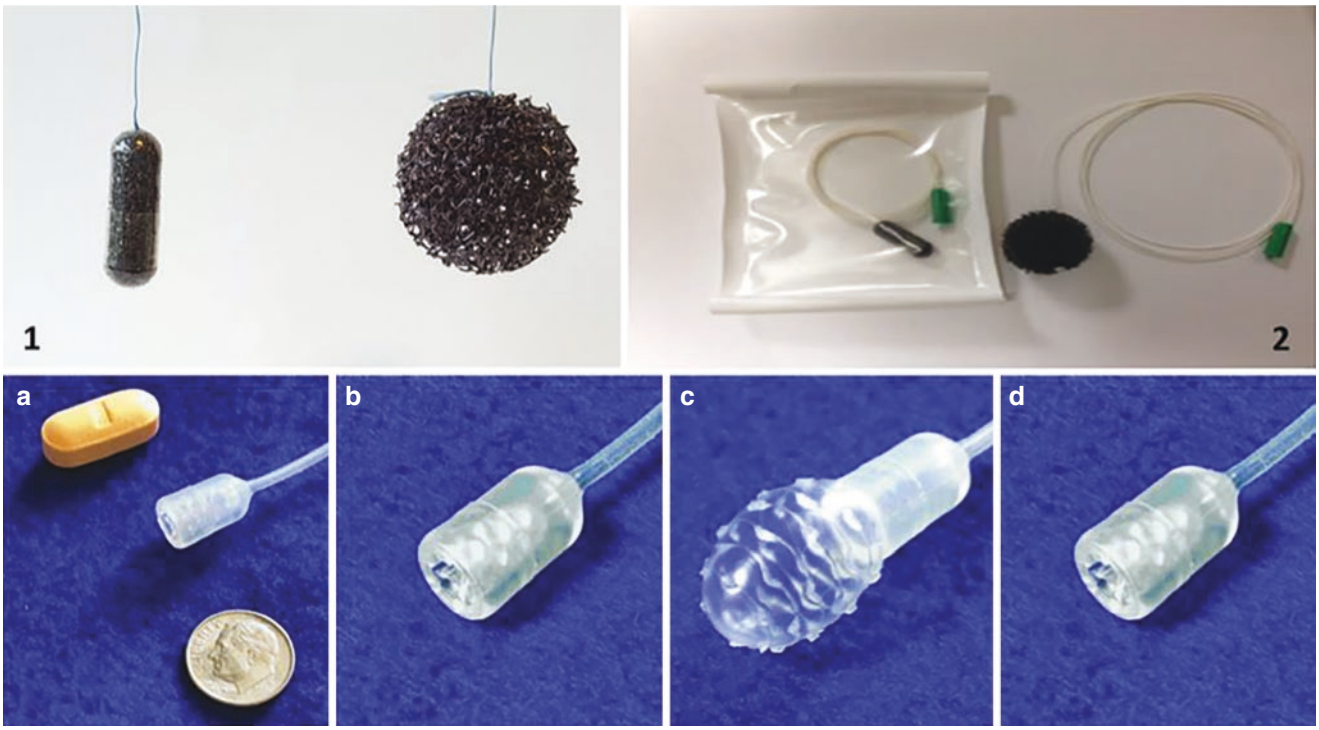

Fig. 16.4 (1) Cytosponge: intact (left) and expanded (right) (2). EsophaCap: intact (left) and expanded (right); (**a** + **b**) EsoCheck device: the device is swallowed with sips of water, inflated with 5 cc of air (**c**), pulled 5 cm proximal to the GEJ, and then deflated into a cap (**d**) before withdrawal to avoid contamination by squamous epithelium [52]

Biomarkers Used for BE Detection in Combination with Swallowable Esophageal Sampling Devices

Trefoil Factor 3

Trefoil factor 3 (TFF3) is a protein biomarker thought to be involved in the recruitment of healthy epithelial cells from the edges of wounds in the process of healing. It is upregulated in BE mucosa, and its role in the nonendoscopic diagnosis of BE has been evaluated in two UK-based studies. TFF3 used in conjunction with the Cytosponge has a sensitivity and specificity of 73.3–79.9% and 93.8%, respectively, compared with cEGD for BE detection [53, 54]. In a large primary care screening randomized trial, the use of the Cytosponge + TFF3 was safe, well tolerated, and led to the diagnosis of not only BE (ten-fold increase compared to the conventional management arm), but also dysplastic BE and early-stage adenocarcinoma: amenable to endoscopic management [55].

Methylated DNA Markers

Aberrant methylation of genes can cause oncogenesis by several mechanisms, and this principle has been used to develop stool-based DNA tests for colorectal cancer screening. Similarly, many investigators have detected aberrant methylation in BE, making it a useful tool for its screening. MDMs can be assayed on cytology samples obtained with the help of swallowable esophageal cell collection devices. In a pilot study with 20 BE cases and 20 controls, 98% of subjects could swallow the device; 19 MDMs were tested with nine markers having an area under the curve (AUC) greater than 0.9. A combination of two MDMs (VAV3 and ZNF 682) produced an AUC of 1.0 [56]. A subsequent marker elimination allowed a five MDM panel to be developed, with an AUC of 0.97 [57, 58]). This panel was subsequently validated in an independent test set using a simpler methylation assay with an AUC of 0.96 [59].

MicroRNAs

MicroRNAs (MIRs) are stable biomarkers involved in cellular development and provide tissue-specific profiles. They have been found to be dysregulated in Barrett's carcinogenesis. Esophageal epithelial microRNAs have been studied to diagnose BE and monitor its progression to EAC. In a 2018 study, the esophageal mucosa of 38 patients with BE and 26 normal controls sampled using the Cytosponge revealed consistently upregulated MIRs, which were quantified by real-time poly-

merase chain reaction (RT-PCR). Results revealed that an optimized multivariable logistic regression model based on expression levels of six MIRs identified BE vs. control mucosa with an AUC of 0.89 at 86.2% sensitivity and 91.6% specificity. A combination of MIR expression with TFF3 increased the AUC to 0.93 at 93.1% sensitivity and 93.7% specificity.

Table 16.5 Summary of performance characteristics of studies utilizing swallowed esophageal cell collection devices combined with various biomarkers

Method	Sensitivity[a] (95% CI)	Specificity[a] (95% CI)
Cytosponge – TFF3		
Kadri 2010 [54]	90.0% (55.5–99.7%)	93.5 (90.9–95.5%)
Ross-Innes 2015 [53]	79.9	92.4
EsophaCap/Cytosponge – MDM panels		
Chettouh 2018 [60]	82.2	95.7
Iyer 2018 [56]	100	100
Iyer 2020 [58]	92% (85–96%)	94% (87–98%)
Iyer 2021 [59]	93%	93%
Moinova 2018 [61]	90.3	91.7
Wang 2019 [57]	78.6	92.8
Cytosponge – miRNA panels		
Li 2018 [62]	86.2	91.6
Bus et al. [63]	78.4	85.7

[a]Compared to gold standard cEGD or biopsy

Results from the various studies done with swallowable esophageal cell sampling devices combined with biomarkers are summarized in Table 16.5.

Volatile Organic Compounds [52]

Breath analysis has been used as a diagnostic modality for several diseases, including cancer. Gas chromatography mass spectrometry (GC-MS) and, more recently, selected ion flow tube mass spectrometry (SIFT-MS) can identify volatile organic compounds (VOCs) in exhaled air, which can identify several disease processes such as celiac disease, *H. pylori*, and SIBO. It is this principle that makes it useful for BE and EAC screening as well.

The electronic nose (E-nose) is a similar device that uses chemical and electrical interfaces to measure subtle VOC profiles by changes in conductance (Fig. 16.5) [64]. This differs from mass spectrometry (MS) since the E-nose can analyze exhaled VOCs in aggregate to create an electronic conductivity profile specific to the VOCs, whereas the mass spectrometer identifies individual VOCs.

Several studies investigating the utility of qualitative or quantitative analysis of VOCs in BE and esophageal and gastric adenocarcinoma have been performed (Table 16.6).

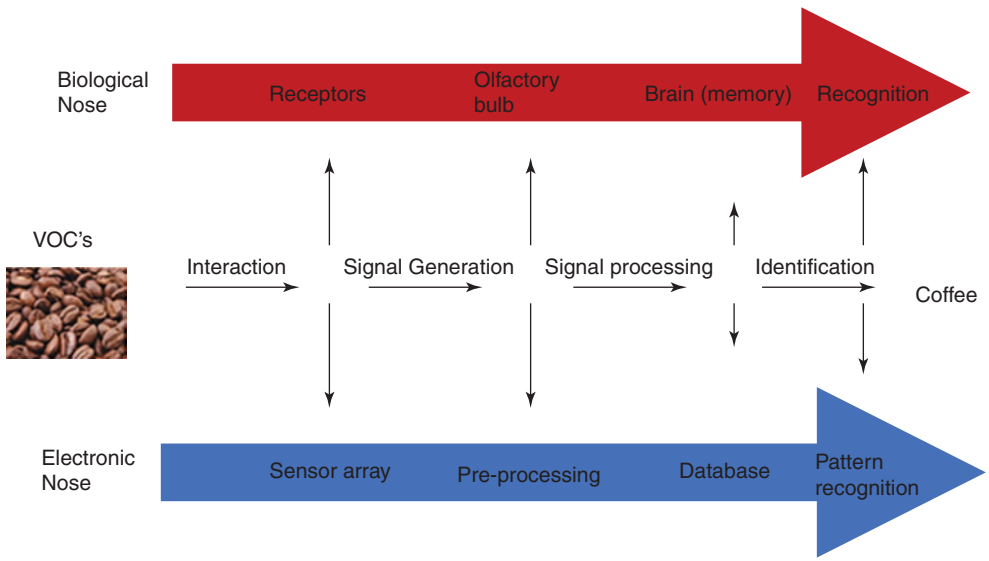

Fig. 16.5 The electronic nose concept is similar to mammalian olfaction. Volatile organic compounds (VOCs) are presented to a metal oxide sensor array. VOCs interact with these sensors based on their chemical characteristics. Combinations of individual sensor measurements generate a digital signal, which can be analyzed by pattern recognition and artificial neural networks. (Adapted from Santos et al. [64])

Table 16.6 Studies assessing the potential utility of circulating and exhaled volatile organic compounds (VOCs) in BE and EAC detection

Study	Study design	Results	Performance characteristics
Kumar et al. (2013) [65]	Studied 17 VOCs among patients with esophageal/gastric cancers, UGI nonmalignant conditions and healthy controls	VOCs – Hexanoic acid, phenol, methyl phenol, and ethyl phenol found to be associated with cancer	AUC 0.91
Kumar et al. (2015) [66]	Studied 81 breath samples (EAC = 48, gastric adenocarcinoma = 33, BE = 16, benign UGI diseases = 62, normal = 51)	12 VOCs found to be significantly higher in the cancer group than the noncancer group (pentanoic acid, hexanoic acid, phenol, methyl phenol, ethyl phenol, butanal, pentanal, hexanal, heptanal, octanal, nonanal, and decanal)	AUC (EAC) 0.97, $P < 0.05$
Chan et al. (2017) [67]	With E-nose device, VOC profiles of 66 patients with BE were compared with 56 patients without BE (post ablation)	Differences in VOC profiles were able to detect BE from controls	Sensitivity 82%, specificity 80%, accuracy 81%, AUC 0.79
Bhatt et al. (2016) [68]	Studied circulating plasma VOCs; in EAC patients ($N = 20$) and GERD patients ($N = 19$)	Nine VOCs were significantly altered in EAC patients compared to GERD patients	AUC 0.83
Peters et al. (2020) [69]	Studied E-nose device in patients with BE ($N = 129$) and without BE ($N = 273$)	VOC profiles distinguished BE patients from patients without BE	Sensitivity 91%, specificity 74%, AUC 0.91

Alterations in Esophageal Microbiome [52]

The oral and gut microbiome has been thought to reflect underlying disease processes. Investigators have shown that *Streptococcus* and *Prevotella* species are abundant in the upper GI tract of patients with BE [70]. A high *Streptococcus*-to-*Prevotella* ratio is correlated with high WHR and hiatal hernia risk, which are in turn risk factors for BE. Cytosponge samples from the upper GI tract have found a higher proportion of Proteobacteria in BE patients compared to controls. A model detecting the presence of certain phyla in salivary samples detected BE with a 96.9% sensitivity, 88.2% specificity, and an AUC of 0.94.

Challenges with BE Screening

Although screening may lead to an earlier diagnosis, not all screening tests have been shown to benefit the person being screened. Other than increasing healthcare costs by overuse, potential side effects of screening the subjects are misdiagnosis, overdiagnosis, creation of anxiety, or a false sense of security. Because of these reasons, proper screening should balance the incidence of the disease with the sensitivity and specificity of the particular screening tool or a combination of tools used. The ultimate purpose of BE screening is to detect and treat BE to prevent its progression to EAC, leading to reduced morbidity and mortality from this cancer. However, EAC has a low incidence at 0.7 per 100,000 person-years with 93% of cases being diagnosed after the onset of alarm symptoms typically indicative of advanced disease. The rationale of halting EAC at the BE stage has limitations due to the low rate of progression from BE to EAC (annual risk of 0.12–0.5%) with the majority of BE patients dying of non-EAC causes. The BOSS trial is a large randomized prospective trial that will look at the impact of BE surveillance on EAC and overall mortality. Requiring symptoms of GERD for BE is another challenge. Symptomatic GERD is neither sensitive nor specific in predicting BE with 40–50% patients with BE or EAC not complaining of heartburn, which excludes them from the screening group. A large majority (85–90%) of EAC cases are detected de novo, meaning that they do not have a history of BE. There is also some evidence to suggest two phenotypes of EAC with one arising from BE and the other potentially arising from a BE-independent pathway and having poorer outcomes [71]. However, a recent modeling study suggested that more than 90% of all incident EACs arise from BE [72]. Another challenge is the failed adherence to established guidelines with only 10% of patients with chronic GERD symptoms undergoing EGD. This is likely due to a combination of limited knowledge among providers, failure of patients to seek care for their symptoms, and hesitancy of patients and physicians to perform screening endoscopy given its invasive nature and the over-the-counter availability of proton pump inhibitors for the treatment of GERD. Another major limitation is the absence of a widely available, cost-effective screening method, leaving cEGD as the only available BE screening modality. Novel nonendoscopic screening methods are being studied and will hopefully allow more complete BE detection in a cost-effective and efficient manner. Additionally, improvements in dysplasia detection and risk stratification of those with BE also have to improve in order to successfully improve outcomes of those with EAC.

Take-Home Points

1. Barrett's esophagus screening and surveillance may offer the potential of reducing EAC incidence and mortality.
2. Several limitations in the current screening and surveillance paradigm lead to <10% of incident EACs being diagnosed in a surveillance program.
3. Development and validation of nonendoscopic tools for BE screening may allow a more comprehensive detection followed by intervention in those at the highest risk for EAC.
4. Pairing nonendoscopic BE detection tools with BE/EAC risk assessment tools will be critical for implementing these tests effectively in the population.
5. Concomitant advances in dysplasia detection and risk stratification are essential to achieving the thus far elusive reduction in EAC incidence and mortality.

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Understanding the Histopathology of GERD and Barrett's Esophagus

17

Parakrama Chandrasoma and Jason B. Samarasena

Introduction

Gastroesophageal reflux disease (GERD) is a common chronic progressive disease. Approximately 30% of the adult population in the United States suffer from heartburn, the main symptom of GERD. What's more, its incidence is increasing worldwide [1].

Present Understanding of the Histopathology of GERD

Gastroesophageal reflux disease (GERD) has three clinicopathological manifestations that represent the progression of disease.

Nonerosive and Erosive Reflux Esophagitis

Gastroesophageal reflux disease is presently defined by the presence of troublesome symptoms [2]. This definition is questionable because patients who are asymptomatic can harbor Barrett's esophagus (BE) [3] and develop esophageal adenocarcinoma (EAC) [4], both known complications of GERD.

Endoscopy in patients with symptomatic GERD may show no abnormality (nonerosive reflux disease) or erosive esophagitis quantified by the Los Angeles classification.

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Histopathological changes of GERD include squamous epithelial erosions, basal cell hyperplasia, dilated intercellular spaces, papillary elongation, and intraepithelial leukocytes. These have low diagnostic specificity and sensitivity and are not useful in diagnosis. Histological reflux esophagitis does not define chronic progressive GERD.

If the success of GERD treatment is the reversal of heartburn and/or esophagitis, proton pump inhibitor therapy has a high success rate. Unfortunately, reversal of symptoms and erosive esophagitis does not prevent progression to BE and EAC [5].

Barrett's Esophagus

Barrett's esophagus is currently defined as columnar lined esophagus (CLE) visible at endoscopy with biopsies showing intestinal metaplasia (IM) [6]. Patients being treated empirically with PPI for GERD have a 10.8% conversion rate from having no visible CLE at endoscopy to CLE in 5 years [5].

Per current guidelines, endoscopy is not indicated in persons who do not have GERD symptoms and patients whose symptoms are controlled by PPI therapy. Without endoscopy, however, there remains the risk that prevalent BE remains hidden [4].

Biopsies are indicated at endoscopy in the GERD patient only if there is visible CLE. Patients who have no visible CLE at endoscopy and those who have CLE but no IM on biopsy do not satisfy the definition of BE in the United States.

Largely because of these guidelines, 85% of patients who develop EAC have never had an endoscopy prior to their presentation with advanced adenocarcinoma.

Patients diagnosed with BE are surveilled to detect dysplasia and early adenocarcinoma. Recent advances in endotherapy have reduced morbidity and mortality in patients who develop EAC during surveillance compared to the high, near 90%, mortality in those who develop EAC outside

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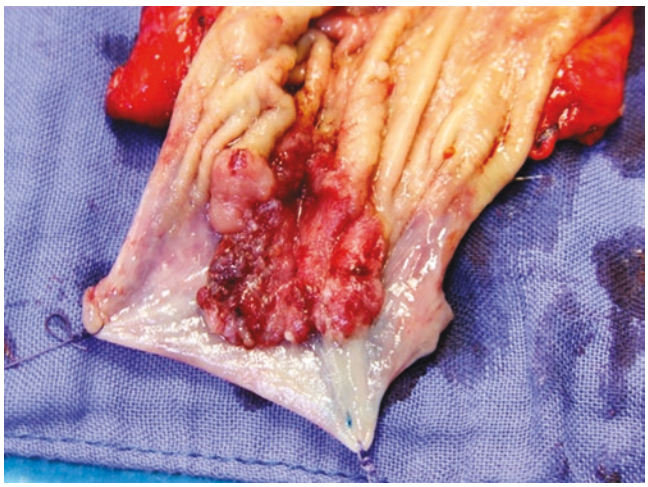


Fig. 17.1 A polypoid ulcerated adenocarcinoma at the SCJ. The proximal edge shows squamous epithelium, and the distal edge is at the proximal limit of rugal folds. There is salmon pink columnar mucosa lateral to the tumor. The epicenter approximates the proximal limit of rugal folds. By present criteria, this will be classified as an esophageal adenocarcinoma

surveillance [7]. Unfortunately, this improvement is limited to the 15% of patients with EAC who have had an endoscopy. The impact on overall cancer mortality is therefore low.

Esophageal Adenocarcinoma (Fig. 17.1)

The only cause of EAC is GERD. The first case of EAC was reported in 1952 [8]. Since 1973, EAC has increased sevenfold from 3.6/million to 25.6/million in the United States [9]. It continues to increase. An estimated 20,000 persons in the United States will develop EAC in 2021.

Histological assessment for neoplasia (dysplasia and/or cancer) presently begins when BE is diagnosed. Once a diagnosis of BE is established, patients undergo surveillance endoscopy to detect neoplasia early enough to allow curative minimally invasive interventions such as ablation and mucosal resection.

Present Understanding of the Normal State

In asymptomatic persons and GERD patients who are controlled with empiric acid suppressive therapy, endoscopy is not indicated. No attempt is made to define the pathological anatomy and histology of this clinically "normal" state. If pathology exists, it falls within the definition of "normal."

In the more advanced stage of GERD where a patient has failed PPI therapy and endoscopy is done, the normal state is defined as (1) the absence of erosive esophagitis, (2) the absence of visible CLE, and (3) the absence of a hiatal hernia. In this normal state, esophageal squamous epithelium meets the proximal limit of gastric rugal folds, which presently defines the GEJ, at or near the point of flaring of the tubular esophagus [10]. Biopsy of the normal SCJ is specifically discouraged [6, 11]. If performed, cardiac mucosa distal to the GEJ, irrespective of amount, is regarded as the normal lining of the proximal stomach. If IM is found, it is termed IM of the gastric cardia, a gastric pathology.

We will show that the presently accepted definition of the GEJ as the proximal limit of gastric rugal folds is incorrect [12]. We will show that cardiac mucosa, when found distal to the incorrect endoscopic GEJ, is not proximal stomach; it is a metaplastic columnar epithelium of the esophagus [13, 14]. These two false dogmas have resulted in an incredible and persistent error in the understanding of the pathology of GERD.

A New Understanding of the Normal State

In 1990, Dr. Tom DeMeester established a Foregut Surgery Unit at the University of Southern California. He routinely employed a unique biopsy protocol that included biopsies at and distal to the GEJ, defined by the proximal limit of rugal folds, in all patients undergoing endoscopy (Fig. 17.2).

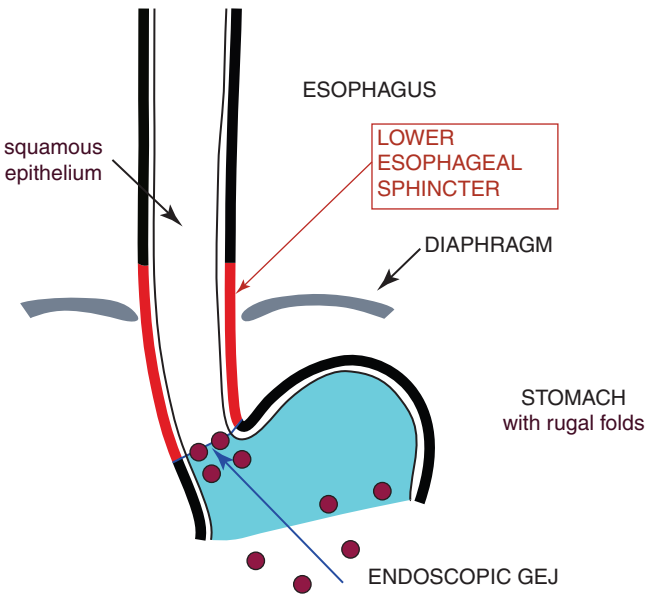


Fig. 17.2 The unique elements of the DeMeester biopsy protocol. In all patients, a biopsy set is taken at the proximal limit of rugal folds (proximal red dots) and another immediately distal to this on retroflex view (distal red dots). Distal gastric biopsies are routinely taken. In patients with visible CLE, biopsies of that segment are taken according to the Seattle protocol

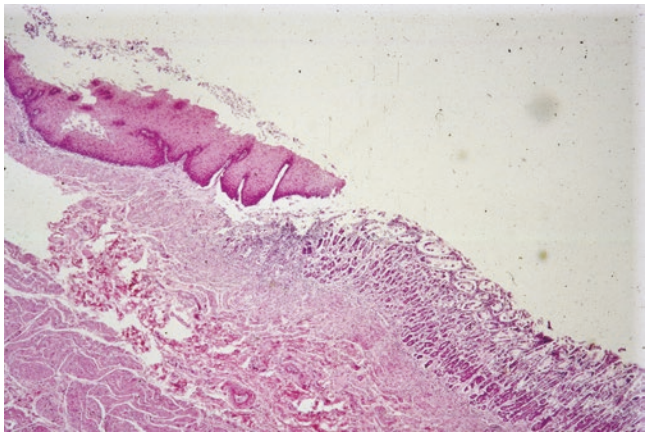


Fig. 17.3 Section across the normal histological SCJ at autopsy in a child. The squamous epithelium transitions at the GEJ to gastric oxyntic mucosa with straight tubular glands. There is no cardiac mucosa

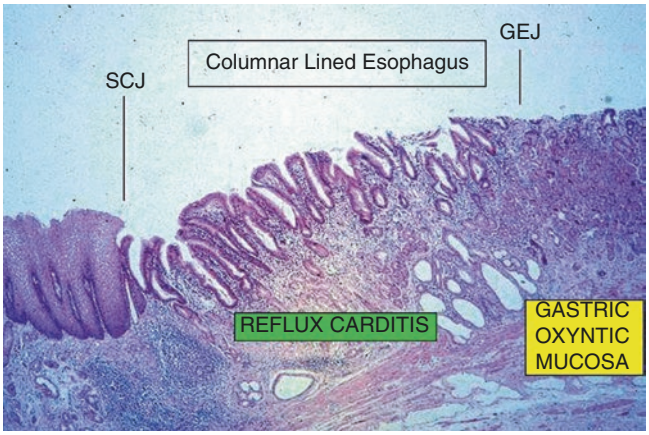


Fig. 17.4 Section across the SCJ in an esophagectomy specimen for squamous carcinoma showing the squamous epithelium (left) separated from gastric oxyntic mucosa (right) by a 2 mm segment of metaplastic inflamed cardiac and oxyntocardiac mucosa. The SCJ has moved cephalad by 2 mm

Within a short period, we recognized that cardiac mucosa was not always found in biopsies at and distal to the GEJ [15]. We confirmed the absence of cardiac mucosa at the normal SCJ at autopsy, showing the direct transition from squamous to gastric oxyntic mucosa [16] (Fig. 17.3). The length of cardiac mucosa and severity of inflammation therein were directly related to the severity of GERD as assessed by a 24-hour pH test and the presence of LES abnormalities [13, 17–19]. These data showed that cardiac mucosa was a metaplastic esophageal epithelium resulting from the exposure of squamous epithelium to gastric juice.

Nearly three decades later, it is increasingly believed that most cardiac mucosa is a metaplastic esophageal epithelium. However, many physicians still believe that 1–2 mm of "native" cardiac mucosa exists in the proximal stomach [20]. This untenable false belief has prevented the utilization of cardiac mucosa in the pathological diagnosis of GERD.

An immediate impact of recognizing that cardiac mucosa is a metaplastic esophageal epithelium is that the true GEJ must be distal to the proximal limit of "gastric" rugal folds by the length of cardiac mucosa. The true GEJ in the patient with GERD is the junction between metaplastic cardiac mucosa and the proximal limit of gastric oxyntic mucosa (Fig. 17.4). This cannot be seen reliably with standard white light endoscopy or gross examination; it can only be defined by microscopy.

With this new understanding, the normal state can be defined by histology as an esophagus lined by squamous epithelium to the SCJ where it transitions into gastric oxyntic mucosa of the proximal stomach (we call this the zero squamo-oxyntic gap [21]). Cardiac mucosa is not normally present.

A New Understanding of the Histopathology of GERD

In our new understanding of the normal state defined by histology, the stem cells in the esophagus are all directed to differentiate into squamous epithelium by a genetic signal, likely related to the Wnt gene complex.

The entire sequence of pathological change in GERD can be divided into three sequential changes in the esophageal epithelial stem cell: (1) a change in the signal from Wnt to a new signal, possibly trefoil family factor 3 (TFF-3 [22]) or bone morphogenesis protein 4 (BMP-4 [23]) that directs the stem cell to shift differentiation from squamous to a columnar cell, resulting in cardiac mucosa, which is microscopic CLE. Cardiac mucosa is easily distinguishable from other columnar epithelial types (Fig. 17.5). (2) A second new signal, likely CDX2, in cardiac mucosa that induces intestinal metaplasia in CLE to form BE (Fig. 17.5) [24]. (3) One or more yet undefined mutational molecular changes in IM leading through increasing dysplasia to adenocarcinoma. Additional signals may appear in cardiac mucosa, leading to the appearance of parietal cells (oxyntocardiac mucosa; Fig. 17.5), Paneth cells, neuroendocrine cells, and pancreatic acinar cells (pancreatic metaplasia). These are not clinically significant and do not progress to neoplasia.

The extent to which this epithelial sequence progresses during a lifetime varies in different persons. It is very uncommon for a person to have zero cardiac mucosa. Eighty percent of patients never progress beyond the first metaplastic change of cardiac mucosa (presently consid-

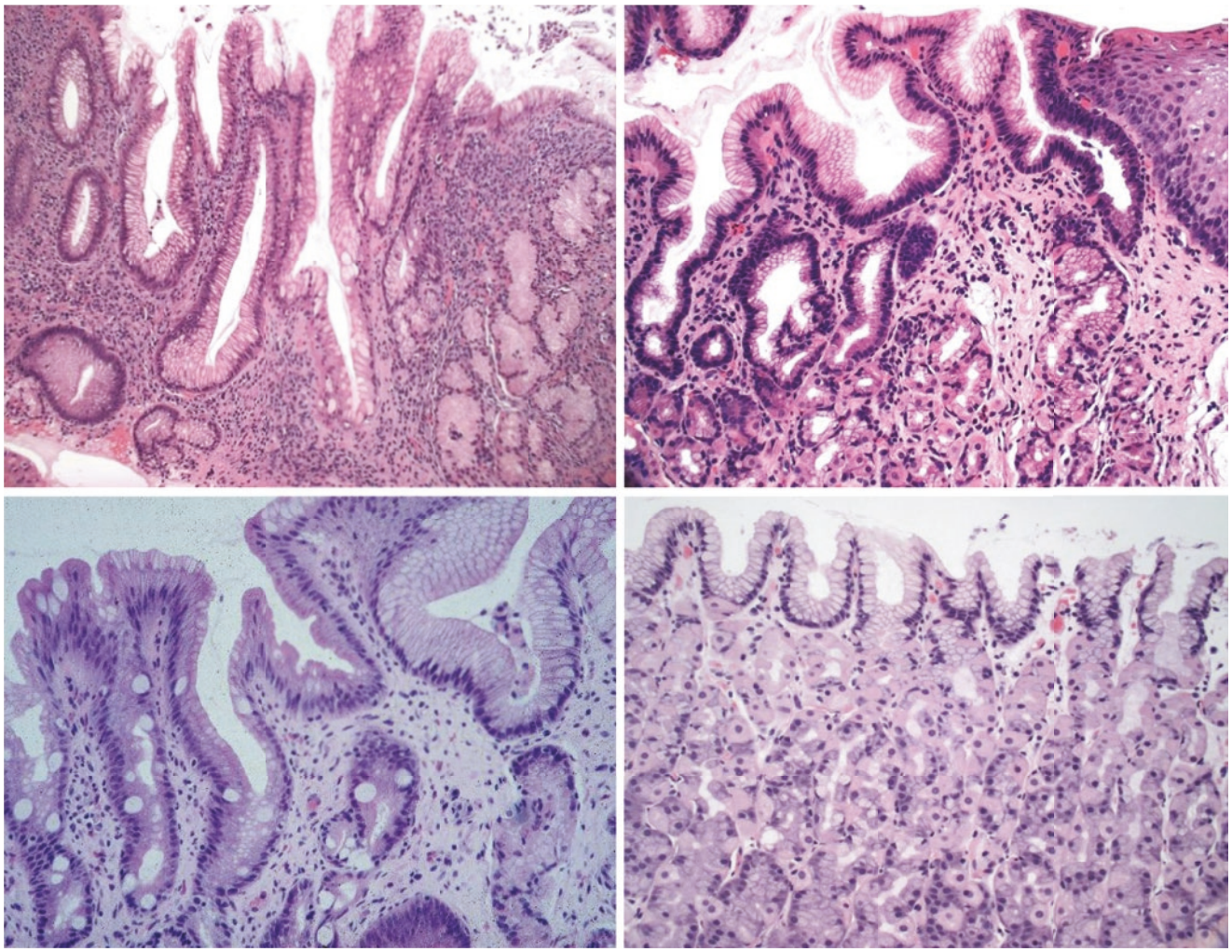


Fig. 17.5 Collage of the four common types of columnar epithelium seen in the esophagus (in CLE) and within 3 cm distal to the proximal limit of rugal folds. *Top left*: cardiac mucosa composed of glands with mucous cells only, associated with marked chronic inflammation and reactive changes. *Top right*: oxyntocardiac mucosa with lobulated glands composed of mucous and parietal cells and mild chronic inflammation. *Bottom left*: goblet cells indicative of intestinal metaplasia in cardiac mucosa. *Bottom right:* normal gastric oxyntic mucosa with a short foveolar region and straight tubular glands composed of parietal and chief cells. There are no inflammatory cells in the lamina propria

ered normal and ignored). In the absence of IM, these persons do not develop EAC. Approximately 20% develop IM (BE). Only a very small percentage of patients with BE progress to dysplasia and EAC. Unfortunately, a small percentage of a large denominator is a high absolute number.

Normal → Early GERD with No Visible CLE at Endoscopy

This is presently an unrecognized pathology of GERD.

The esophageal squamous epithelium is protected from exposure to gastric juice by the lower esophageal sphincter (LES). In the normal person, the SCJ coincides with the end of the LES and the proximal limit of gastric oxyntic mucosa at the GEJ (Figs. 17.4 and 17.6).

With normal-sized meals, the stomach fills without any alteration of the anatomy at the GEJ. The SCJ stays above the pH transition point at the end of the functional LES. The acid pocket that develops at the top of the food column in the stomach does not come into contact with the squamous epithelium [25]. Gastric oxyntic mucosa below the GEJ is resistant to acid in the acid pocket. There is no pathological change. Normality is maintained.

However, with heavy meals that over-distend the stomach, the anatomy at the GEJ becomes altered [26, 27] (Fig. 17.6). The LES becomes effaced at its distal end and dynamically shortens. The SCJ descends below the pH

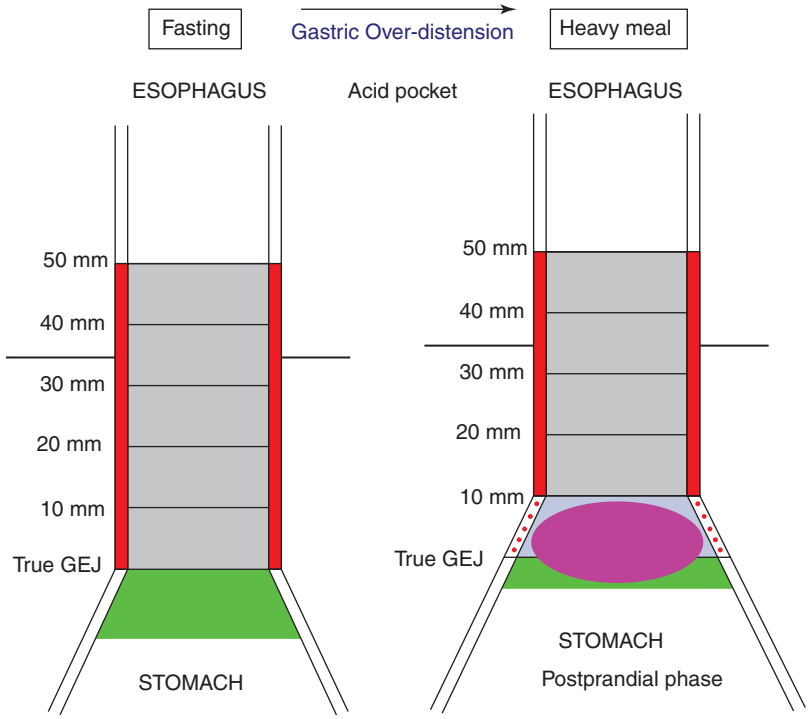
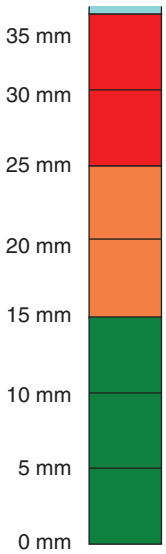


Fig. 17.6 Diagram of changes at the SCJ due to gastric over-distension by a heavy meal. The LES has become effaced and shortened by 10 mm; the distal squamous epithelium is below the pH transition point and exposed to the acid pocket (purple) at the top of the food column



STAGE OF GERD	REFLUX	CELLULAR CHANGES
Severe GERD	Severe	Presence or Risk of Visible CLE Erosive esophagitis CE in DDE
Mild GERD	Postprandial Mild	Erosive esophagtis NERD CE limited to DDE
Phase of compensated LES damage	None	CE limited to DDE

Fig. 17.7 Correlation of length of cardiac mucosa with severity of GERD, showing three stages: with cardiac mucosal lengths of 0–15 mm, the LES is competent even when challenged with a heavy meal. Patients are asymptomatic with histological cardiac mucosa <15 mm as the only abnormality. With cardiac mucosal lengths 15–25 mm, the LES is competent at rest but fails when challenged by a heavy meal. Patients have mild postprandial reflux without BE. In the final stage, with cardiac mucosal lengths >25 mm, the LES is defective at rest. Severe GERD with treatment failure and BE may occur

transition point, becoming exposed to the acid pocket. Such exposure of the distal esophagus is common; acid exposure is much higher in a pH detector placed at 0.5 cm above the SCJ than in one placed 5 cm above the LES in the traditional pH test [28].

Damage to the squamous epithelium by acid results in dilated intercellular spaces [29] and increased permeability [30]. Derakhshan et al. [22] showed that the expression of TFF-3 increased with repetitive squamous epithelial damage. Metaplasia into cardiac mucosa occurred when TFF-3 levels reached a critical level.

With this metaplastic change, the esophagus changes from normal (no cardiac mucosa; Fig. 17.3) to GERD (cardiac mucosa present). The SCJ becomes separated from the true GEJ defined by the proximal limit of gastric oxyntic mucosa (Fig. 17.4). The squamo-oxyntic histological gap composed of cardiac mucosa is invisible in its early stages except by histology. Endoscopy appears normal and the pH test remains normal. Cardiac mucosa is presently mistaken at biopsy as normal proximal stomach. This is the presently ignored histological definition of asymptomatic subclinical GERD (Fig. 17.7).

Progression of GERD with No Visible CLE at Endoscopy

Progression of GERD occurs by repeated insults to the distal esophageal squamous epithelium by chronic overeating. Increasing cardiac metaplasia of the distal esophagus causes the squamo-oxyntic gap to increase in length very slowly. Histologically, the SCJ moves increasingly cephalad as the length of cardiac mucosa increases [16, 17, 31].

The rate of increase in the length of cardiac mucosa can be likened to a battle between the amount and frequency of overeating and the resistance of the squamous epithelium to undergo metaplasia when exposed to gastric juice. The variable impact of this battle in different people determines who will develop clinical GERD with symptoms, an abnormal pH test, and BE.

Autopsy study of patients without symptomatic GERD during life shows that the length of cardiac mucosa in the squamo-oxyntic gap is often <5 mm, particularly in young persons, and maximally 1.5 cm [16, 32, 26]. In esophagectomy specimens, the squamo-oxyntic gap was a mean of 11 mm in patients with squamous carcinoma (non-GERD related [33]).

This suggests that metaplastic cardiac mucosal length progresses from 0 to 15 mm without any clinical evidence of GERD. The LES, though likely damaged by the cardiac metaplasia, is still sufficiently competent to prevent abnormal reflux sufficient to produce symptoms. This asymptomatic stage of GERD has a normal pH test and no endoscopic abnormality (Fig. 17.7).

From this point, histopathology of GERD progresses with increase in cardiac mucosal length > 15 mm. The further damaged LES is initially competent in the fasting state but dynamic shortening during meals results in LES failure and episodic reflux into the thoracic esophagus, causing heartburn [34]. In this stage of GERD with intermittent postprandial reflux, heartburn is usually mild and controllable with empiric PPI therapy (Fig. 17.7). Reflux into the thoracic esophagus is insufficient to produce an abnormal pH test or visible CLE.

The Pathological Anatomy of Early GERD: The Dilated Distal Esophagus

This early stage of GERD defined by increasing metaplasia of squamous epithelium to cardiac mucosa produces dramatic changes in the anatomy of the distal abdominal esophagus. The histological squamo-oxyntic gap distal to the proximal limit of rugal folds and the point of flaring of the esophagus is dilated and distends with gastric filling, grossly resembling and functioning like the proximal stomach (i.e., "gastricized"). By present definition of the endoscopic GEJ, this dilated distal esophagus is mistaken as proximal stomach [35] (Fig. 17.8).

We provided evidence for the dilated distal esophagus in a study of 10 esophagectomy specimens (eight with adenocarcinoma and two with squamous carcinoma) that had a well-defined proximal limit of rugal folds (the GEJ as presently defined) that coincided with the point of flaring of the tubular esophagus [12] (Fig. 17.9). The area lined by cardiac mucosa was dilated with rugal folds exactly like the proximal stomach. The length of cardiac mucosa between the proximal limit of rugal folds and the proximal limit of gastric oxyntic mucosa was 3–5 mm in the two patients with squamous carcinoma and 10–20 mm in the eight patients with adenocarcinoma. That this area was esophagus was shown by the presence of esophageal submucosal glands that were concordant with the length of cardiac mucosa (Fig. 17.10). Submucosal glands were never seen below gastric oxyntic mucosa.

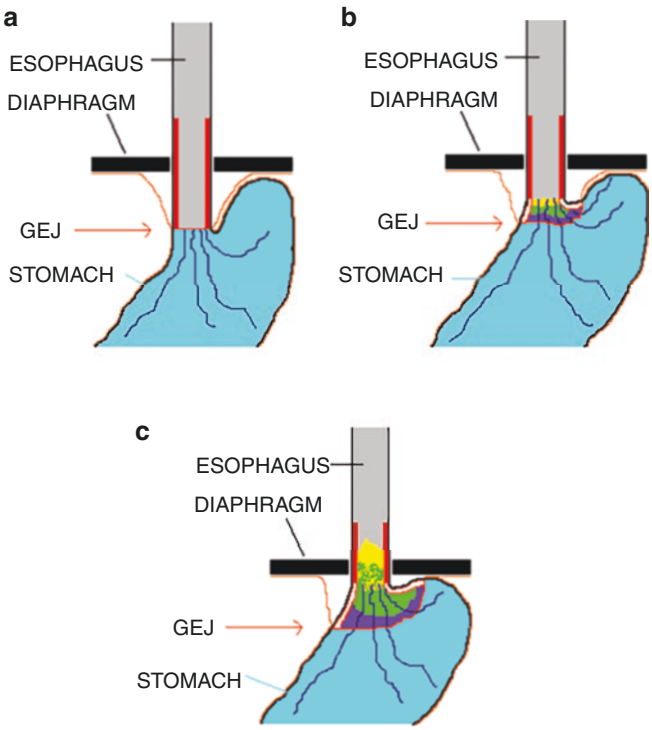


Fig. 17.8 Three stages of GERD as defined by histology: 1(a) is the normal state with no cardiac mucosa; 1(b) shows cardiac mucosa limited to the area distal to the proximal limit of rugal folds with a dilated distal esophagus and abdominal LES damage (white replacing red in esophageal wall; and 1(c) shows increased length of cardiac mucosa in the dilated distal esophagus associated with traditional BE with visible CLE at endoscopy

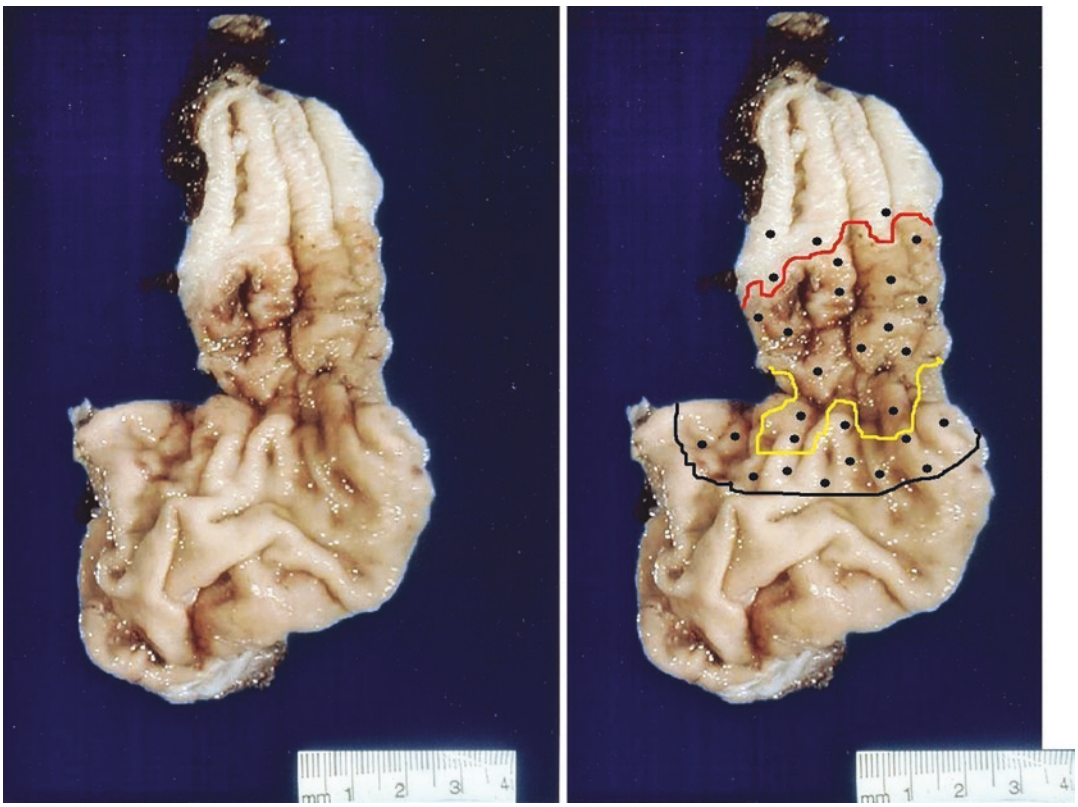


Fig. 17.9 Resected esophagus in a patient with EAC arising in BE. The proximal limit of rugal folds coincides with the end of the tubular esophagus. Histological mapping shows the extension of intestinal metaplasia (between red and yellow lines) extending into the dilated distal esophagus distal to the proximal limit of rugal folds. Metaplastic cardiac mucosa extends to 20 mm distal to the proximal limit of rugal folds and end of the tubular esophagus. Submucosal glands (black dots) are concordant with the extent of cardiac mucosa, proving the concept of the dilated distal esophagus

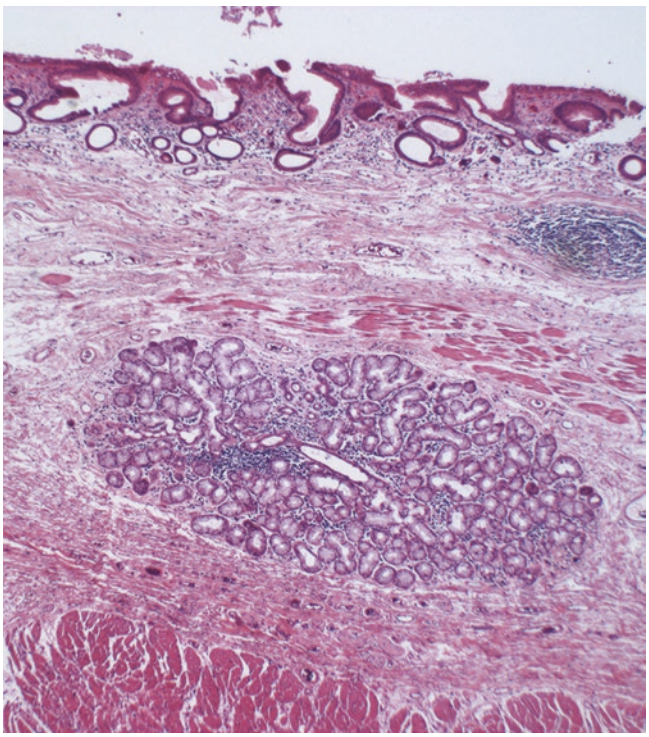


Fig. 17.10 Section taken from the dilated distal esophagus showing submucosal glands under metaplastic cardiac mucosa

This study, ignored since 2007, confirmed that 3–20 mm distal to the proximal limit of rugal folds was a dilated distal esophagus lined by metaplastic cardiac mucosa. Sarbia et al. [33] reported that the dilated distal esophagus lined by cardiac mucosa with underlying submucosal glands had median and maximum lengths of 11 mm and 28 mm in 36 patients with esophagectomy for squamous carcinoma.

Two studies suggest that the dilated distal esophagus has a trumpet-like shape in its fasting state. With increasing length, the measured internal circumference of the cardia [36] and the external circumference at the peritoneal junction at surgery [37] increased from normal to GERD to BE.

The dilated distal esophagus is the only pathological anatomy of GERD prior to the endoscopic appearance of visible CLE. It is defined by the presence of CLE (cardiac mucosa) between the present incorrectly defined endoscopic GEJ and the true histological GEJ (proximal limit of gastric oxyntic mucosa). It is presently mistaken for the proximal stomach.

When the progression of CLE changes from endoscopic to histologic, clarity and order emerge. Endoscopic change goes from normal to visible CLE in one step. Histologically, CLE (metaplastic cardiac mucosa) progresses from zero length, increasing millimeter by millimeter to the length of visible CLE. This coincides with increasing destruction of the LES.

Pathophysiology of the Dilated Distal Esophagus (Lower Esophageal Sphincter Damage)

There is concordance between the length of cardiac mucosa distal to the end of the tubular esophagus and the dilated distal esophagus. This begs the question: Why does the distal esophagus dilate when its mucosa changes from squamous to cardiac?

Tonic contraction of smooth muscle in the LES responsible for its resting high pressure is likely maintained by a local intramural reflex arc controlled by the myenteric plexus. If the afferent nerve endings of this reflex arc are in the mucosa, metaplasia from a highly innervated squamous epithelium [38] to a cardiac mucosa devoid of nerve endings would lead to a loss of LES tone. The residual functional LES then shortens to an amount identical to the length of cardiac mucosa. Shortening of the abdominal LES is a well-recognized abnormality of GERD.

Loss of the high-pressure zone in the abdominal esophagus causes it to express the intraluminal positive pressure that is otherwise suppressed by the LES. The distal esophagus dilates with the stomach when distended and collapses when empty. Repeated dilatation is a stimulus for the development of rugal folds (Figs. 17.8 and 17.9).

The concordance of the length of cardiac mucosa distal to the endoscopic GEJ, the dilated distal esophagus, and shortening of the abdominal segment of the LES is of incredible significance. It allows, for the first time, a pathological test of abdominal LES damage: the length of cardiac mucosa distal to the proximal limit of rugal folds (the SCJ in the endoscopically normal person) is a measure of shortening (damage) of the abdominal LES.

Late (Severe) GERD with Visible CLE

Visible CLE, which is the first pathological manifestation of GERD that is recognized by present criteria, is a late manifestation of GERD. It is commonly associated with abnormal reflux in the 24 hour pH test defined as a pH < 4 for 4.5% of the day, that is, 64 minutes daily, at a point 5 cm above the LES. A defective LES, defined by a length of its abdominal segment of <10 mm, is present in 80% of patients with BE [39]. The normal abdominal LES measures >35 mm [40]; a < 10 mm length means a shortening of >25 mm (i.e., >70%).

Visible CLE has a different pathogenesis than invisible CLE limited to the dilated distal abdominal esophagus. While the latter is a slowly progressive columnar metaplasia resulting from repeated over-distension of the stomach, visible CLE occurs when the abdominal LES becomes defective [39]. Reflux of gastric contents into the esophagus occurs constantly, leading to severe exposure of the thoracic esophagus to acidic gastric juice [34]. This results in the relatively rapid development of visible CLE [5, 41], associated with the long dilated distal esophagus associated with a defective LES (Fig. 17.8).

The Second Metaplasia: IM in Cardiac Mucosa (Barrett's Esophagus)

The second metaplastic event in GERD is the development of IM in cardiac mucosa (Fig. 17.5). This occurs in two situations:

1. Traditional BE (Figs. 17.8 and 17.9): The presence of IM favors the proximal region of the segment of CLE. As the length of visible CLE increases, the prevalence of IM increases. At a Prague M length 5 cm of visible CLE, IM is found in nearly 100% of patients [42]. During reflux, a pH gradient is established where the pH increases from acidic at the end of residual LES to near neutral at the height of reflux [43]. These data suggest that CDX2 activation in cardiac mucosa is favored by higher pH, that is, less acid, milieu. Acid-suppressive therapy, which has as its objective the alkalinization of gastric juice, may theoretically promote IM in cardiac mucosa.
2. Intestinal metaplasia in the dilated distal esophagus (IM of the "cardia"; Fig. 17.8): There are limited data linking length of CM in the dilated distal esophagus to IM therein. Leodolter et al. [41] showed that 25.8% of GERD patients with IM at the normal SCJ progressed to traditional IM within 5 years. Yung et al. [44] showed that the presence of IM at normal SCJ had a significant association with traditional BE.

The Third Histological Change: Neoplastic Mutations in Barrett's Esophagus (Fig. 17.1)

The neoplastic progression of BE through increasing dysplasia to adenocarcinoma has been studied intensively. Neoplasia is likely caused by carcinogens in the gastric refluxate that interacts with intestinalized CLE. There is evidence that bile acid products may be the carcinogens involved. Unfortunately, no method of preventing progression to adenocarcinoma in BE has been developed. Surveillance directed at early detection has allowed endotherapy in high-grade dysplasia and intramucosal adenocarcinoma that has led to a marked improvement in survival.

Progression of GERD Defined by Abdominal LES Damage and Correlative Histology

Shortening of the abdominal segment of the LES to <10 mm, detected by manometry, is a criterion of a defective sphincter that is a primary cause of GERD. Manometry, endoscopy, and gross pathology cannot detect LES damage. LES shortening begins at its distal end with exposure of esophageal squamous epithelium to acid during repetitive gastric over-distension. Damage is manifested as cardiac metaplasia and loss of sphincter pressure (i.e., shortening from an unknown normal length).

If it is true, as limited data suggest, that LES damage is concordant with the measured length of cardiac mucosa distal to the SCJ in patients without visible CLE on endoscopy, a new method of measuring LES damage emerges [45]. This opens the door to a new etiology-based system of defining the progression of GERD. The following stages of GERD can be recognized (Fig. 17.7):

1. Normal (= no GERD): This is defined as the absence of cardia mucosa between the SCJ and gastric oxyntic mucosa. The abdominal LES is undamaged and approximately 35 mm in length [40].
2. Histological GERD without significant reflux: This is defined as a cardiac mucosal length of >0 to <15 mm. The person has a residual abdominal LES length >20 mm; the LES remains competent even with heavy meals.
3. Pre-visible CLE mild GERD: This is defined as a cardiac mucosa length of 15–25 mm. The LES, though competent at rest, cannot withstand the stress of gastric distension [34]. Postprandial reflux of gastric juice into the thoracic esophagus occurs with increasing probability as residual LES length decreases from 20 to 10 mm.
4. Severe GERD with possibility of visible CLE: This is defined as a cardiac mucosal length >25 mm. The residual functional abdominal LES length is <10 mm and is defective at rest; the 24-hr pH test is abnormal. At this level of damage, LES failure can occur without gastric over-distension [34]. Patients with severe GERD are likely to be those who fail medical therapy, develop BE, and progress to EAC.

Conclusion

Unfortunately, accurate measurement of the length of cardiac mucosa, which is the basis of this understanding, is not possible at endoscopy with available technology. Ideally, a new biopsy instrument that can remove a vertical strip of intact mucosa 20–25 mm long is needed. In the interim, tools such as probe-based laser endomicroscopy may be useful for this measurement during endoscopy; this is being currently studied. Early measurement of LES damage long before visible CLE develops can open new doors to the prevention of progression of LES damage to a point where patients become at risk for developing BE and EAC [45].

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Management of Nondysplastic Barrett's Esophagus

18

Michael S. Smith, F. P. Buckley III, F. Scott Corbett, and Reginald C. W. Bell

Defining Barrett's Esophagus

Barrett's esophagus, first described by Dr. N.R. Barrett in 1950 [1], is defined as replacement of the normal stratified squamous epithelium of the tubular esophagus with columnar epithelium containing mucin-producing goblet cells. This metaplastic change, often referred to as specialized intestinal metaplasia (IM), is identified visually during upper endoscopy by the presence of salmon-colored mucosa extending proximally from the esophagogastric junction into the esophageal lumen. It can take on multiple forms, from focal proximal displacement in the shape of mucosal "tongues" or "islands," to include circumferential displacement of the pearly off-white squamous epithelium.

Normally the esophagus should remain empty except for the brief periods when a swallowed bolus transits through the esophagus and into the stomach. Intestinal metaplasia is thought to arise as a protective response to gastroesophageal reflux, resulting in repeated exposure of the distal esophagus to various components of gastric contents, most commonly acid but also bile and perhaps other substances. Squamous epithelium, thought to be more susceptible to these caustic exposures, is therefore at a higher risk of ulceration and stricture formation. Specialized intestinal metaplasia, which is akin to small bowel mucosa, is less susceptible to acid, bile, chyme, and other digestive contents. Risk factors for the development of Barrett's metaplasia closely mirror those for gastroesophageal reflux disease (GERD), and include advanced age, White race, male sex, the presence of obesity (especially central type), early-onset and prolonged duration of GERD symptoms, and the presence of anatomic abnormalities like a hiatal hernia that predispose to reflux.

Within the United States, the diagnosis of Barrett's esophagus requires both the presence of salmon-colored mucosa and tissue sampling confirming the presence of goblet cells. The length of a segment of columnar metaplasia also may play a role in determining whether a diagnosis of Barrett's esophagus is made. For example, the American College of Gastroenterology's guidelines state that the condition is present only when there is at least 1 cm of salmon-colored mucosa extending into the distal esophagus [2]. (In the United Kingdom, only visual recognition of >1 cm of salmon-colored mucosa is required. [3]).

Implementation of the "Prague Classification" system in the mid-2000s provided a uniform framework to describe endoscopic findings and the current recognized standard [4]. Two key measurements – the craniocaudal extent in centimeters of completely circumferential columnar mucosa (the "C" component), and the maximum (M) height of contiguous metaplastic tissue – are taken starting at the top of the gastric folds. The Prague system does not currently consider the presence of separate proximal islands of columnar mucosa, nor does it share the extent or percentage of surface area where metaplastic change is found.

Risks Associated with Barrett's Esophagus

The greatest risk of Barrett's is the potential for progression through the metaplasia–dysplasia–neoplasia pathway and developing into adenocarcinoma of the esophagus. Progression rates from nondysplastic disease have varied

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between studies, though the current consensus is that the rate is between 0.12 and 0.5% per year [5]. There are no definite epidemiological factors that predict greater risk of progression once nondysplastic Barrett's is diagnosed. Dysplasia and esophageal cancer are discussed in detail elsewhere in this book.

Minimizing Risk of Dysplastic Progression: Medical Therapy

Nonprocedural medical management of nondysplastic Barrett's esophagus has revolved around reducing exposures of the distal esophagus that might drive progression of the metaplasia–dysplasia–neoplasia sequence. Any intervention that decreases the frequency, quantity, or causticity of the gastric refluxate theoretically should decrease the likelihood of developing dysplasia. Dietary and lifestyle modification remains the easiest interventions to minimize GERD. Acid reduction therapy, particularly with proton pump inhibitors (PPIs), has been shown to decrease the likelihood of dysplasia development [6]. It is unclear whether histamine type 2 receptor blockers are effective in decreasing progression.

Minimizing Risk of Dysplastic Progression: Anatomic Intervention

Whether antireflux surgery (ARS) fares better than PPI therapy in minimizing the risk of developing Barrett's requires large, population-based cohorts that cannot reliably account for the severity of GERD in both groups. It is not surprising that many studies show no difference between PPIs and ARS in the risk of developing Barrett's [7]. However, a meta-analysis of ARS and PPI-treated patients with 100,479 person-years in the ARS and 400,459 in the medically treated group did show a decreased IRR in the ARS group (0.89, 95% CI 0.66–1.19) [8].

Regression of Barrett's after ARS has been reported and appears to be length dependent. Dunn et al. [9] reported on 74 of 87 patients with NDBE after magnetic sphincter augmentation at a mean follow-up of 2.5 years. In total, 16/18 (89%) patients with <1 cm NDBE demonstrated resolution and no patient developed increased length of Barrett's. Of 50 patients with SSBE, 56% resolved and 10% improved. Three of six patients with LSBE improved, and no patient in the study developed dysplasia. These results are similar to those reported after laparoscopic Nissen fundoplication where ~70% of patients with <1 cm Barrett's resolve. This should be compared to PPI therapy, where <1 cm Barrett's is found to progress in length in 26% of patients at 2 years.

Whether ARS is superior to PPIs in limiting the progression of nondysplastic Barrett's to EAC has been the topic of vigorous debate in both meetings and in the medical literature [10]. The most referenced study is a systematic review and meta-analysis by Maret-Ouda, which found the incidence rate ratio (IRR) for developing EAC was 0.46 (95% CI 0.20–1.08) for ARS compared to medical therapy, and 0.26 (95% CI 0.09–0.79) when restricted to publications after 2000 [11].

A recent meta-analysis reported that in patients with Barrett's, regression of metaplasia/LGD occurred in only 24.7% (n = 37) of those receiving medical therapy versus 43.5% (n = 104) of surgery patients. Similarly, progression to dysplasia/EAC was less common in the ARS group (4.6%) than in the medical group (n 9.2%) [12].

Meta-analyses lack the ability to assess the success of ARS in controlling gastric reflux. Most ARS in large cohort studies are performed in nonspecialized centers. Patients undergoing surgery have more severe GERD than those treated with PPIs, have risk factors including large hiatal hernias that increase the potential for developing Barrett's, and present greater challenges for surgical success. Data from specialized foregut programs with high rates of successful antireflux surgery even in the more complex patients demonstrate a decreased risk of progression over that seen population-based studies or meta-analyses. In fact, results from specialized foregut surgery programs indicate that the risk of progression of NDBE in patients with a *successful* surgery is minimal [10].

The Rationale for Endoscopic Surveillance of Nondysplastic Barrett's Esophagus

The vast majority of patients with nondysplastic Barrett's esophagus never progress to adenocarcinoma. For those who do develop neoplasia, the duration of time between the development of specialized intestinal metaplasia and progression to esophageal adenocarcinoma is variable, but in most patients it is thought to take many years. Theoretically this leaves ample time for repeated endoscopic assessment to identify progression. Theoretically once dysplasia is found, intervention can eradicate the tissue before cancer forms. The mortality benefit of surveillance was described over two decades ago when the primary intervention being performed was esophagectomy, a procedure with high relative mortality [13]. Timely discovery of dysplastic progression, combined with current endoscopic eradication therapies, substantially decreases the risk of the patients dying from esophageal adenocarcinoma. The problem, as we shall see, is in the timely discovery of dysplastic progression.

Major medical societies all have endorsed surveillance protocols for nondysplastic Barrett's esophagus with intervals of 3–5 years [2, 14–16].

Assessment for Dysplasia within Barrett's Mucosa

The risk of progression to adenocarcinoma from the Barrett's segment with confirmed dysplasia is significantly higher than that of nondysplastic disease [14]. The development of

dysplasia within Barrett's mucosa is a focal and patchy process, often without obvious features that would allow reliable biopsy of the site where dysplasia exists [17]. The current gold standard technique is to perform four quadrant forceps biopsies every 1 or 2 centimeters throughout the length of the circumferential Barrett's segment, with biopsies taken of each tongue or island if the disease is not confluent [2]. While this "Seattle Protocol" approach has been shown to improve dysplasia detection, it has major shortcomings. First, it only samples ~5% of the tissue [18]. Second, it is time-consuming to sample Barrett's segments, especially longer ones, using this technique. In the community setting, adherence to the Seattle Protocol is low, with only around half of endoscopists providing a minimum acceptable number of biopsies based on the reported length of the Barrett's segment sampled [19].

A number of techniques have improved dysplasia detection. Taking additional time to evaluate the Barrett's segment helps. In one study, detection of high-grade dysplasia and cancer increased fourfold when increasing inspection time from a minimum of 2 min to a minimum of 7 min, regardless of segment length [20]. Other studies have demonstrated the value of digital (electronic) chromoendoscopy, also called narrow-band imaging (NBI), which utilizes particular wavelengths of light to assess the mucosal and vascular pattern of the Barrett's segment [21]. Both techniques are now considered part of a high-quality Barrett's examination. Chromoendoscopy is recognized as standard of care in the societal guidelines with the number needed to diagnose (NND) low-grade dysplasia is ~4 [16, 21]. Use of mucosal cleaning agents such as N-acetylcysteine and acetic acid is thought by many high-volume Barrett's endoscopists to aid in assessment, as is the use of a distal attachment cap to hold open the mucosal folds and overcome any tortuosity within the esophagus, permitting more definitive inspection of the complete Barrett's segment [22].

Multiple techniques have assessed the means of sampling, recognizing that more of a brush-based approach could increase the amount of surface area sampled and increase the likelihood of finding dysplasia. While it would not necessarily localize the abnormality, increased detection would allow for more accurate staging of disease. Attempts to use softer brushes, such as those employed to obtain samples for cytology and fungal infections, did not demonstrate a significant increase in dysplasia yield.

Over the past decade, multiple studies have evaluated a new technique termed WATS (Wide Area Transepithelial Sampling with Three-Dimensional Computer-Assisted Analysis, CDx Diagnostics, Suffern NY). This approach employs a stiff-bristled brush that then can be deployed through the working channel of the endoscope and scraped along the surface of the Barrett's segment to pick up ~100,000 cells or cell clusters (termed microbiopsies). Some of these cells are then plated onto a slide, creating a smear that is up to 150 micrometers in thickness. This sample would not be evaluable via conventional microscopic techniques, but proprietary computer-assisted analysis [extended depth of field processing (EDF)] allows for the cells to be assessed in 3 micrometer layers, which are then reconstructed in a single three-dimensional image. Artificial intelligence (AI) then identifies the 100 most concerning cells or cell clusters within the slide, and presents these to a pathologist in rank order for review. The cells that were not smeared are placed into a cell block, which is evaluated using both hematoxylin and eosin staining, as well as several immunohistochemical stains. This multifaceted and enhanced approach to diagnosis shows a much improved interobserver agreement for the detection of all grades of dysplasia than that seen with forceps biopsies [23].

Results have demonstrated that WATS provides a significant additional yield in detecting both nondysplastic and dysplastic Barrett's beyond standard forceps biopsies. This yield has continued to improve with technique refinement and an ever-increasing data pool to inform AI [24]. In the largest published study, patients with an established diagnosis of Barrett's esophagus undergoing surveillance endoscopy were sampled with both forceps biopsies and WATS. Of the 722 patients found to have nondysplastic Barrett's on forceps sampling, WATS found 72 patients with indefinite dysplasia and 3 patients had at least high-grade dysplasia on brush sampling. The number needed to test (NNT) to upstage a patient from nondysplastic to possible or confirmed dysplasia was 10. For the entire cohort of 12,899 patients, WATS increased the yield of finding goblet cell metaplasia by over 150%, and finding dysplasia by over 240%. A smaller study conducted at high-volume Barrett's centers with patients undergoing surveillance of known Barrett's esophagus demonstrated an adjunctive yield of 428% for high-grade dysplasia or cancer when WATS was added to forceps biopsies [25]. These data, along with other studies, led to the proposal of using WATS as an adjunctive technique to Seattle Protocol forceps biopsies in the surveillance of known Barrett's esophagus [16].

Evaluating a Nondysplastic Barrett's Segment for Risk of Progression to Dysplasia

Recently developed technology (TissueCypher) uses artificial intelligence-assisted analysis of esophageal biopsy biomarkers to assess the risk of progression of a particular Barrett's segment. Both quantitative and morphometric factors are accounted for in a verified algorithm [2, 26], which generates a tiered risk score for progression to high-grade dysplasia or adenocarcinoma. This algorithm was devised by evaluating expression patterns of both progressors and nonprogressors.

In the first published paper regarding this assay, high-risk patients were found to have a 9.4-fold increased risk of developing advanced disease compared to those patients who scored in the low-risk category. A subsequent study looked at progressors and nonprogressors from within a cohort of patients with nondysplastic Barrett's, those with Barrett's indefinite for dysplasia, and those with low-grade dysplasia [27]. The risk of progression for high-risk scores was 46-fold higher than for low-risk patients. In a third study, the algorithm was able to identify a subset of patients with high-risk nondysplastic Barrett's esophagus at baseline who progressed to high-grade dysplasia or cancer at a rate of (26%), at the 5-year mark, even higher than patients with expert pathologist-confirmed low-grade dysplasia (21.8%) [28].

A blinded, nested case–control study assessed the predictive performance of this assay on a cohort of nondysplastic Barrett's patients [29]. All previously available tissue samples were evaluated for expression patterns. Nondysplastic patients placed at high risk using this assay had an annualized risk of progression to high-grade dysplasia or cancer of 6.9%, similar to published rates for confirmed low-grade dysplasia patients. While the assay identified only 31% of progressors when a single biopsy level was used, the sensitivity rose when additional samples from other levels of the same procedure or from biopsies were taken during a different endoscopy. Specificity was high at 95%.

WATS and TissueCypher are a welcome addition to the armamentarium of the endoscopist who evaluates and follows nondysplastic Barrett's esophagus. Early identification of dysplasia or a higher risk of its development would allow for more frequent surveillance, or better yet endoscopic eradication therapy well before the appearance of any cancer. It is not yet clear whether patients found not to have any dysplasia or high-risk features could have their surveillance intervals lengthened.

The Argument for Endoscopic Eradication Therapy to Treat Nondysplastic Barrett's Esophagus

Most cancers with an identifiable precancerous stage are treated at this precancerous stage to prevent or minimize the risk of cancer. This is true for actinic keratosis, gynecological lesions, cervical dysplasia, and colonic polyps. Adenocarcinoma of the esophagus was not addressed in this fashion until recently as there had not been a safe or effective way to eradicate its precursor, Barrett's esophagus. Early eradication technologies, such as photodynamic therapy (PDT), and early spray cryotherapy (mid-1990s) had multiple problems that decreased their applicability. Research in the 1990s focused on finding better ways to detect dysplasia so that these potentially risky eradication techniques could be offered to those at greatest risk.

In 2001, the FDA approved the Barrx Halo radiofrequency ablation device for the "treatment of Barrett's esophagus" (and not just for the treatment of dysplastic Barrett's). The device provided a reasonably safe and more uniform removal of Barrett's tissue. With the process having limited depth of injury, stricture formation was infrequent, typically easy to manage; far different from photodynamic therapy or early cryotherapy techniques. The community experience paper by Lyday et al. [30] had met with initial resistance to publication as nearly half of the subjects had nondysplastic Barrett's. This registry of 429 patients from four community centers was one of the largest series on Barrett's ablation to date when eventually published in 2010, demonstrating that the RFA technology was at least as safe and effective in the community setting as it was in the academic arena.

The US multicenter RFA Patient Registry compiled the results of radiofrequency ablation treatments on over 5000 patients performed by 330 physicians at 148 different sites (113 of which were community-based and 35 academic-affiliated) from 2007 to 2011 and followed until 2014 (Wolf et al. [31]). The average length of Barrett's segment was 4.1 cm. Of the 4982 patients meeting inclusion criteria, 2346 (47%) had a baseline diagnosis of NDBE. Of the patients with NDBE treated with RFA, only three ultimately developed EAC (none of whom died from this diagnosis), for an incidence of 0.5 per 1000 patient-years (PY) compared to an expected historical incidence of 5.0 per 1000 PY [32] for those followed by surveillance alone, a ten-fold risk reduction for EAC favoring RFA over surveillance. All three patients with NDBE who developed EAC despite treatment had baseline long-segment disease (7, 10, and 11 cm). The cancer incidence in nondysplastic patients with baseline short-segment disease (< 3 cm) treated with RFA was zero.

Additional data from the Registry (Li et al. [33] confirmed findings of prior studies [34] that the mere diagnosis of Barrett's esophagus results in increased anxiety in patients regarding their health. Oddly, those with nondysplastic Barrett's demonstrated greater anxiety than those with dysplasia. Successful eradication of Barrett's resulted in a concomitant beneficial decrease in patients' anxiety and improvement in their quality of life.

In the United States, upward of 14,000,000 colonoscopies each year are performed for colon cancer screening and surveillance with providers removing most any lesion that resembles a polyp, whether a precursor to colonic adenocarcinoma or not. This has decreased the risk of colon cancer in the general population.

Although the incidence of EAC is low compared with colorectal cancer, the incidence has been steadily and rapidly increasing in the last three decades. According to SEER data and the National Polyp Study [35], the risk of a colonic ade-

noma left in situ becoming cancerous or developing HGD is 0.58% per pt./yr. Meanwhile, the risk of untreated nondysplastic Barrett's becoming cancer (0.5% per pt./yr) or HGD (0.9% per pt./yr) presents 2–3x the risk of that for a colonic adenoma left in situ. If surgery is required for colonic neoplasia, it generally requires a resection with low morbidity and mortality, a reasonable post-surgical quality of life, and a 66–90% five-year survival for all stages. The latter is not true for EAC, with esophagectomy often leaving patients with a poor quality of life and an 8–15% five-year survival. In patients unlucky enough to not be resectable, the 5-year survival is less than 1%, giving EAC the worst prognosis of any human solid malignancy.

The prevailing strategy of the last 30 years of performing various degrees of surveillance with hope of detecting dysplasia or early cancer at a stage where it is curable by either endoscopic or surgical therapy has failed [36]. The death rate for EAC remains dismal and largely unchanged. Over 50% of patients presenting with EAC do not ever recall having reflux symptoms. Screening only those with reflux symptoms would still leave a vast majority of patients still at risk. Noninvasive or minimally invasive screening strategies (Cytosponge, Esocheck, etc.) offer the opportunity to screen and detect Barrett's in at-risk populations who may be asymptomatic (e.g., White males age 50+ with BMI over 25). However, if we merely detect Barrett's in these asymptomatic at-risk individuals and then offer them a strategy of surveillance alone that has not proven effective in preventing EAC, are we unnecessarily increasing the anxiety in this group? This increased anxiety would be amplified when societal guidelines suggest withholding a safe and effective means of eradicating nondysplastic Barrett's that decreases the risk of EAC. Surveillance exams create anxiety as well as risk and cost for the patient. Not all patients with Barrett's should get eradication therapy. Risk stratification, patient education, and a combined decision between patient and physician are necessary to decide whether any individual with NDBE should be offered eradication and should not be dictated by third-party payers. Withholding eradication therapy from all nondysplastic patients is a policy that misses an opportunity to prevent cancer and improve a patient's quality of life.

Barrett's occurs and progresses through the metaplasia–dysplasia–cancer sequence by an accumulation of genetic changes over time. Nondysplastic Barrett's already contains several of the genetic and morphological cellular changes of neoplastic progression that conform to the definition of neoplasia [37]. Detection of these genetic and other biomarkers is helping to define subgroups of nondysplastic patients that are more likely to progress to EAC [38]. Nondysplastic Barrett's may be easier to treat, more durable once cleared, and perhaps offer an opportunity to prolong or discontinue surveillance at some point after sustained clearance of intestinal metaplasia is confirmed [39].

In 2011, the AGA guidelines committee conceded that selected patients with nondysplastic Barrett's esophagus at greater risk for EAC should be offered RFA without defining this subgroup [15]. A subsequent industry-sponsored consensus conference consisting of recognized academic and community experts defined a subgroup of Barrett's patients at greater risk to progress to EAC [40]. This included but was not be limited to Caucasian race, male gender, age over 50, onset at early age, disease duration of 10 years or more, disease segment of 3 cm or more with risk increasing for every cm greater than 3 cm, presence of a circumferential segment, presence of hiatal hernia, BMI over 30 (increasing risk 1.5×), smoking history greater than or equal to 20 pk-yrs, or a family history of Barrett's esophagus or EAC. The presence of certain chromosomal biomarkers and polysomy was also felt to infer increased risk.

Suppose we are able to find and are willing to ablate those with nondysplastic Barrett's in an effort to prevent EAC in the 95% of patients at risk who do not know they are at risk of developing EAC. We know EAC only develops from the metaplastic change that pathologically we call Barrett's and that approximately half of EAC arises without a visible length of Barrett's, sometimes without pathologically identifiable Barrett's. The metaplastic/dysplastic change likely starts in a small focus (such as in the crypts with crypt dysplasia) that may be overtaken by the rapidly growing cancer, though this rate of progression to cancer may be lower than those with >1 cm of Barrett's. If we only perform biopsies on patients with identifiable (>1 cm) CLE, we will miss diagnosing metaplastic change before it becomes cancer in a large number of patients. Discouraging an endoscopist from sampling an abnormality just because it is less than a predetermined length should be viewed with caution. You could "cure" poverty just by changing the definition.

Conclusion

To affect the incidence of esophageal adenocarcinoma, we must utilize less costly and risky screening techniques than upper GI endoscopy. When endoscopy is performed, biopsies should not be limited to CLE >1 cm, and perhaps any patient with high risk of Barrett's should be biopsied regardless of symptoms. Forceps biopsies should be supplemented by WATS to increase the diagnostic yield of all stages of Barrett's. Biomarker assays stratify the risk of progression in patients even in patients with NDBE. When performed in specialized centers, antireflux surgery is more successful than PPI therapy at decreasing the progression of NDBE to dysplasia. Patients should be informed of the shortfalls of surveillance and benefit of eradication discussed. Falling short of an ideal protocol of offering eradication to any patient with nondysplastic Barrett's, patients

considered to be at a high risk of progression by any means (crypt dysplasia, biomarkers, demographics) should be considered for ARS performed by experts and/or eradication therapy.

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Management of Dysplastic Barrett's Esophagus

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Introduction

Attention to the condition known as Barrett's esophagus (BE) has been heightened since the recognition by Hawe and colleagues in 1973 that it was a precursor for esophageal adenocarcinoma (EAC). As the incidence of EAC rose throughout the 1970s and 1980s, there was also recognition of dysplastic changes among BE patients with and without concomitant adenocarcinoma. Barrett's esophagus results from chronic exposure to gastroenteric fluid, and with sustained insults, progresses to dysplasia and eventually adenocarcinoma. Much work has focused on identifying BE patients who are at most risk for neoplasia. The presence of dysplasia remains the most important factor for predicting malignant transformation in these patients. Eradication therapy of BE with dysplasia has now become the standard of care in most of these patients. This chapter focuses on the significance, identification, and management of BE with dysplasia.

Epidemiology

A 2021 meta-analysis of 42 studies encompassing over 26,000 GERD patients reported a BE pooled prevalence of 7.2%. In the North American subgroup, BE prevalence was highest, 14.0%. Population-based studies may not fully represent the true prevalence of BE as the diagnosis of GERD in these patients is predominantly clinical and many patients may be asymptomatic. In a 2006 study of 402 US patients with GERD symptoms, 67.9% were confirmed to have significant esophageal exposure to gastroenteric fluid on 24-hour ambulatory pH monitoring. Of the patients with confirmed, pathological acid and/or bile exposure, 60.8% had biopsies with BE, suggesting a BE prevalence of 41% in patients with GERD symptoms. The rate of asymptomatic BE is particularly challenging due to limited screening, but a 2021 study did find a rate of 8.6% among 371 asymptomatic US veterans. Despite the frequency of BE in patients with GERD, dysplasia is less common. In the previously mentioned meta-analysis, of the 7.2% of patients with BE, only 13.9% showed dysplastic changes and 80.7% were categorized as low-grade dysplasia. Another study of 74,943 pooled BE patients found that male sex, older age, smoking, central obesity, and increasing length of BE segment were all associated with development or progression of dysplasia.

Definitions and Terminology

Once the pathological diagnosis of BE is confirmed, it can be further characterized using the Vienna classification as nondysplastic (NDBE), indefinite (indeterminate) for dysplasia (IDBE), low-grade dysplastic (LGD), or high-grade dysplastic (HGD). Nondysplastic BE is characterized by crowding of glands, basal hyperchromatic nuclei, preserved polarity, and surface maturation. For LGD, nuclei remain hyperchromatic but enlarged, with preserved polarity and glands may be less crowded. Decreased surface maturation with abrupt transition zone is also seen. High-grade dysplasia is highlighted by marked architectural derangement with even further nuclear enlargement, but the hallmark of the diagnosis is loss of cellular polarity. Extensive examination of HGD is required as carcinoma may insidiously occur among cells. The diagnosis of IDBE is typically used when a specimen cannot be classified as NDBE or LGD usually due to signifi-

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cant inflammation. While these discrete diagnoses provide consistency, dysplasia falls along a spectrum, and there may be heterogeneity of interpretation among pathologists.

Identification of Dysplasia

A 3–5-year surveillance interval has been advocated for patients with nondysplastic BE (NDBE). If any dysplasia is suspected, review by a second, preferably gastrointestinal-trained pathologist is advised. For BE indefinite for dysplasia, maximal antisecretory therapy, followed by repeat biopsy is typically undertaken to reduce confounding inflammation. Patients with persistent or multifocal indefinite for dysplasia may be managed like low-grade dysplasia (LGD) as studies have demonstrated similar rates of malignant potential in these patients. In the case of newly diagnosed low-grade dysplasia (LGD), it is now recommended that these patients undergo repeat biopsy in 3–6 months following aggressive acid suppression, to reevaluate for a visible lesion that is amendable to endoscopic intervention. In the absence of a discrete, resectable lesion, recent studies lead to the recommendation of endoscopic eradication therapy in medically fit patients. However, a surveillance interval of 1 year may be considered. If HGD is confirmed, eradication is warranted.

In addition to high-definition white-light endoscopy, chromoendoscopy is of significant value, providing a 9% improvement in BE dysplasia detection rate. Chromoendoscopy is a technique that uses different stains or frequencies of light to detect subtle mucosa irregularities that are not initially apparent. Dye-based chromoendoscopy for BE is performed using either acetic acid, methylene blue, or indigo carmine. Acetic acid is the most commonly used dye and disrupts surface epithelium, temporarily staining BE white. Dysplastic regions will typically lose this white color earlier than other areas and has a sensitivity and specificity of 96.6% and 84.6%, respectively.

Virtual chromoendoscopy uses optical filters that can assist in dysplasia detection without the need for tissue staining solutions. Narrow band imaging (NBI)(Olympus America, Center Valley, PA) is probably the most commonly used version of this technology. The red–green–blue filter in NBI-capable and commercially similar endoscopes captures shorter wavelengths (400–540 nm) targeting the light spectrum of light absorbed by hemoglobin. This causes the appearance of surface capillaries to appear brown with submucosal vessels taking a turquoise color. Dysplastic regions of BE can appear dark brown or even black, and typically exhibit erratic vessel patterns in relation to the surrounding tissue (Fig. 19.1). Most importantly, virtual chromoendoscopy is fast, convenient, and cost-efficient, with dysplasia detection rates equivalent to dye-based chromoendoscopy. Use of chromoendoscopy during BE evaluation is recommended by both the ACG and American Society for Gastrointestinal Endoscopy (ASGE).

Seattle protocol biopsies alone may only sample 4–6% of a BE segment, yielding a diagnostic accuracy of 35–48%. Wide-area transepithelial sampling (WATS) is a cytological modality that was developed to address this sampling deficit. The WATS technique involves applying an abrasive brush, circumferentially over a segment of BE, sampling nearly the entire surface area. Brushings are then reconstructed and analyzed using three-dimensional computer software. The

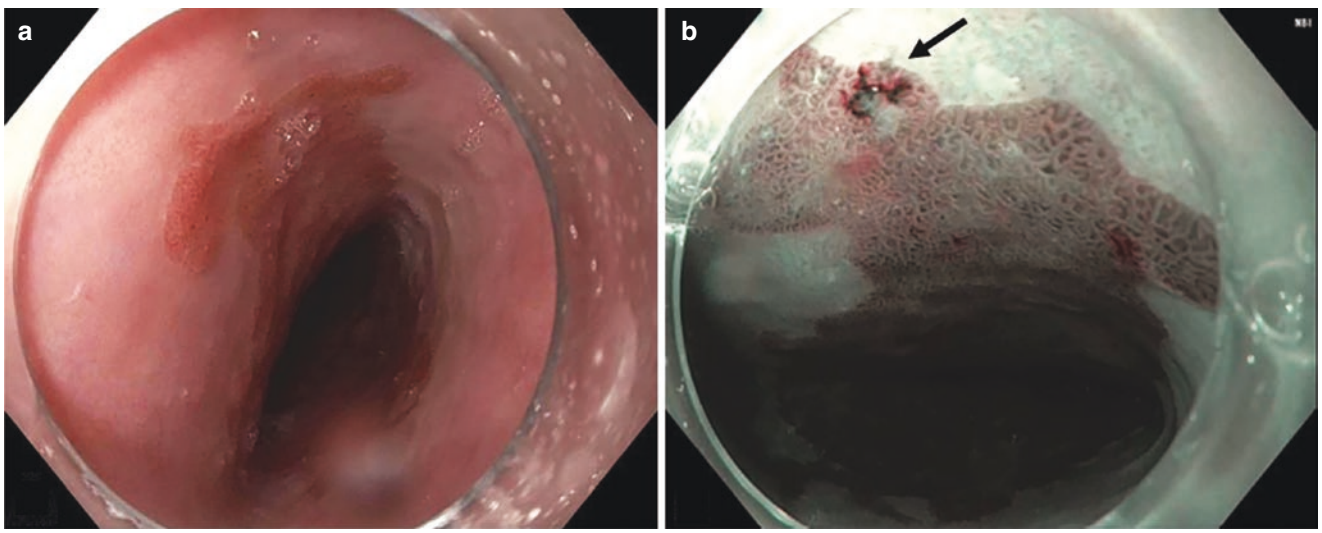

Fig. 19.1 Comparison of white-light and NBI chromoendoscopy (Olympus America, Center Valley, PA). (**a**) A tongue of BE mucosa is pictured left. (**b**) Note that on NBI, an irregular surface vascular pattern (black arrow) is seen, which is suspicious for dysplasia

modality is commercially available as WATS3D (CDx Diagnostics, Suffern, NY). A 2020 meta-analysis of 11 studies including 20,392 endoscopies found a statistically significant 2% increase in dysplasia detection compared to biopsies alone. Incorporation of routine WATS has been slow within society recommendations, particularly due to the high number needed to treat as well as cost. The ACG currently views WATS as investigational; however, WATS was conditionally included in the 2019 ASGE guidelines.

Endomicroscopy is another modality that has been utilized to improve dysplasia detection. The basic principle of this modality is use of a probe that emits laser-frequency light that is reflected by the tissues back to a sensor, similar to the concept of ultrasound devices. This generates a microscopic, cross-sectional image of the mucosa in real time. Confocal laser microscopy (CLE) was the initial version of the modality and requires intravenous administration of fluorescein. The major drawback to CLE is the relatively narrow field of view, particularly with long-segment BE.

Volumetric laser endomicroscopy (VLE) is the most recent endomicroscopy advancement. It is commercially available as Nvision VLE (Ninepoint Medical, Bedford, MA). Unlike CLE, VLE does not require use of fluorescein. It utilizes infrared light balloon probe with optical coherence tomography to generate high-resolution cross-sectional images of the mucosa and is able to survey 6 cm of esophagus at a time at a depth of 3 mm. Additionally, computer software can assist in identifying concerning areas. A marking laser within the probe can then be used to target identified lesions for subsequent biopsy/resection. Similar to CLE, VLE can be time-consuming with a steep learning curve. Neoplasia detection appears to be promising; however, constant product advancements make data comparison challenging. Insurance coverage of VLE is sporadic in the United States, and major societies do not advocate for routine use in BE surveillance at this time.

Management

Throughout the majority of the twentieth century, esophagectomy was the only treatment option for high-grade Barrett's esophagus and esophageal adenocarcinoma. Progressive innovation has led to a stark change in endoscopic capabilities, and endoscopic eradication therapy (EET) is now considered the standard of care for most instances of dysplastic BE and early-stage EAC. EET involves early medically optimization of GERD, endoscopic destruction or removal of all BE tissue, diligent surveillance of new squamous ingrowth, and ensuring long-term GERD control. This is not always straightforward and may be tedious, especially in patients with long-segment BE as well as those with severe GERD.

The goal of EET is to achieve complete remission of intestinal metaplasia (CRIM). While complete remission of dysplasia (CRD) is also considered a positive end point, a 2019 meta-analysis showed a 12% dysplasia recurrence with CRD compared to 5% in CRIM following EET. Eradication can be accomplished with removal in the form of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Alternatively, ablative techniques, including radiofrequency ablation (RFA), cryoablation (CA), argon plasma coagulation (APC), or photodynamic therapy (PDT), can also accomplish eradication. Surgery does remain an option for high dysplastic burden, particularly in the setting of other derangements or those who fail EET (Table 19.1).

Table 19.1 Comparison of endoscopic ablative therapies

Modality	CRIM (%)	CRD (%)	Recurrence (%)	Stricture (%)	Bleeding (%)	Pain/discomfort (relative)	Cost (relative)
RFA	70–86	87–95	9–18	3–7	1–2	☹☹☹	$$
Spray CA	57–88	87–93	11–23	7	2	☹	$$$
Balloon CA	88	95%	NA	3–13	2	☹	$$$
APC	58–78	67	NA	4	4	☹☹	$
PDT	43–53	77–80	13–15	36	<1	☹☹	$$$$

RFA Radiofrequency ablation, *CA* Cryoablation, *APC* Argon plasma coagulation, *PDT* Photodynamic therapy, *CRIM* Complete remission of intestinal metaplasia, *CRD* Complete remission of dysplasia

Indications for EET

Potential EET candidates should be extensively counseled on their BE or EAC diagnosis and presented with all available options. This discussion should be focused on the risk of progression or cancer prognosis, coupled with the anticipated outcomes and risks of potential treatment pathways. Patient variables, endoscopist experience, and institutional capabilities will also factor into the discussion. At present, EET indications include confirmed LGD, HGD, and T1a EAC, as well as T1b EAC lesions in very select cases.

Low-grade dysplasia carries an approximately 1.7% annual risk of progression to HGD or EAC. Because of recognized interobserver heterogeneity among pathologists in large-scale analyses, this may potentially underestimate the true malignant potential. One study showed that LGD, which was confirmed by a seasoned gastrointestinal pathologist, showed a 13.4% annual risk compared to a 0.49% annual risk in specimen downgraded to NDBE. Multiple studies have demonstrated that EET for LGD drastically improves outcomes. A prospective trial of 136 patients with confirmed LGD randomly assigned to EET or surveillance found a 3-year progression rate (to HGD or EAC) of 26.5% and 1.0%, respectively (51). Surveillance group independent predictors or progression included time since BE diagnosis, number of endoscopies with dysplasia, and length of circumferential BE. A 2017 meta-analysis of 19 studies including 2746 patients showed relative risk of progression of 0.14% in patients who underwent EET using RFA compared to those undergoing surveillance. EET is now recommended for LGD by most major societies.

High-grade dysplasia has an estimated 7% annual progression rate to EAC. These cells have considerable genomic instability and may be observed as discrete, nodular lesions on endoscopy. Approximately one-third of these lesions have been shown to harbor underlying adenocarcinoma. Because of this, any irregular or nodular areas should undergo endoscopic resection. Additionally, resection of nodular lesions ultimately flattens the mucosa, which is beneficial for future ablation. Rates of CRIM and CRD have been found to be 73% and 93%, respectively, when using this endoscopic resection-ablation approach for HGD. A multicenter, randomized controlled trial of 127 patients with dysplastic BE, comparing EET with RFA to surveillance, found that EET with RFA in patients with HGD resulted in a 2.4% rate of 1-year progression to EAC vs. 19% in the surveillance arm.

T1a EAC, also referred to as intramucosal adenocarcinoma, frequently occurs within a background of dysplastic cells. Similarly, T1a EAC may be multifocal within a BE segment. These very early-stage cancers carry only a <2% risk of nodal metastasis and are highly amendable to EET. Studies have shown no significant difference in short- or long-term survival with fewer complications for T1a EAC treated with EET compared to those who underwent esophagectomy. Although local recurrence rate was higher, the majority of recurrences are easily amendable to re-resection. EET is recognized as appropriate treatment for T1a EAC under the National Comprehensive Cancer Network (NCCN) guidelines for esophageal and esophagogastric junction cancer.

EAC, which penetrates the submucosa, is staged as T1b. Any patient with known or potential submucosal involvement should undergo endoscopic ultrasound (EUS). Although EUS cannot reliably differentiate between T1a and T1b tumors, it is useful to rule out muscular invasion as well as nodal metastases. In this case (≥T2 and/or ≥N1), endoscopic therapy is contraindicated. Because of the rich plexus of lymphatics and vessels within the submucosa, the rate of metastases is considerably higher. T1b EAC can be subclassified into SM1, SM2, and SM3. This system is based on division of the submucosa into thirds, such as SM1 represents the superficial one-third, and SM3 is the deep one-third. A study of 258 patients with T1b EAC found that 12% of SM1, 11% of SM2, and 20.9% of SM3 patients had lymph node metastases following esophagectomy. Boys et al. investigated multiple risk factors for T1b EAC nodal metastases, including lymphovascular invasion, depth >500 nm, and poor cellular differentiation. In this study, 26% of T1b patients had positive lymph nodes on surgical resection. Nodal metastases were found in 25%, 33%, and 50% of T1b patients with one, two, or three of the risk factors, respectively. Given this information, EET for T1b EAC may be reasonable for very shallow tumors with favorable histology. Ultimately, cases should be thoroughly paneled at multidisciplinary review, and all potential treatment outcomes explicitly discussed with patients.

Endoscopic Resection

Endoscopic resection techniques are most useful when discrete abnormalities within BE are identified under white-light endoscopy or advanced imaging. Complete removal of the mucosa containing the lesion allows for adequate staging and is potentially curative, but submucosal invasion may affect resectability. The Paris classification has been developed to assist with determining the likelihood of such submucosal involvement and nodal metastases, based entirely on the gross endoscopic appearance. Submucosal injection is another way to assist in this decision-making. Lesions that do not easily elevate with infiltration of the submucosal plane are likely more advanced, and further workup must be considered. Establishing orientation is paramount to these procedures and should be reported using consistent and reproducible methods. An example of this is pooling of fluid in a supine patient, signifying the posterior or 6 O'clock position.

Endoscopic Mucosal Resection (EMR)

Endoscopic mucosal resection can be accomplished using banding or cap-snare techniques, with similar safety and efficacy profiles. A submucosal injection or "lift" is not always required but may better delineate the lesion and serve as a heat buffer between electrocautery and the underlying muscle. For band EMR, the target lesion is aspirated into a cap and a rubber band is deployed to form a "pseudopolyp." The artificial polyp is then resected with snare electrocautery. Band EMR kits are commercially available as Duette (Cook, Limerick Ireland) and Captivator (Boston Scientific, Marlborough, MA). The cap-snare method is similar; however, the tissue of interest is aspirated into the cap and directly resected with a pre-looped, crescent-shaped, electrocautery snare at the tip of the cap. Band EMR seems to be the more popular approach, likely due to faster learning curve (Fig. 19.2).

EMR can be used to resect lesions up to 15 mm en bloc or larger regions in an overlapping piecemeal fashion. Specimen extraction is accomplished via the cap under suction, or with forceps and other retrieval devices. Rotation and flipping makes orientation of individual specimen unreliable in many instances. When performing piecemeal resections, however, special attention is needed to orient individual specimen as "pieces of a map" as this is critical for establishing margins. Additionally, specimen will quickly shrivel, or curl once resected, and should be fixated flat using pins or a compressive cassette prior to placement in preservative. Closure of the mucosal defect is typically not performed unless there is concern for deeper injury. Subsequent structuring is relatively uncommon for defects <50% of the luminal circumference.

Studies have shown EMR to be safe and effective for dysplastic BE and early-stage EAC. One study of 24 patients with HGD and/or T1a EAC found an 87.5% eradication rate following multistage EMR sessions at a median of 28-month follow-up. Complications were minor with two patients needing intraprocedural hemostasis, and three patients requiring balloon dilation for subsequent stricture. Another study of 1000 patients with T1a EAC who underwent EMR showed a 96.3% complete response to treatment at 5 years. Additionally, only 15 patients (14 bleeding, 1 perforation) experienced direct complications, all of which were able to be conservatively managed.

Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection is a "third space" procedure where the submucosal plane is accessed by the endoscope. Its primary use is for en bloc resections of larger mucosal lesions (>15 mm), particularly those with irregularly shaped borders. The procedure usually begins with marking of the lesion's mucosal margins using small electrocautery burns. Unlike EMR, initiation of the plane using generous submucosal injection is absolutely required. A mixture of saline and methylene blue has been traditionally used. Methylene blue assists by staining the areolar, submucosal tissues for differentiation of anatomy. Commercially available agents, including Eleview (Aries Pharmaceuticals, San Diego, CA) and Orise Gel (Boston Scientific, Marlborough, MA), contain high osmolar molecules that can maintain lift longer than saline and may increase efficiency.

Once the lesion is elevated away from the muscularis propria, the mucosal margin is incised using an endoscopic electrocautery knife. The submucosal plane is entered using with a cap that provides retraction allowing the areolar tissues to be visualized and divided under tension with electrocautery. After the submucosal dissection is complete, the remaining mucosal margin is cut, eventually freeing the specimen. Maintenance of orientation, fixation, and margin labeling is critical to the completion of the procedure.

The efficacy and safety of ESD in the current literature is quite favorable. One ESD study that included 87 early-stage

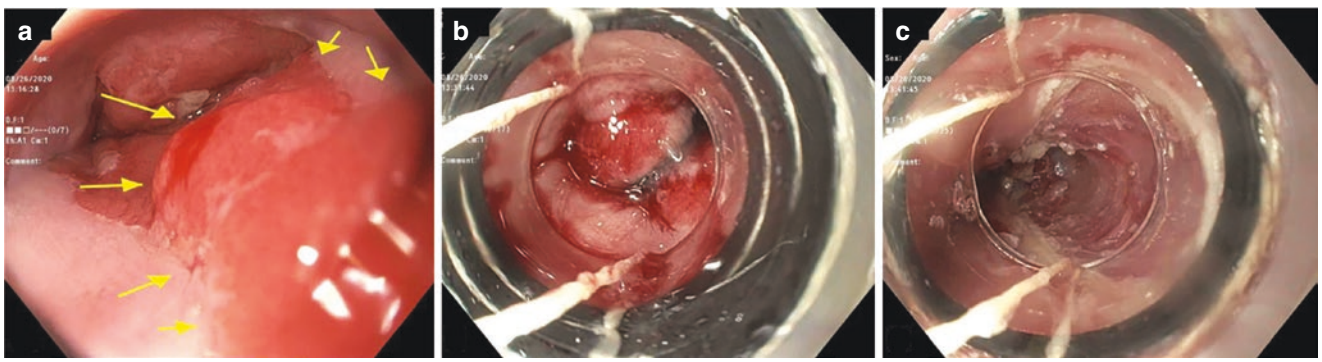

Fig. 19.2 Endoscopic mucosal resection (EMR). (**a**) Note the nodular area of BE demarcated by yellow arrows, (**b**) this region of mucosa is then suctioned into the cap and banded, and (**c**) the resulting "pseudopolyp" is resected with snare electrocautery, exposing the underlying circular muscle

EAC patients found rates of en bloc and R0 resection of 95% and 84%, respectively. R0 resection was higher for short-segment (≤3 cm) BE. Disease-free survival was 97% and overall survival 96% at a mean of 24-month follow-up. No perforations were encountered; however, bleeding and stricture occurred in 1% and 11%, respectively. In the largest North American ESD study to date by Dragonov et al., 181 esophageal lesions (165 BE or EAC) were included. The authors found en bloc, R0, and curative resection rates of 97%, 86%, and 77%, respectively. Complications included bleeding (1.7%), perforation (2.2%), and stricture (14.4%). Fortunately, most complications can be managed on index or subsequent endoscopy; however, data on the long-term ESD outcomes are limited at this time.

Initially ESD was felt to have more complications than EMR, but when directly compared, both appear to have similar safety and efficacy. A 2017 trial of 40 patients with HGD or mucosal EAC, equally randomized to ESD or EMR, found no significant difference in remission or adverse events at 3 months. ESD was associated with higher en bloc R0 resection rate compared to EMR. Another recent study found that ESD was associated with decreased histopathological uncertainty compared to EMR. The major criticisms of ESD include its time-consuming nature as well as a steep learning and efficiency curve. Additionally, ESD-type procedures have been not been covered by most US health insurance carriers. For these reasons, ESD remains considerably more popular in Asia and Europe.

Ablation

Endoscopic ablation therapy has been established as the mainstay treatment of flat dysplastic BE and associated neoplasia. Unlike endoscopic resection, ablation works by in situ mucosal destruction. As such, ablation should only be considered after thorough examination, tissue sampling, and removal of nodular portions of BE have been accomplished. Although multiple modalities have been studies, RFA has supplanted all others as the standard. Treatments are typically repeated every 8–12 weeks to address any residual BE segments.

Radiofrequency Ablation (RFA)

Radiofrequency ablation is the most common and most studied ablation technique for dysplastic BE. It uses bipolar electrodes to induce direct thermal injury to mucosa by which it contacts. Because direct contact of the RFA electrodes is so crucial, selection of the proper equipment is needed, and ablation may require several sessions. Circumferential and focal devices are currently available.

Circumferential RFA uses a balloon-based probe to force electrodes against the flattened target mucosa. Previously circumferential RFA required use of a sizing balloon to determine RFA probe size. New devices, such as the Barrx 360 Express (Medtronic, Minneapolis, MN) have bypassed this issue, with an easy single-step process. Focal RFA has cap-based and channel-based probes. Cap-based probes come in multiple sizes and are particularly useful for "tongues" (Prague M) of BE, which commonly arise above the circumferential (Prague C) portion. Channel-based probes may be better suited for small BE "islands" or "touch-up" work. During most RFA sessions, two applications of energy are delivered where the superficial, white "slough" is cleared with a cap between applications. Fully ablated regions should have a "golden-brown hue" (Fig. 19.3).

The utility of RFA has been strongly validated by both the AIM dysplasia and SURF studies. AIM dysplasia was a multicenter, clinical trial that randomized 127 BE patients with dysplasia to RFA or sham procedure (2:1 ratio). Of patients with LGD treated with RFA, 90.5% had eradication at 12 months compared with 22.7% in the sham group ($p < 0.001$). HGD patients saw an RFA eradication rate of 81.0% compared to 19.0% sham-treated patients ($p < 0.001$).

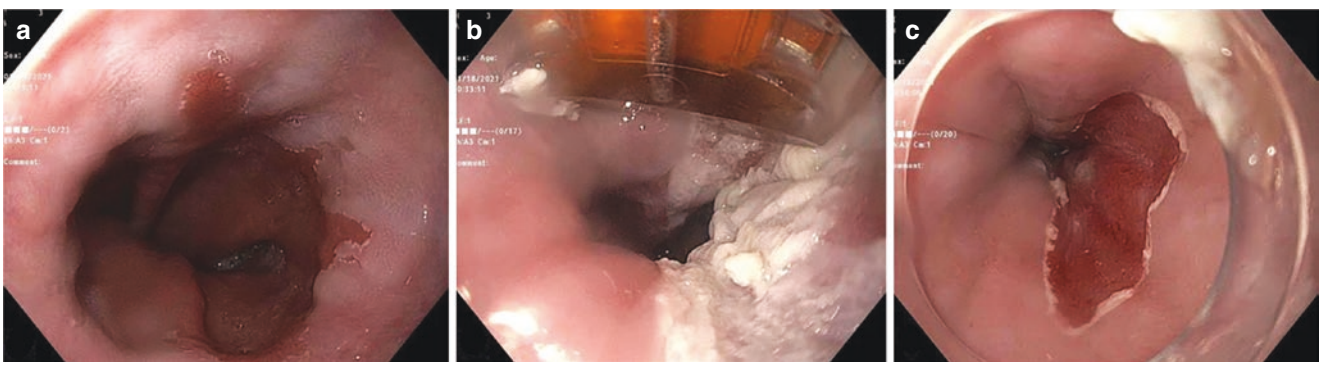

Fig. 19.3 Radiofrequency ablation (RFA) using a Barrx focal cap (Medtronic, Minneapolis, MN). (**a**) Note multiple tongues of flat BE mucosa above the gastric folds, (**b**) the RFA cap is then pressed against the mucosa for energy delivery, and (**c**) after cleaning and a second round of ablation, the mucosa appears with a brownish hue

Progression of dysplasia was 3.6% vs. 16.3% and incidence of EAC was 1.2% vs. 9.3% between RFA and control groups, respectively. Chest pain was significantly more common in the RFA arm but resolved within 1 week. Delayed bleeding occurred in <1% and occurred in 6% of RFA-treated patients.

The SURF study was a multicenter randomized controlled trial from Europe, which compared RFA to surveillance (1:1) among 136 patients with LGD. CRIM and CRD were achieved in 88.2% and 92.6% in the RFA arm. As mentioned earlier, the study found rates of 3-year progression to HGD or EAC of 1.0% of those treated with RFA compared to 26.5% who underwent surveillance. RFA-associated adverse events were reported in 19% the most common of which was stricture (11.8%). Serious adverse events only occurred in three patients, all of whom were managed with medical or endoscopic therapy.

Cryoablation (CA)

Rapid freezing, followed by slow thawing, induces cellular injury via three mechanisms: (1) initial osmotic dehydration, (2) subsequent oxidation-mediated apoptosis, and (3) delayed microvascular stasis. CA harnesses these principles with spray-delivered liquid nitrogen or balloon-applied nitric oxide (NO). Carbon dioxide-based system was also used but is no longer commercially available. Spray CA uses a through-the-scope catheter to apply liquid nitrogen to BE mucosa. Due to the risk of barotrauma, a decompressive orogastric tube is needed to vent the rapidly expanding nitrogen gas prior to the application. Typically, 2–4 freeze–thaw cycles are administered per session. An advantage of spray CA is that it can be used over irregular contours such as stricture or angulated regions. By the same token, application is user-dependent and can be uneven. Spray CA is currently approved for use in the United States under the truFreeze system (STERIS, Mentor, OH) (Fig. 19.4).

Balloon CA is commercially available as C2 CryoBalloon Ablation (PENTAX Medical, Redwood City, CA). This system uses a through-the-scope NO delivery catheter, with a rotatable diffuser, which is covered by a balloon. The balloon is inflated to contour to the esophageal wall, and then NO is administered within the balloon. A hand-piece controller is used to direct the application of NO. All expanding gas collects within the balloon and is vented through the catheter. Multiple styles are available, including a focal (small areas), pear-shaped (gastroesophageal junction and strictures), and more circumferential balloons. Balloon CA is less dependent on the endoscopist, and regions can be more evenly treated compared to spray CA.

The majority of the CA studies have utilized the spray method, and multiple studies are confounded by use of other eradication modalities before or during the study interval. Earlier retrospective studies demonstrated rates of CRIM and CRD with spray CA ranging from 53–57% and 87–88%, respectively. Similar results were seen in a 2016 prospective study of 32 LGD and 64 HGD patients undergoing spray CA, with CRIM and CRD achieved in 61% and 81%, respectively, at a mean of 21-month follow-up. Patients with ≤3 cm BE segments more frequently achieved CRIM and CRD. Longitudinal outcomes of spray CA are less certain; however, one retrospective study did show that 81% of patients with initial CRIM ($N = 26$) maintained this status at 5 years.

Initial balloon CA studies demonstrated 90–100% initial response to small regions of BE treated for 10 s. In a more recent prospective study of 41 patients who underwent balloon CA for LGD, HGD, or T1a, EAC found that CRIM and CRD were achieved at 1 year in 88% and 95%, respectively. A median of three sessions were required. Similar to spray CA, long-term results are largely unknown.

Argon Plasma Coagulation (APC)

Argon is an inert gas that can conduct electrical current. APC takes advantage of this physical property by delivering monopolar energy to mucosa without direct contact. The

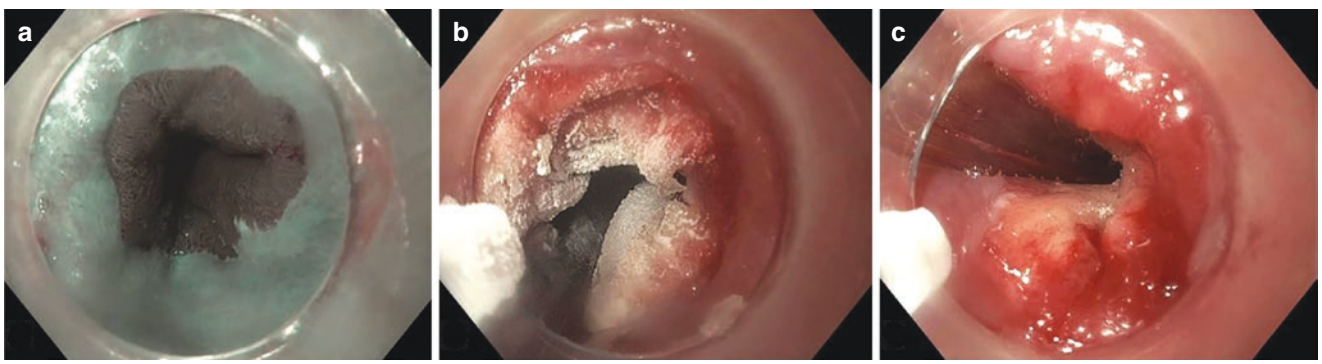

Fig. 19.4 Spray cryoablation. (**a**) Note the circumferential rim of flat BE mucosa above the gastric folds, (**b**) liquid nitrogen is then applied via a catheter to freeze tissue, and (**c**) the ablated region then thaws

device involves a simple catheter that is placed through the endoscope working channel that emits ionized argon on the target tissues. Traditionally APC was used for endoscopic hemostasis of raw, slow-bleeding surfaces due to its superficial dispersal. Several studies have shown that APC can also be used for EET, with CRIM rates for short-segment BE ranging from 61 to 100%. Another study of 13 patients with longer dysplastic BE segments (median 5 cm) found only 15% complete regression at 12 months. Although BE segment length is factoring in all EET modalities, this does highlight the user-dependent nature of APC.

Often small residual islands of BE may be observed "between burns" on follow-up endoscopy. Additionally, buried BE tissue can persist beneath new epithelium. A new technique known as hybrid APC has been developed to combat these issues, which involves generous submucosal injection prior to ablation. Mucosal lift helps to obliterate folds, but also to serve as a heat buffer, allowing higher doses of energy. A pilot study of 50 patients treated with a mean of 3.5 sessions of hybrid APC found CRIM in 78% at 3 months. In the same study, stricture was observed in only one patient, and no major complications reported. The BRIDE trial prospectively evaluated BE response in 76 patients randomized to either hybrid APC or RFA. Both modalities showed similar efficacy and safety at 12 months; however, hybrid APC was substantially cheaper. Until larger, longitudinal studies are conducted, the role of APC will likely be limited to small, focal areas of BE.

Photodynamic Therapy (PDT)

Photodynamic therapy involves systemic administration of a photosensitizing drug, which has higher affinity for neoplastic cells, followed by exposure of the cells to light. Cells then undergo oxygen-free radical-induced apoptosis. The result is preferential destruction of premalignant and malignant tissue, occurring in the days following therapy. Intravenous pofimer sodium, commercially known as Photofrin (Pinnacle Biologics, Bannockburn, IL), is the agent used in the United States; however, other photosensitizing drugs are available globally. Two days after administration, patients undergo endoscopy where a fiberoptic filament is passed through the working channel, which emits red, laser-frequency light. Two intervals of light exposure are performed, and commonly patients undergo a second treatment endoscopy 2 days later. PDT with Photofrin is currently approved for the treatment of HGD and palliation of obstructive EAC.

An early study of PDT in 100 patients with dysplastic BE and early-stage EAC found CRIM in 43% and CRD in 79% at a mean of 19-month follow-up. Of note, stricture was observed in approximately one-third of patients. A later multicenter trial, which randomized 208 BE patients to either PDT or omeprazole therapy, showed that 52% of PDT patients vs. 7% of omeprazole patients achieved CRIM at 24 months. Longitudinal follow-up at 5 years showed CRIM in 48% and 4% of the study groups, respectively. Additionally, 15% of PDT patients progressed to EAC vs. 29% of those treated with omeprazole. In a previously mentioned clinical trial by Ragunath and colleagues, cost-effective analysis was performed among 26 patients with dysplastic BE randomized to PDT or APC. Efficacy between groups was quite similar; however, PDT showed an advantage in dysplasia eradication at 1 year (PDT 77%, APC 67%). This PDT advantage came at 82% increased cost per percentage of BE segment reduction.

Complications of PDT primarily include stricture and photosensitivity reactions. Stricture may occur in 15–36% of PDT-treated patients. Photosensitivity has been reported in upwards of two-thirds of patients undergoing PDT and occurs in light-exposed regions, including the hands, arms, and face. For this reason, patients must judiciously protect themselves from sunlight or bright indoor lighting for up to 6 weeks following drug administration. The burden of prolonged light avoidance is often cited as a major barrier to PDT. The cumbersome nature of PDT coupled with significant expense has caused it to fall out of favor at many centers.

Conclusion

Currently, the presence and degree of dysplasia is the best marker that we have to predict BE progression to adenocarcinoma. Early acid suppression therapy is needed to halt oxidative stress and the nuclear deterioration in these cells. Patients with BE should undergo thorough and comprehensive endoscopy with chromoendoscopy to identify regions that may be at higher risk for dysplasia. Although several novel imaging modalities are available, further research is needed to evaluate for additional diagnostic benefit. Any regions of BE with nodularity and areas of mucosal irregularity must be first considered for endoscopic resection as this provides most accurate staging and is potentially curative for early-stage EAC.

High-grade dysplasia has been the longest standing indication for endoscopic eradication therapy. More recent studies have now shown that EET is a cost-effective strategy for high-performance patients with LGD for preventing malignant complication. Following initial endoscopic resections, EET is usually accomplished with ablative modalities. Of these, RFA has been best studied and is considered the standard. Newer modalities such as cryoablation appear promising, particularly in patients with disease refractory to RFA. Hybrid APC may offer a cost-effective option for patients with smaller areas of residual disease. Despite its

positive outcomes for palliation of obstructive EAC, the role of PDT in the management of the dysplastic BE is most limited by subpar efficacy, prolonged light avoidance, and high cost. Across all modalities, length of the initial BE segment is a major influencer in response to treatment. Following EET, aggressive medical or surgical control of GERD is paramount for preventing recurrence.

Questions

A 59-year-old man with BMI of 46 presents to clinic with complaint of heartburn and regurgitation for over 20 years. His PCP initiated esomeprazole 40 mg twice daily, which improved his symptoms initially; however, he continued to have breakthrough symptoms and 3 months ago sucralfate was also added. On endoscopy, he is found to have C3M4 salmon-colored mucosa proximal to the gastric folds, as well as a 3 cm type I hiatal hernia, and retrograde flow of bile through the pylorus. Virtual chromoendoscopy reveals a 5 mm cluster of tortuous mucosal vessels within the tongue of salmon mucosa above the circumferential portion.

1. In addition to four-quadrant 1–2 cm interval biopsies, what is the best additional course of action?
   A. Volumetric laser endomicroscopy (CLE)
   B. Endoscopic mucosal resection (EMR) of the 5 mm cluster of vessels
   C. Endoscopic submucosal dissection (ESD) of the 5 mm cluster of vessels
   D. Wide-area transepithelial sampling (WATS)

Answer: B. The cluster of vessels within the Barrett's esophagus segment is suspicious for dysplasia, thus endoscopic resection should be pursued. Of the two resection techniques, EMR (Answer B) would be ideal from a simplicity and efficiency perspective. ESD (Answer C) is more useful for en bloc resection of lesions larger than 15 mm. WATS (Answer D) could be used as an adjunctive modality in this patient; however, it is less important than endoscopic resection. Endomicroscopy (Answer A) remains novel at this time, and while some data support its utility, routine use is not recommended.

2. A week after the procedure, you are reviewing the pathology report and note that "goblet cell intestinal metaplasia, indefinite for dysplasia" was seen in the specimen at 37 cm from the incisors. All other specimens show no dysplasia. You see that the report was signed by two pathologists. Which of the following is the next best step for this patient?
   A. Surveillance endoscopy in 1 year
   B. Surveillance endoscopy in 3 years
   C. Focal-cap radiofrequency ablation (RFA)
   D. Circumferential balloon radiofrequency ablation (RFA)

Answer: D. This patient has Barrett's esophagus, which was confirmed as indefinite for dysplasia (IDBE) by two pathologists. Usually IDBE is confounded by inflammation, and repeat endoscopy is recommended several months after high-dose acid suppression as many patients will convert to nondysplastic. This patient is already taking esomeprazole twice daily as well as sucralfate. Additionally, some element of bile reflux may be contributing. At this point, IDBE may be treated like low-grade dysplasia (LGD). Because 3 cm of Barrett's esophagus is circumferential, balloon RFA would cover this region best.

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Management of Early Esophageal Cancer

20

Nasim Parsa, Steven R. DeMeester, Daniela Molena, and Stavros N. Stavropoulos

Key Points

- In the past two decades, endoscopic therapy has revolutionized the treatment of early-stage esophageal adenocarcinoma with favorable safety outcomes compared with esophagectomy, while providing similar oncological outcomes in appropriately selected patients.
- At the same time, minimally invasive esophagectomy has been more frequently utilized as an alternative to traditional open esophagectomy with fewer complications but requires surgical expertise.
- A limitation of endoscopic therapy is the inability to assess for lymph node metastases, which would imply a higher risk of incomplete treatment compared with esophagectomy.
- As early-stage esophageal adenocarcinoma is a curable disease in most patients, several factors such as patients' health status, depth of tumor invasion, severity of reflux disease, and risk factors for nodal metastases should be carefully assessed in order to maximize the likelihood of long-term survival with good quality of life.

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Introduction

Esophageal cancer is the seventh leading cause of cancer-related mortality in men in the United States [1]. Although squamous cell carcinoma is more common worldwide, adenocarcinoma arising from Barrett's esophagus (BE) accounts for the majority of cases in Western countries, with incidence rates that continue to increase [2, 3]. Overall, esophageal adenocarcinoma has a poor prognosis, mainly due to the advanced stage of the disease at the time of diagnosis. However, in a paradigm shift, it is now clear that most patients with early-stage esophageal adenocarcinoma (EAC) can be cured of the disease. While the importance of early detection through BE surveillance programs is clear, surveillance is often done poorly and sporadically within the United States [4–6]. The goal of surveillance is to detect dysplasia or early cancer that can be treated endoscopically, without the need for chemotherapy, radiation, or surgical resection of the esophagus. Ablation of dysplastic BE has been shown to reduce the risk of progression to adenocarcinoma and is now accepted as standard therapy [7]. In patients with a nodule or lesion within the columnar-lined esophagus (CLE), ablation carries the risk of inadequate treatment. In this setting, endoscopic resection is necessary to determine whether the lesion is an adenocarcinoma and pathologically evaluate the depth of invasion. While endoscopic ultrasound (EUS) is often used to stage these superficial lesions, it has been repeatedly shown that it lacks sufficient accuracy to be useful as a routine study [8].

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Instead, endoscopic resection techniques allow reliable assessment of the depth of invasion as well as assessment of critical risk factors for potential node metastases. Frequently, the endoscopic resection is both diagnostic and therapeutic in these patients.

The combination of endoscopic resection and/or ablation is termed endotherapy (ET) and has replaced esophagectomy for most patients with intramucosal (T1a) esophageal adenocarcinoma.

Endoscopic resection (ER) includes the traditional technique of endoscopic mucosal resection (EMR) and the more novel technique of endoscopic submucosal dissection (ESD). EMR achieves resection via a monopolar electrosurgical snare applied around a polyp created by cap assisted suction of the target lesion with or without band ligation. ESD uses an electrosurgical knife to achieve en bloc microsurgical resection of the target lesion in a fashion that allows the operator to pursue an adequate deep and lateral negative margin actively and precisely (Fig. 20.1). ET has been shown to provide excellent long-term oncological outcomes similar to esophagectomy in patients with intramucosal adenocarcinoma, with significantly lower rate of morbidity (1–3%) and mortality (0–1%) [6–9]. It is important to note that the excellent outcomes of ET are the result of careful patient selection, skillful endoscopic resection techniques, expert pathological assessment, and careful post-ET surveillance programs that require patients' commitment to multiple procedures [6, 8].

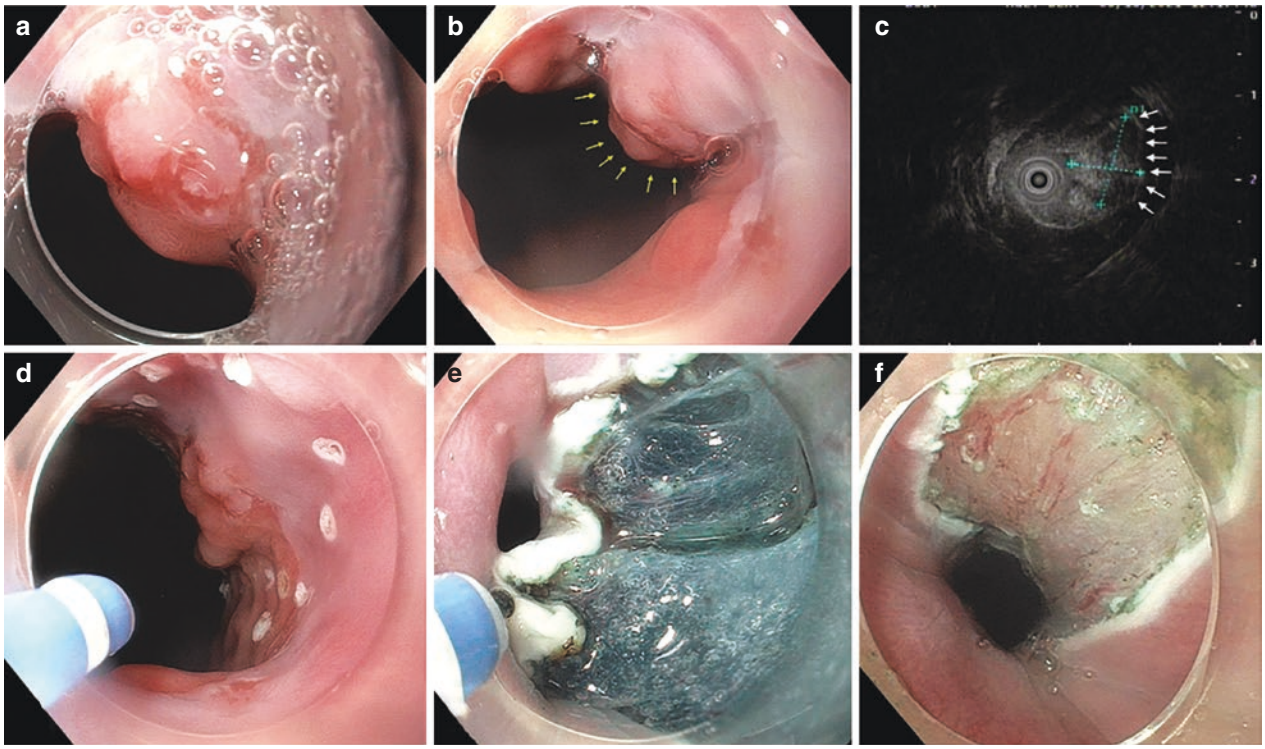

Fig. 20.1 ESD for Barrett's T1 carcinoma. A 68-year-old woman with GERD symptoms for 10 years on daily PPI for the past several years had surveillance EGD on August 19, 2021, by a general gastroenterologist who did not note any focal lesions and biopsied an "irregular Z line." Pathology: "specialized metaplastic columnar mucosa with goblet cells consistent with Barrett's esophagus if supported by endoscopic findings. High-grade dysplasia." The patient was referred for further expert evaluation. EGD on September 13, 2021, revealed a focal 1–2 cm Paris 2a lesion spanning the Z line in ultra-short-segment Barrett's (**a**, **b**). High-frequency EUS (20 MHz) revealed intact submucosa (white arrows) between the deepest extent of the tumor (hypoechoic lesion marked by calipers) and the muscularis propria (uT1) and no paratumoral lymph nodes (**c**). ESD was performed to achieve R0 resection of this suspected carcinoma that would necessitate a resection specimen of ≥3–4 cm (1–2 cm lesion plus ≥1 cm margin to guard against the frequent, well-described, endoscopically inconspicuous, subepithelial extension of Barrett's carcinomas of ≥5 mm). ESD: marking of the lesion (**d**); submucosal dissection (**e**); final resection crater, esophageal (**F**), and EGJ (**g**) views; closure of ESD defect with clips (**h**) to minimize further the low risk of delayed bleeding and perforation and accelerate healing. Pinned resection specimen view with ruler (**i**), 4 × 4 cm square-shaped specimen, 2 × 2 cm lesion. As can be seen on the time stamp of the images, the ESD resection time was <46 min (ESD speed 20.8 cm^2/h., well above the proficiency benchmark of 9 cm^2/h). NBI view demonstrating the disruption of the Z line by the tumor (**j**) and close-up view demonstrating the subtle boundaries of this 2 cm lesion (which necessitate generous resection margins to ensure R0 resection) (**k**). Final pathology: T1a, Nx. Intramucosal carcinoma invading muscularis mucosae (T1a m3), maximal thickness of carcinoma 0.4 mm, neg. Perineural/lymphovascular invasion, deep margin negative for dysplasia/carcinoma (1.1 mm from carcinoma; 1.3 mm from HGD), lateral margin negative for carcinoma and HGD

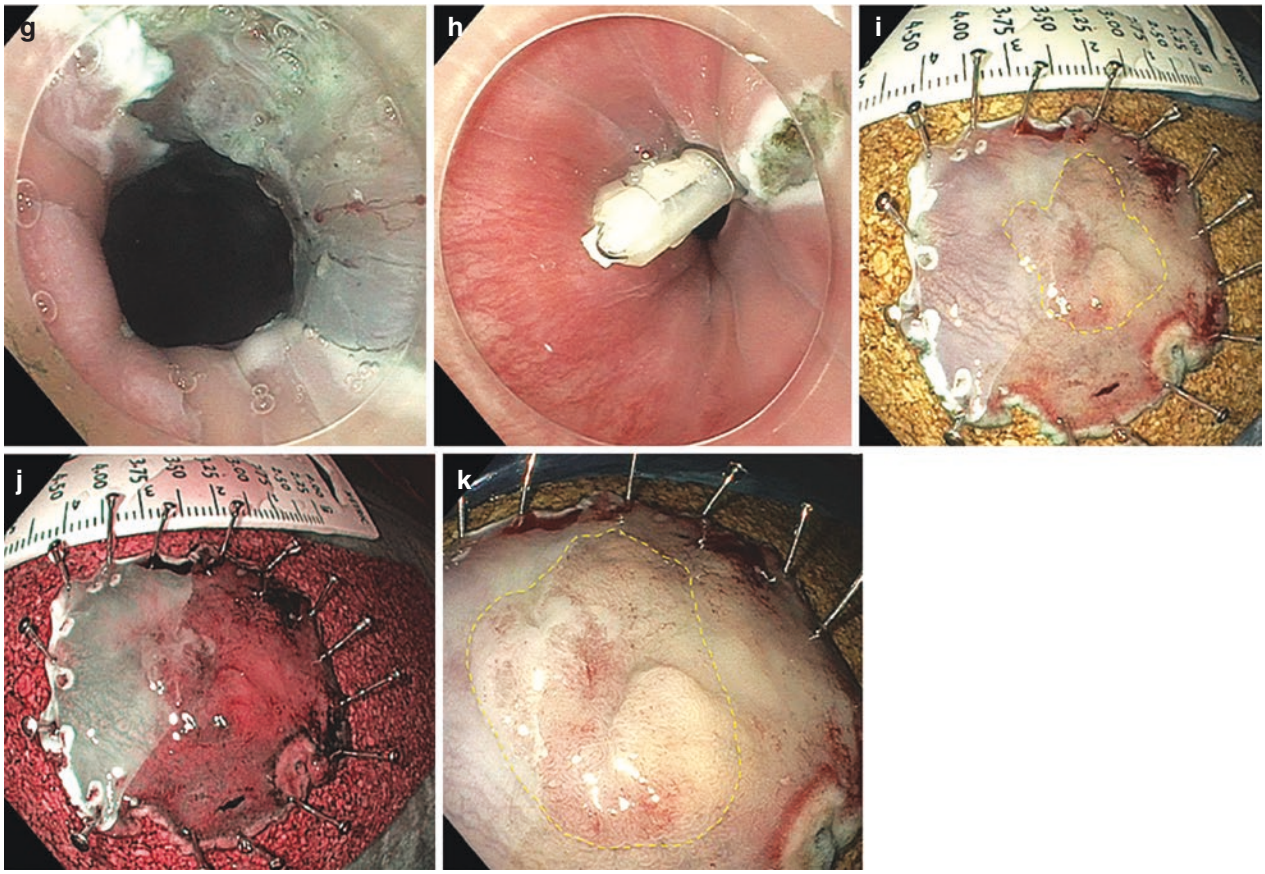

Fig. 20.1 (continued)

Current Status of Endotherapy in the United States

Owning a Hammer Does Not Make you a Contractor

It is of paramount importance to recognize that intramucosal adenocarcinoma is esophageal cancer, and if not treated appropriately, will progress, leading to patient death from cancer. Traditionally, gastroenterologists would diagnose cancer on endoscopy, and perhaps assist in staging with EUS, but rarely participate in cancer treatment. Consequently, many gastroenterologists are unfamiliar with cancer treatment and follow-up protocols. Now that there are endoscopic options for treating superficial esophageal cancer, gastroenterologists are participating in cancer therapy. It is critical that anyone treating esophageal cancer, even early-stage cancer, be diligent in therapy, follow-up, and review of the current literature to ensure optimal outcomes in these patients with curable lesions. Long gaps between treatment sessions, inappropriate therapy selection, and lost-to-follow-up situations can all lead to poor outcomes with ET. Aggressive ablation of residual BE after endoscopic resection of a superficial cancer is necessary to prevent metachronous cancer development. Ablation of nodular BE or poor contact with the columnar mucosa during radiofrequency ablation (RFA) can lead to inadequate treatment and disease progression. Patients must agree to the treatment and follow-up protocol for ET or they might be better served with an esophagectomy. Currently, follow-up after successful ET should represent a lifelong commitment [9].

It is an absolute failure to detect a curable cancer in a patient and have them ultimately die from esophageal cancer because of inappropriate treatment or follow-up as part of an ET program. An ET program is labor-intensive for the endoscopist who must aggressively treat these patients every 8–12 weeks until all intestinal metaplasia (IM) has been eradicated. It is also labor-intensive for the office staff who must make sure patients return on time and do not miss treatment sessions and manage pain or dysphagia issues between sessions. Furthermore, errors in interpretation of ER specimens are common by inexperienced pathologists, and it is incumbent on the endoscopist to have the ER specimens reviewed by an outside expert pathologist until there is con-

fidence in the internal pathology reading [10]. A T1b tumor interpreted as a T1a lesion on an EMR specimen can be a death sentence for the patient, and the endoscopist should be familiar with the complexity of pathological interpretation of EMR specimens to understand where areas of uncertainty exist in the diagnosis. Consequently, the decision to begin an ET program is not one that should be made lightly.

Patient Selection and Pretreatment Evaluation

Selecting the appropriate treatment for patients with EAC requires a comprehensive understanding of local tumor extent and the risk of lymph node metastases (LNM). Endotherapy can provide a definitive cure in patients with superficial tumors and no LNM. The problem is that a small <2 cm primary tumor typically will not have large lymph node metastases, limiting the utility of EUS and PET-CT in this setting. Instead, known risk factors for LNM must be used to determine the relative risk in each patient, and that risk weighed against the risk of esophagectomy with lymph node dissection. In healthy patients with more than a 5–10% risk of LNM, the optimal treatment is surgical resection at an experienced center since modern operative mortality rates are well below this level of risk and untreated nodal disease will lead to death from cancer [11]. Known risk factors for LNM include tumor size ≥2 cm, poor differentiation, presence of lymphovascular invasion, and invasion depth beyond the superficial submucosa (>500 μ) (T1b cancer). Data from the surgical literature have shown that the risk of LNM increases with the depth of invasion, with intramucosal and submucosal lesions having up to 1.3% and up to 50% rate of LNM, respectively [10, 11]. Overall, patients with none of these risk factors have a negligible risk of LNM, while those with multiple risk factors are at increased risk of up to 50% for LNM [11].

Endoscopic therapy has been shown to provide excellent long-term outcomes for the treatment of T1a cancers. Pech et al. evaluated the long-term outcomes and safety of EMR in 1000 patients with intramucosal adenocarcinoma and reported a 91.5% five-year survival and 96.3% complete remission rate, with 14.5% recurrence at a median of 26.5 months, which was successfully treated with repeat EMR in 82% of patients [9]. Overall, ET is recommended as first-line treatment in patients with T1a cancer, except for patients unwilling or unable to go forward with potential serial endoscopic interventions to eradicate all the intestinal metaplasia, followed by long-term surveillance endoscopy to assess for recurrence. Esophagectomy might be more appropriate in these patients, as well as those with severe and uncontrolled reflux, aspiration, dysphagia, poor esophageal body function, or ultra-long-segment BE with multifocal cancer. It is well established that shorter lengths of BE are much easier to eradicate than long segments, and that ongoing reflux can interfere with successful ET [12].

T1b Cancer

As mentioned earlier, the risk of LNM in T1b lesions can be significant. Therefore, in patients with T1b cancer who are fit for surgery, the standard of care is esophagectomy with regional lymphadenectomy. Some studies have reported promising survival data for ET in patients with T1b EAC with "low-risk features," defined as lesions <2 cm, with moderately or well-differentiated histology, and superficial submucosal invasion (<500 μ) [13, 14]. However, it is important to note that these features and risk factors are not always easily assessed. For example, some studies have shown significant interobserver variability in the histopathological interpretation of endoscopic resection specimens with regard to the depth of invasion [15]. In a study of patients with EAC who were staged as T1b based on staging endoscopic resection and subsequently underwent esophagectomy, 26% were found to have positive LNM (although most of these cases had only 1–2 LNs involved) [16]. Encouragingly, however, none of these T1b patients had LNMs unless they had at least one high-risk histological feature in the ER specimen (poor differentiation, lymphovascular invasion, or deep ≥500 micrometer SM invasion). At the same time, surgical techniques have evolved from morbid open esophagectomy to minimally invasive or robotic esophagectomy with data from high-volume centers demonstrating ~1% mortality and favorable post-esophagectomy quality of life, as well as excellent 5-year disease-specific survival rates [16, 17]. Based on these data, ER is a reasonable initial approach for T1 cancers with salvage surgical resection reserved for non-curative endoscopic resection of T1b cancers (i.e., positive or nonassessable deep ER margin, poor differentiation (G3), lymphovascular invasion, or ≥ 500 micrometer SM invasion). We should emphasize here that, given the high stakes involved in the assessment of T1b cancer ER specimens, review by expert pathologists is paramount with a low threshold for salvage esophagectomy. In patients clinically unfit for esophagectomy, ER can be performed as an alternative approach, while appreciating, however, that ER alone will not be a definitive cure in patients with a high likelihood for LNM. For such patients, adjuvant chemoradiation can be considered. However, this remains investigational at present. Preliminary data are equivocal and of low methodological quality and most come from Asian series with a preponderance of squamous carcinomas [18, 19]. Among surgical candidates, selected patients with multiple risk factors for node metastases may be offered neoadjuvant therapy, whereas

those with advanced nodal disease as shown by final pathological analysis of the esophagectomy specimen are often recommended for adjuvant therapy.

Endotherapy Techniques

The ultimate goal of ET is to achieve curative resection of focal early neoplasia, eradication of dysplasia, and complete remission of intestinal metaplasia (CRIM) through ER and serial endoscopic ablations (EA).

Endoscopic Resection

The basic principles of ER include resection of all visible nodules or lesions within columnar mucosa with clear lateral and deep margins down to the muscularis propria to accurately determine the depth of invasion and minimize the risk of a positive deep resection margin in patients with submucosal tumor invasion [20]. ER is generally safe but associated with some complications, including bleeding (5%), perforation (EMR <1%, ESD 1–3%), and stricture formation [21]. Strictures can occur with ablation or ER and are more common with longer lengths of treated mucosa, particularly when circumferential [21]. ER can be performed either by cap-assisted endoscopic mucosal resection (cEMR) (using the cap-and-snare or band-ligation techniques), or by endoscopic submucosal dissection (ESD). The multiband ligation device, originally from Cook (Duette, Cook Group Inc., Bloomington, IN) but now also available from other companies, is the preferred cEMR technique since it is faster and easier and allows overlapping resections. Larger lesions (>12–15 mm, the average size of cEMR pieces) will require piecemeal cEMR, which leads to more artifacts and prohibits accurate assessment of the lateral margins. More recently, ESD has been utilized for resection of larger lesions (Fig. 20.1). ESD has been shown to have higher en bloc, R0, and curative resection rates and lower recurrence rate compared with EMR, albeit with longer procedure times and higher risk of perforation (longer duration by 64 minutes by weighted means difference, and odds ratio for perforation of 2.47 in the most recent comprehensive meta-analysis of ESD vs. EMR for esophageal carcinoma). In this meta-analysis, most of the benefits of ESD were realized in lesions >1–2 cm [22]. Accordingly, recent Western ESD practice guidelines from Europe and the United States recommend EMR for most smaller esophageal lesions, reserving ESD for selected cases, such as lesions larger than 15 mm, poorly lifting lesions, and lesions at risk for carcinoma with submucosal invasion [23, 24]. Endoscopists engaged in ET for adenocarcinoma should be proficient in both EMR and ESD to provide optimal care for these patients. ESD is complex and has a protracted learning curve. In our ESD learning curve analysis based on the largest single-center ESD series published in the West, we demonstrated that, with a typical Western ESD case mix that includes a significant proportion of more difficult colonic lesions, it took approximately 170 ESD cases for the operator to reach proficiency in "Western" esophageal ESD (i.e., consisting mostly of Barrett's lesions straddling the EGJ rather than technically easier squamous lesions in the more proximal tubular esophagus that comprise most esophageal ESD cases in Asia) [25].

Most of the operators in the publications of Table 20.1 clearly had not accumulated the number of cases required to reach proficiency, resulting, for example, in ESD R0 rates as low as 39% and 42% in a European study from 2012 and a US study from 2019. A non-R0 resection can have significant consequences for the patient. An interesting recent "real-world" cohort study of EMR vs. ESD for

Table 20.1 Western ESD series

Author, year	Study design	Number, total/ carcinoma	Specimen size, mm	Time, min	En bloc resection, %	R0 (≥Tis/HGD cancer), %
Neuhaus (2012) [37]	Cohort	30/24	25	75	90	39
Probst (2015) [38]	Cohort	87/87	39	140	95	74
Chevaux (2015) [39]	Cohort	73/55	53	117	90	64
Hobel (2015) [40]	Cohort	22/20	44	114	96	82
Barret (2016) [41]	Cohort	36/29	51	191	89	72
Coman (2016) [42]	Cohort	36/13	49	88	100	81
Yang (2017) [43]	Retrosp MCT	46/26	45	121	96	76
Subramaniam (2017) [44]	Retrosp MCT	143/117	31	80	91	79
Terheggen (2017) [45]	RCT- EMR vs. ESD	15/20 vs. 20/17	14 vs. 16	22 vs. 54	15 vs. 100	12 vs. 59
Podboy (2019) [26]	Cohort EMR vs. ESD	31/17 vs. 20/10	14 vs. 17	45 vs. 103	52 vs. 100	20 vs. 81
Genere (2019) [46]	Case–control EMR vs. ESD	72/18 vs. 72/34	19 vs. 21	37 vs. 79	NA vs. 83	NA vs. 42

Only 3 out of 11 met the operator proficiency benchmark for ESD of ≥80% R0 resection

Barrett's lesions amply illustrates this point [26]. The EMR and ESD groups in this study had similar proportions of early Barrett's carcinoma (54% and 50%, respectively) but far more carcinomas in the EMR group had "equivocal pathology" ("at least intramucosal carcinoma") (65% vs. 0%, $p = 0.003$) and indeterminate deep margin (77% vs. 0%, $p = 0.001$). Unfortunately, this resulted in more potentially unnecessary esophagectomies for very early-stage lesions (3/5 esophagectomies for cancers with ≤T1a stage in the EMR group vs. 0/3 in the ESD group). Importantly, when doing band EMR it is critical to cut below the band to allow pathological assessment of the submucosa and minimize the risk of a positive deep margin that might have been negative had the snare been applied below the band. The bands are not strong enough to lift the muscularis propria, so even overlapping resections have an extremely low risk of full-thickness injury.

Endoscopic Ablation

ER should be followed by endoscopic ablation (EA) of the remaining Barrett's mucosa until CRIM in the esophagus and GEJ (replacement of BE with neo-squamous epithelium) is achieved to minimize the rate of metachronous neoplasia. Studies by the Wiesbaden group emphasize the importance of following ER of early carcinoma by EA of all residual Barrett's epithelium. In their initial study in which 49% of patients received EA after curative EMR of early carcinoma, the rate of metachronous cancers was 11% over a mean follow-up period of 36.7 months. In a subsequent longer-term study by the same group in which 20% of patients received EA after curative ER of early carcinoma, the incidence of recurrent/metachronous cancer was 21.5% during a mean follow-up period of 63.6 months [27, 28].

Several endoscopic ablative technologies exist for eradication of BE, including radiofrequency ablation (RFA), cryotherapy, photodynamic therapy, argon plasma coagulation, and multipolar electrocoagulation.

It is important to note that despite appropriate ET some patients will not achieve CRIM. Studies have shown that several factors such as long-segment BE, older age, and ongoing uncontrolled gastroesophageal reflux are predictors of failure for achieving CRIM [12, 29].

Staging

Because of the important relationship between depth of invasion and the risk of LNM, ER has become perhaps the most definitive and accurate staging approach for early esophageal carcinoma as it permits precise determination of depth of invasion and other histological predictors of LNM. If the resection margins are negative and the tumor has low-risk features as outlined above, ET is considered curative. If there is incomplete resection (particularly a positive deep margin) or the tumor has high-risk features such as submucosal invasion depth >500 micrometers, poor differentiation (G3), or lymphovascular invasion, then surgery should be the recommended treatment. Endoscopic ultrasound (EUS) has some utility in excluding regional nodal involvement and deep (>T2) invasion. However, the accuracy of EUS in differentiating T1a from T1b tumors is low. EUS accuracy is only ~50% for detecting submucosal invasion [30]. Some studies have even demonstrated a high rate of overstaging and understaging of T2 cancers by EUS and suggested a role of ER for staging even selected uT2 cancers. For neoplasms without evident advanced stage (≥T2 or >N0 by EUS or CT), ER is perhaps the most accurate staging method. This is particularly true for small esophageal nodules, which are almost always T1 carcinomas and for which EUS assessment of presence and depth of SM invasion would be of low accuracy. ER is mandatory for such lesions as a staging and potentially curative approach [31, 32].

Surveillance Post-Endotherapy

After ET of EAC, patients remain at risk for recurrence of intestinal metaplasia, dysplasia, and cancer over time. Therefore, it is of paramount importance that patients have careful long-term follow-up in order to detect and treat any possible recurrences [33]. Current guidelines recommend the use of high-definition white-light endoscopy and optical chromoendoscopy, careful inspection of the neo-squamous mucosa, and careful retroflexed inspection of the gastric cardia with particular focus on the area within 5–10 mm distal to the top of the gastric folds at 3, 6, and 9 months and annual intervals thereafter [34]. Suspicious areas should be biopsied or resected. The role of random biopsies of the neo-squamous mucosa is unclear, but most studies suggest it is unnecessary and seldom finds pathology [20]. In patients with T1b lesions who undergo ET, routine EUS/FNA is recommended to assess for the development of LNM [35] possibly with the addition of annual PET/CT or CT in selected patients.

Endotherapy Failure

Despite the high curative success rate for ET, tumor recurrence is not uncommon [36]. In these cases, repeat endotherapy is recommended and typically successful [28]. Based on our experience (88% five-year disease-specific survival and no postoperative mortality) and other expert opinions, we recommend minimally invasive or robotic esophagectomy for recurrent T1b lesions [16]. Systematic lymphadenectomy

is essential with T1b lesions to provide the best opportunity for cure. Repeat ET may be considered in high-risk patients, in combination with chemoradiation in more extensive recurrences. Again, to minimize the risk of recurrence, clinicians caring for patients with EAC should discuss the advantages and disadvantages of each treatment modality in detail, and provide recommendations supported by data instead of a misguided effort to avoid esophagectomy at all costs, particularly in patients where esophagectomy would provide the best guarantee of long-term disease-free survival. Further, careful long-term endoscopic surveillance is essential.

Post-Endotherapy Reflux Management

As GERD is implicated both in the development of BE and its progression to EAC, protection against acid reflux, using either acid suppression medications or antireflux surgery, is essential in order to achieve CRIM and prevent recurrence of intestinal metaplasia. At the current moment, there is no long-term high-quality data on post-endotherapy reflux management. Most patients follow the usual protocol of lifelong PPIs and close surveillance. However, an alternative is surgical fundoplication after completion of endotherapy. Surgical fundoplication has been shown to be effective in controlling symptoms in patients with BE, who frequently suffer the manifestations of severe reflux disease. Surgery also eliminates the need for patient compliance with medical therapy, which commonly requires lifelong treatment in daily or more frequent doses. Currently, neither approach has shown superiority in preventing recurrent IM after successful ET.

Conclusion

In recent years, endotherapy has emerged as an alternative to esophagectomy for the treatment of superficial EAC. Most T1 tumors can be completely resected with current ER techniques. This provides precise staging as well as potentially curative resection. Careful histological analysis of the ER specimen by expert pathologists permits assessment of the risk of LNM and the ability to determine whether ET is curative, or the patient would be better served from an oncological standpoint by esophagectomy. To recommend the most appropriate treatment plan for patients with EAC, clinicians must carefully evaluate several factors such as the overall fitness of the patient, extent of mucosa disease, severity of underlying reflux disease and esophageal function, and relevant risk factors for nodal metastases. This requires expertise on the part of the endoscopist and a thorough knowledge of the pros and cons of ET. These patients have highly curable cancers and therefore the ultimate goal should be to maximize long-term survival with good quality of life.

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Cancer of the Esophagus: Epidemiology and Genetics

21

David H. Wang, Eric M. Lander, and Michael K. Gibson

Objectives

1. Understand the differences in epidemiology between esophageal squamous cell carcinoma and esophageal adenocarcinoma
2. Understand the risk factors for esophageal squamous cell carcinoma and esophageal adenocarcinoma
3. Understand the molecular genetics of esophageal cancer

Introduction

Squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) remain the predominant histological types of esophageal cancer worldwide. The trends in incidence of each are shifting across different continents because their etiologies differ and patient lifestyles are changing. We will review the epidemiology, etiology, and genetics of esophageal cancer (EC).

Epidemiology

EC remains the eighth most common cause of cancer and the sixth most common cause of cancer death worldwide [1] with over 600,000 cases (Fig. 21.1) and 500,000 deaths annually. ESCC is the more common histology, constituting approximately 87% of EC. However, ESCC is decreasing in frequency in the United States and other Western countries, whereas EAC is increasing.

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Incidence

Age-adjusted incidence rates of EC in 2020 varied significantly by continent (Fig. 21.2), highest in Eastern Asia (12.2 per 100,000) followed by Eastern and Southern Africa (8.3 and 7.4 per 100,000, respectively) [2]. Incidence was lowest in Central America (1.0 per 100,000). The highest incidence was in Malawi in Southeastern Africa, with 18.7 cases per 100,000.

The United States represents 3.5% of EC cases worldwide, with an estimated 18,309 cases in 2020, which is 40% lower than the worldwide rate (5.6 versus 9.3 per 100,000). While ESCC has been decreasing in the United States, the incidence of EAC is increasing—685% among men and 261% among women from 1975 to 2009. The rates of EC vary by geographic region (Fig. 21.3). According to the CDC, the Midwestern and Northeastern United States had the highest rates while the Southwestern and Southeastern states had the lowest.

Caucasians constituted 85% of the 87,100 newly diagnosed cases from 2013 to 2017, including 94% of EAC but just 66% of ESCC. Among African Americans and Asian/Pacific Islanders, EC was predominantly ESCC (76% and 69% of cases by race, respectively), while people of Hispanic ethnicity had mostly EAC (56% of cases). About 88% of EC cases worldwide are in people older than 55. Males comprise 70% of all EC cases worldwide, and compared with females, are 7–10 times more likely to develop EAC and 3–4 times more likely to develop ESCC.

Survival

EC has a poor prognosis due to late diagnosis. In the United States, 40% of cases present with spread to distant organs

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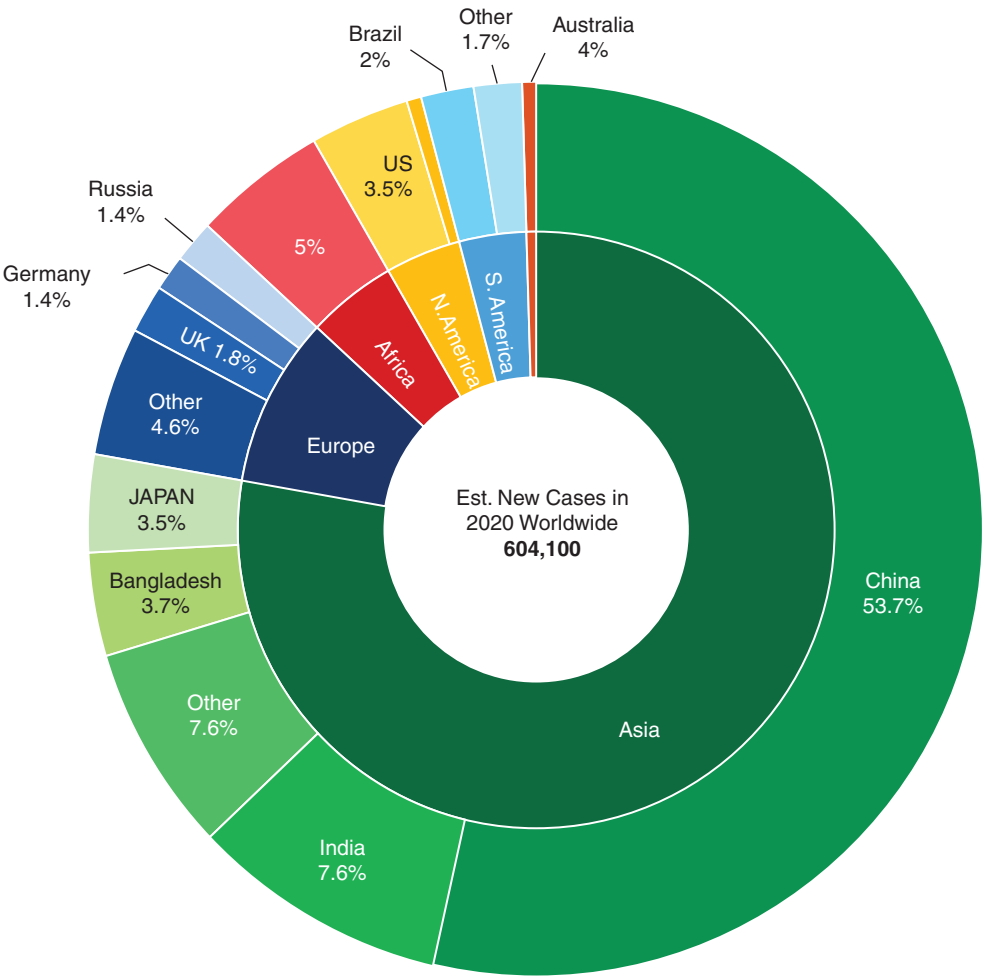

Fig. 21.1 Estimated number of new cases of esophageal cancer worldwide in 2020. Data represents the estimated number of new cases of esophageal cancer in 2020 by continent (inner ring) and major contributing countries (outer ring). Data was adapted from GLOBOCAN 2020 database, accessed through the Cancer Today website (https://gco.iarc.fr/today/home). Data was accessed in April 2021

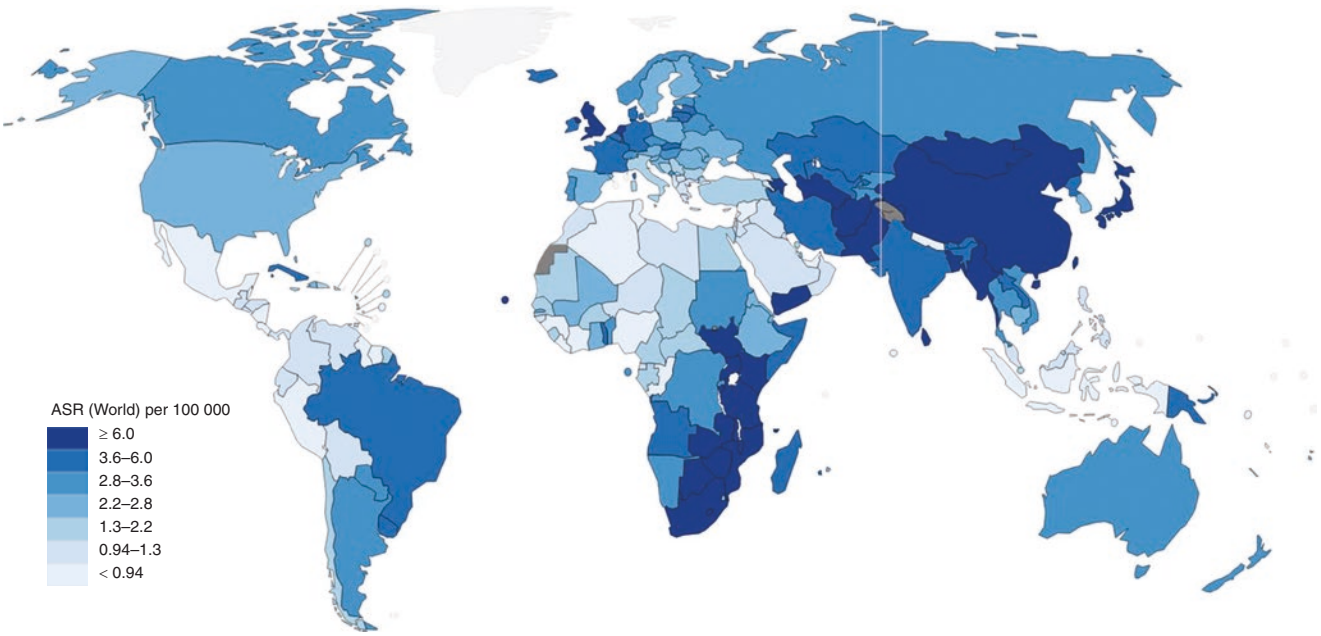

Fig. 21.2 Estimated age-standardized incidence rates worldwide of esophageal cancer in 2020. Data represents the estimated age-standardized incidence rates of esophageal cancer in 2020 by country, worldwide. Data and figure generated from GLOBOCAN 2020 data-based accessed through the Cancer Today website (https://gco.iarc.fr/today/home). Data was accessed in April 2021

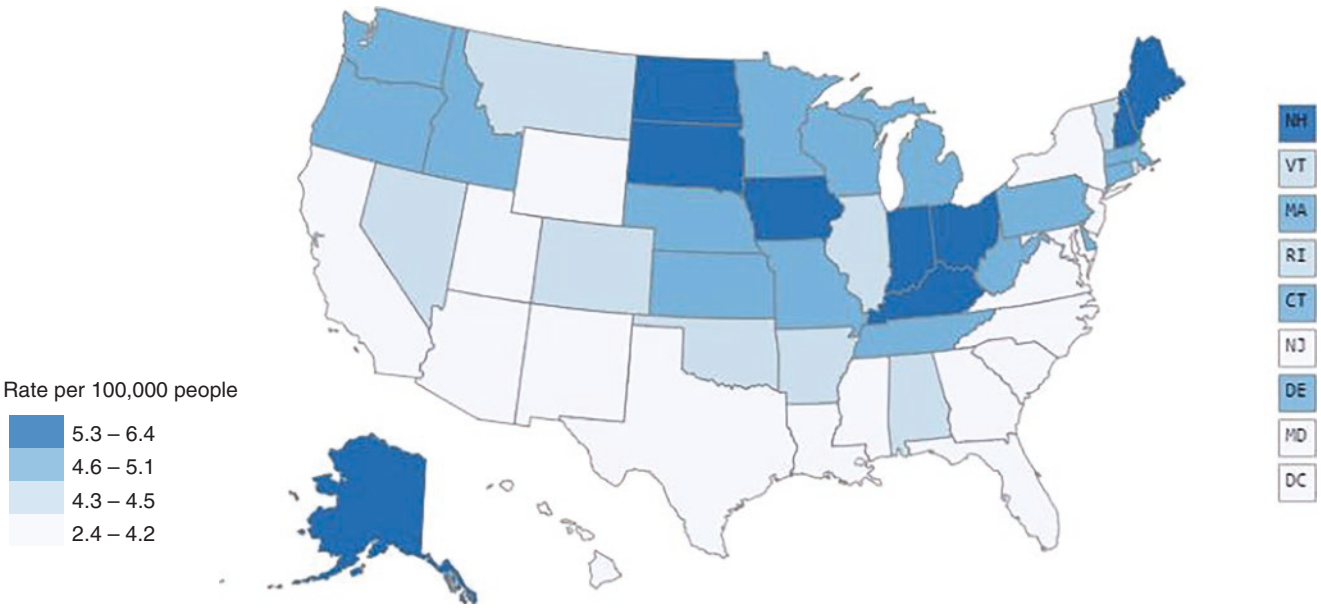

Fig. 21.3 Rate of new cases of esophageal cancer in the United States 2017. Data represents the incidence rates of esophageal cancer in 2017 by state. Data and figure generated from United States Cancer Statistics Data visualization website (https://gis.cdc.gov/Cancer/USCS/DataViz.html) and is overseen by the CDC. 2017 is the latest date of cancer incidence available for the United States. Incidence data are compiled from cancer registries meeting US Cancer Statistics data quality criteria. Data was accessed in April 2021

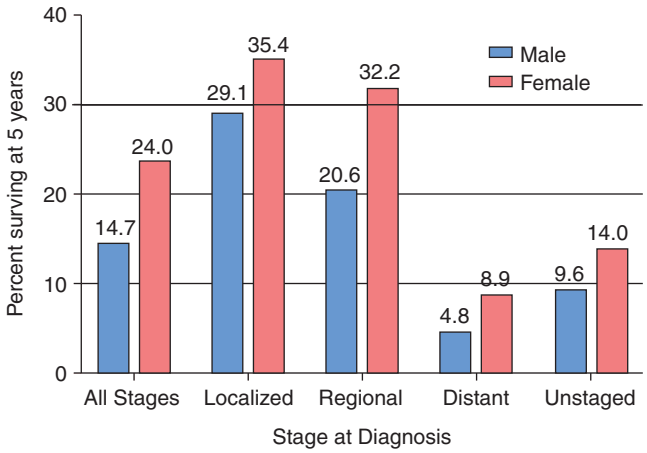

Fig. 21.4 The 5-year survival rates for patients with esophageal cancer, by sex and stage at diagnosis in the United States. Data represents SEER relative survival rates from 2010–2016 obtained from the SEER Cancer Statistics Review (https://seer.cancer.gov/archive/csr/1975_2016/). Data was accessed in April 2021

while another 32% have regional lymph node involvement. EC accounts for 5.3% of cancer-related deaths worldwide but is only 3.2% of cancer diagnoses. The 5-year survival rate varies by geographic region. In the United States, it is 19.9%, in China 21.0%, and in Europe 9.8%.

Five-year survival rates of patients in the United States with localized disease (stage I or II), regional metastases to lymph nodes (stage III), and distant metastases (stage IV) from 2010 to 2016 are illustrated in Fig. 21.4. The 5-year overall survival rate varies by race, in African Americans 13% and in Caucasians 21%. The median overall survival time for patients with localized, regional, and distant disease is 30, 13, and 6 months, respectively.

The majority of survival data were collected before the use of modern trimodality therapy and immunotherapy [3–5]. As such, future survival is expected to improve.

Etiology

EC most often arises from chronic inflammation that generates genetic changes and disrupted cell signaling. The most common etiologies of ESCC are smoking, alcohol use, and hot beverages. Alternatively, EAC most commonly arises from long-standing gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), obesity, and smoking. Diets low in fruits and vegetables confer a higher risk of developing either type. Other factors are reviewed in the next section, organized by histological type (Table 21.1).

Squamous Cell Carcinoma

Nonmodifiable Risk Factors

The incidence of EC by gender varies by geographic region. While ESCC is more common among males in the United States, the disease has no gender specificity in high-incidence regions worldwide. The incidence is also higher in urban areas and in people with a low socioeconomic status [6].

Table 21.1 Risk factors responsible for the development of and protection against esophageal cancer by histological type [1, 6, 7]

	Esophageal cancer histological type	
Risk factor	Squamous cell carcinoma	Adenocarcinoma
Nonmodifiable		
Gender	Male > female	Male > female
Race	African American > White	White > Hispanic > African American
Socioeconomic status	Low	High
Peutz–Jeghers	↑	↑
Fanconi anemia	↑↑↑	↑↑↑
Genetic mutations	TP53, CDKN2A, RB1, NFE2L2, CHEK1, CHEK2, NOTCH1, NOTCH3, RHBDF2	MGST1
Genetic overexpression	EGFR, CCND1, CDK4/CDK6, MDM2	CCNE1
Achalasia	↑↑	–
Human papillomavirus infection	Possible ↑	–
Helicobacter pylori	–	↓
Atrophic gastritis	↑	–
Tylosis	↑↑	–
Modifiable		
Smoking	↑↑↑	↑
Alcohol use	↑↑↑	–
Barrett's esophagus/GERD	–	↑↑↑
Obesity	–	↑
Hot beverages/foods	↑	–
N-nitroso compounds	↑	↑
Low fruit/vegetable diet	↑	↑
Poor oral hygiene	↑	–
NSAIDs	–	–
Statins	↓	↓
Proton pump inhibitors	–	↓

In prospective studies of men with head and neck cancer, the incidence of synchronous or metachronous EC ranged from 3 to 14%. Other medical conditions are related to ESCC development. Atrophic gastritis results in a two times higher risk, and achalasia confers a 16-fold increased risk during the first 24 years following diagnosis. Tylosis is a rare condition characterized by hyperkeratosis of the palms and soles of the feet. The inherited form (Howell–Evans syndrome) is strongly linked with ESCC. Over 100 studies examined the relationship between ESCC and human papillomavirus (HPV) infection, especially serotypes 16 and 18. One meta-analysis of 66 case–control studies found that patients with HPV infection were 3.32 times more likely to develop ESCC compared to patients without (95% CI 2.26–4.87) [7]. However, there was significant heterogeneity across studies, likely explained by the differences in populations and HPV DNA detection methods and subtypes. The association was weaker than the link between HPV and cervical and oropharyngeal cancers.

Modifiable Risk Factors

Tobacco and alcohol use increase the risk of ESCC. While each is independently associated with ESCC, consumption of tobacco products and alcohol synergistically increases risk. ESCC risk is higher with consistent cigarette smoking than with cigar or pipe smoking. The risk decreases after 5 years of smoking cessation, yet 10 years following smoking cessation, the risk remains two times higher compared to nonsmokers. The quantity of alcohol consumption is more strongly linked to ESCC than the type of alcohol consumed. In population studies, alcohol consumption was not associated with EAC. Maintenance of good oral health is additionally important as poor oral health may be associated with ESCC.

Numerous dietary factors influence ESCC risk in Asian patients. High consumption of fruits and vegetables is protective—namely, 160 g of nonstarchy vegetables and 20 g of fruits daily. Conversely, low fruit and vegetable intake is associated with increased risk of both ESCC and EAC. Diets high in red meats and foods containing N-nitroso compounds, such as pickled vegetables and cured meats, are linked to increased ESCC risk. Diets low in selenium, zinc, and folate also increase ESCC risk. Obesity has an inverse relationship with ESCC, but this may be confounded by the varying prevalence of central obesity worldwide.

Adenocarcinoma

The majority of EAC arise from BE; therefore, conditions and lifestyles that predispose to BE are strongly linked to the pathogenesis of EAC.

Nonmodifiable Risk Factors

In the United States, the incidence of EAC is 7.2 times higher in men than women, likely due to a higher burden of obesity and GERD among men. Estrogen and breastfeeding decrease the risk of EAC; thus, hormonal differences may affect EAC burden.

Caucasians make up greater than 90% of EAC cases, followed by people of Hispanic and African American ethnicity. Family history of hiatal hernia confers an increased risk of EAC. One population study suggested a slightly higher incidence of EAC among people with a history of cholecystectomy. It was proposed that hiatal hernia and cholecystectomy may lead to increased reflux of stomach and bile acids.

H. pylori is associated with decreased EAC risk, which is thought to be due to the bacteria's suppression of gastric acid secretion and subsequent decreased reflux. The decreased incidence of *H. pylori* in the United States may be partially responsible for the rise in EAC incidence. In contrast, *H. pylori* causes gastric cardia inflammation, which leads to intestinal metaplasia, a precursor lesion for gastric cardia adenocarcinoma.

Modifiable Risk Factors

Shifts in lifestyles in Western countries have led to a dramatic rise in the incidence of EAC, gastroesophageal junction (GEJ) adenocarcinoma, and gastric cardia cancers over the past three decades. BE is the biggest risk factor for EAC, with the risk of EAC in patients with BE at least 30-fold above that of the general population. Despite this higher risk, patients with nondysplastic BE have a risk of developing EAC estimated to be about 0.1–0.4% per year. This risk increases if dysplasia is also present on biopsy.

GERD is the primary cause of BE, but less than 50% of patients with EAC report symptomatic acid reflux. Despite this finding, patients in Sweden with chronic acid reflux (>20 years) and severe acid reflux have a 43.5-fold higher risk of EAC compared to control patients. Other studies show an increased risk of EAC among patients with symptomatic acid reflux, supporting GERD as an independent risk factor for EAC. However, the absolute risk of GERD causing EAC remains low in the United States, where up to 44% of people experience acid reflux symptoms at least monthly.

Smoking is another risk factor for EAC. This risk rises with increasing pack-years of smoking, and unlike ESCC, the risk of EAC does not decrease following smoking cessation. A meta-analysis of over 20 studies found no association between alcohol use and EAC.

Based on numerous meta-analyses of datasets, a genome-wide association study (GWAS) and a SEER-Medicare database analysis, obesity and metabolic syndrome are risk factors for EAC, independent of GERD. This is likely due to proinflammatory effects of obesity and metabolic syndrome, increased intragastric pressure, increased risk of hiatal hernia, and altered esophageal sphincter function. For every increase of 5 kg/m^2 in BMI, the relative risk of EAC rises 1.5-fold. Diets high in cereal fibers are protective against EAC. Further protective dietary elements may include folate, vitamins B6 and C, beta-carotene, and fiber. Moreover, diets with high vegetable and fruit intake may protect against BE via antioxidant properties that decrease oxidative stress and inflammation. Diets high in animal protein, cholesterol, and vitamin B12 are associated with increased risk of EAC. Unlike ESCC, hot beverages are not well-studied in EAC.

Multiple medications may potentially decrease the risk of EAC. Based on pooled epidemiological data, aspirin, and other NSAIDs, which inhibit cyclooxygenase (COX), are associated with a lower risk of developing EAC. However, one trial that randomized patients with BE to celecoxib (selective COX2 inhibitor) versus placebo showed no prevention of BE progression to EAC following 48 weeks of celecoxib therapy. Proton pump inhibitors should be used in patients with BE based on the AspECT trial, which showed PPIs, particularly in combination with aspirin, decreased the composite endpoint of death, EC, and high-grade dysplasia [8]. Statin medications, especially in synergy with NSAIDs, decrease the risk of progression to EAC. Following the diagnosis of EC, regardless of histological subtype, the use of statins has been associated with decreased overall and cancer-specific mortality. No known randomized controlled trial to date has examined statin use in patients with EC.

Genetics

Insight into the molecular genetics of EC comes from clinical syndromes that predispose to its development, GWAS, and alterations identified in precursor lesions such as squamous dysplasia and BE. International collaborative next-generation sequencing efforts such as the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) program have identified additional pathogenic genes and introduced molecular classifications of ESCC and EAC. While there are genes common to the pathogenesis of these two histological types of esophageal cancer, distinct differences also occur.

Patients with tylosis, Bloom syndrome, and Fanconi anemia can develop ESCC. Tylosis, an autosomal-dominant hyperproliferative squamous cell disorder, is caused by missense mutations in the Rhomboid 5 homolog 2 (RHBDF2)

gene that enhances secretion of the epidermal growth factor receptor (EGFR) ligand amphiregulin (AREG). Mice with an Areg P189L gain-of-function mutation develop alopecia, rapid cutaneous wound healing, squamous hyperplasia, and hyperkeratosis. Signaling downstream of EGFR then occurs through RAS-RAF-MEK-ERK and PI3K-AKT-mTOR. Bloom syndrome is an autosomal-recessive disorder caused by mutations in the BLM gene, an ATP-dependent DNA helicase involved in DNA replication and repair of double-stranded DNA breaks. Patients with Bloom syndrome develop carcinomas at a young age, including those of the head and neck, esophagus, skin, cervix, breast, and colon. Fanconi anemia is an autosomal- or X-linked recessive genetic bone marrow failure state caused by a mutation in at least one of 22 FANC genes. Since FANC proteins participate in DNA repair, patients are susceptible to developing acute myeloid leukemia, myelodysplasia, and solid tumors such as squamous cell carcinomas of the head and neck and esophagus. These genetic disorders demonstrate the important role of the EGFR and DNA damage repair pathways in ESCC pathogenesis.

A family history increases the risk of developing ESCC up to eightfold in those with two parents with ESCC. Despite BE and EAC being complications of chronic GERD, roughly 7% occur in familial clusters defined as two or more first- or second-degree relatives diagnosed with BE or EAC. In these families, one gender or ethnicity is not favored as occurs in sporadic BE or EAC, and inheritance is autosomal-dominant with incomplete penetrance. Candidate genes identified in familial BE and EAC include APC, MSR1, ASCC1, and CTHRC1 [9] (Table 21.2). To identify other relevant genes in familial esophageal cancer, GWAS, observational studies in which genetic variants with higher prevalence in affected individuals are associated with that disease, have been undertaken. In Asian patients, GWAS identified loci corresponding to IGFBP2, ST6GAL1, ALDH, ALDH1B, SLC10A2, TMEM188, HEATR3, PAPD5, XBP1, and CHEK2 that are associated with ESCC [10] (Table 21.2). Interestingly, the risk for single-nucleotide polymorphisms (SNP) found at 4q23 was higher in drinkers than nondrinkers. This may be explained by the finding that the 4q23 locus encodes alcohol dehydrogenase family members. In EAC, GWAS have identified associated loci corresponding to the MHC locus, FOXF1, CRTC1, BARX1, FOXP1, CFTR, MSRA, BLK, KHDRBS2, CEP72, TMOD1, SATB2, HTR3C, GDF7, TBX5, and ABCG5 genes [11] (Table 21.2).

ESCC typically arises from squamous hyperplasia and dysplasia while EAC typically arises from BE with increasing degrees of dysplasia. Analysis of molecular alterations that occur in the hyperplasia–squamous dysplasia–ESCC and BE–dysplasia–EAC sequences has identified many more genes in their pathogenesis (Figs. 21.5 and 21.6 and Table 21.3). In an analysis of hyperplasia, squamous dysplasia, and ESCC from 70 Chinese patients [12], expression of phosphorylated histone H2AX, a marker of double-stranded DNA breaks, was higher in dysplastic lesions than in normal epithelium. In addition, mutation rate, copy number alterations (CNA), and structural variations (SV) were significantly higher in ESCC than normal epithelium, with even higher numbers in dysplastic epithelium. Large-scale chromosomal deletions at 9p21 (CDKN2A) and 2q35 (ASCL3,

Table 21.2 Genes associated with esophageal cancer in clinical syndromes and by GWAS

Gene	Name	Chr	Histology
ABCG5	ATP-binding cassette Subfamily G Member 5	3q27	EAC
ALDH	Aldehyde dehydrogenase	4q23, 12q24	ESCC
APC	APC regulator of WNT signaling pathway	5q21	EAC
ASCC1	Activating signal cointegrator 1 complex subunit 1	10q22	EAC
BARX1	BARX homeobox 1	9q21	EAC
BLK	BLK Proto-oncogene, Src Family tyrosine kinase	8p23	EAC
BLM	BLM RecQ Like Helicase	15q26	ESCC
CEP72	Centrosomal Protein 72	5p15	EAC
CHEK2	Checkpoint kinase 2	22q12	ESCC
CFTR	CF Transmembrane Conductance Regulator	7q31	EAC
CRTC1	CREB Regulated Transcription Coactivator 1	19p13	EAC
CTHRC1	Collagen triple helix repeat containing 1	8q22	EAC
FANC	FA Complementation Group	Various	ESCC
FOXF1	Forkhead box F1	16q24	EAC
FOXP1	Forkhead box P1	3p14	EAC
GDF7	Growth differentiation factor 7	2p24	EAC
HEATR3	HEAT repeat containing 3	16q12	ESCC
HTR3C	5-Hydroxytryptamine Receptor 3C	3q27	EAC
IGFBP2	Insulin-like growth factor binding protein 2	2q22	ESCC
KHDRBS2	KH RNA binding domain containing signal transduction Associated 2	6q11	EAC
MHC locus	Major histocompatibility complex	6p21	EAC
MSR1	Macrophage scavenger receptor 1	8p22	EAC
MSRA	Methionine sulfoxide reductase A	8p23	EAC
PAPD5	Terminal nucleotidyltransferase 4B	16q12	ESCC
RHBDF2	Rhomboid 5 Homolog 2	17q25	ESCC
SATB2	SATB Homebox 2	2q33	EAC
SLC10A2	Solute carrier family 10 member 2	13q33	ESCC
ST6GAL1	ST6 Beta-galactosidase alpha-2,6-sialyltransferase1	3q27	ESCC
TBX5	T-box transcription factor 5	12q24	EAC
TMEM188	CTD Nuclear envelope phosphatase 1 regulatory subunit 1	16q12	ESCC
TMOD1	Tropomodulin 1	5q22	EAC
XBP1	X-box binding protein 1	22q12	ESCC

FEV) and amplifications at 11q13 (CCND1), 5p15, 8q24, 2q31 (NFE2L2), 8p11, 7q22, and 3q27 (SOX2) were common in both dysplastic and ESCC samples. Amplification of 3q26-3q28, 8q24, and 12p13 in ESCC samples was higher than in dysplastic samples, suggesting that genes such as ATR, MECOM, PIK3CA, BCL6, MYC, and CCND2 are important in the transformation of ESCC from dysplasia.

Loss of heterozygosity (LOH) at the TP53 loci was identified in 44% of ESCC samples and 30% of dysplastic samples, while a similar incidence of LOH of CDKN2A (12% and 15%), FAT2 (24% and 11%), NOTCH family genes (32% and 19%), RB1 (16% and 11%), and YAP1 (12% and 11%) was found in ESCC and dysplastic samples. Further signaling analysis suggested that TP53, NOTCH, ERBB2-PI3K, DNA repair pathways, NFE2L2-KEAP1, and SWI/SNF complexes were significantly altered during ESCC progression. While mutations in TP53 and CDKN2A occurred frequently in dysplasia, mutations in NOTCH1, FAT1, KMT2D, and ZFHX4 grew to clonal dominance during carcinogenesis as trunk events (shared by ≥10% in paired dysplasia/ESCC samples). The shared CNAs of CCND1, CDKN2A, FGFR1, and trunk mutations indicated they were the early driver events during carcinogenesis. TP53 and CDKN2A were identified as the early mutated driver genes in dysplasia (Fig. 21.5).

To order genetic changes during BE transformation into EAC, a discovery set of 22 EAC tumors, 17 containing BE, were submitted for whole-genome sequencing (WGS) [13]. The most common mutation type was a TA > GC transversion. Twenty-six genes mutated at a higher rate than background or belonging to pathways of interest were then validated in a larger cohort of 90 EAC, 40 nondysplastic BE, and 39 high-grade dysplasia patients by sequencing of a targeted gene panel. Of 15 genes found mutated in at least four patients from the discovery and validation cohorts, only TP53 and SMAD4 distinguished disease stages (Fig. 21.6). TP53 was often mutated in high-grade dysplasia (72%) and EAC (69%) but was only found in one case of nondysplastic BE (2.5%) while SMAD4 was found mutated in EAC (13%) but not in dysplasia or BE. Another study performed whole-exome sequencing (WES) of paired normal epithelium, BE, and EAC trios in 25 patients [14]. In total, 14 had no dysplasia, 11 had dysplasia, and 6 had findings consistent with high-grade dysplasia. In 14 trios, BE and EAC arose from the same genetic clone. Mutational densities increased from 2.8 mutations/Mb in BE to 4.9 mutations/Mb in dysplasia and 4.1 mutations/Mb in EAC. Focal deletions increased from 10.43 in BE to 20.73 in dysplasia to 40.20 in EAC, and amplifications increased from 0.42 in BE to 0.91 in dysplasia to 8.44 in EAC. In some patients, TP53 mutations were identified even in nondysplastic BE. In these patients, it was found whole genomic doubling (WGD) occurred during dysplasia and EAC. In a separate larger set of 144 EAC tumors, WGD was found in 62.5% and was preceded by a TP53 mutation. CDKN2A and SMAD4 mutations were found in 8% and 1%, respectively, of WGD tumors but in 19% and 20% of non-WGD tumors. Based on these findings, two pathways for BE progression to EAC were postulated: expansion of a TP53 mutant clone that undergoes WGD in the dysplastic stage followed by genomic disruption and oncogene amplification or progressive accumulation of tumor suppressor gene loss leading to genomic instability and oncogene amplification (Fig. 21.6).

One of the first large-scale attempts to genomically characterize EAC performed WES on 149 fresh, frozen untreated EAC and GEJ tumors and paired normal tissue from North American patients with 15 normal-tumor pairs undergoing additional WGS [15]. In this cohort, EAC had a median mutation frequency of 9.9 mutations/Mb, third highest behind lung cancer and melanoma. A somewhat unique finding was the frequency of AA>AC transversions in EAC. In EAC, 26 genes were found to be significantly mutated, with TP53 and CDKN2A having the highest significance. Other

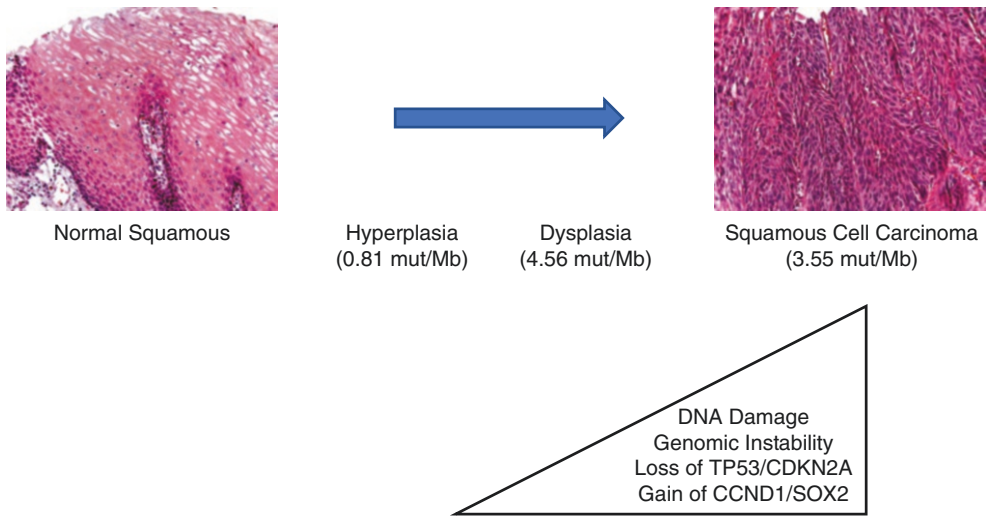

Fig. 21.5 Genetic alterations that occur in the esophageal hyperplasia-squamous dysplasia-squamous cell carcinoma sequence. Mutation rate of dysplasia and carcinoma exceed that of hyperplasia. Genetic alterations begin to occur in hyperplasia and greatly increase in dysplasia and carcinoma

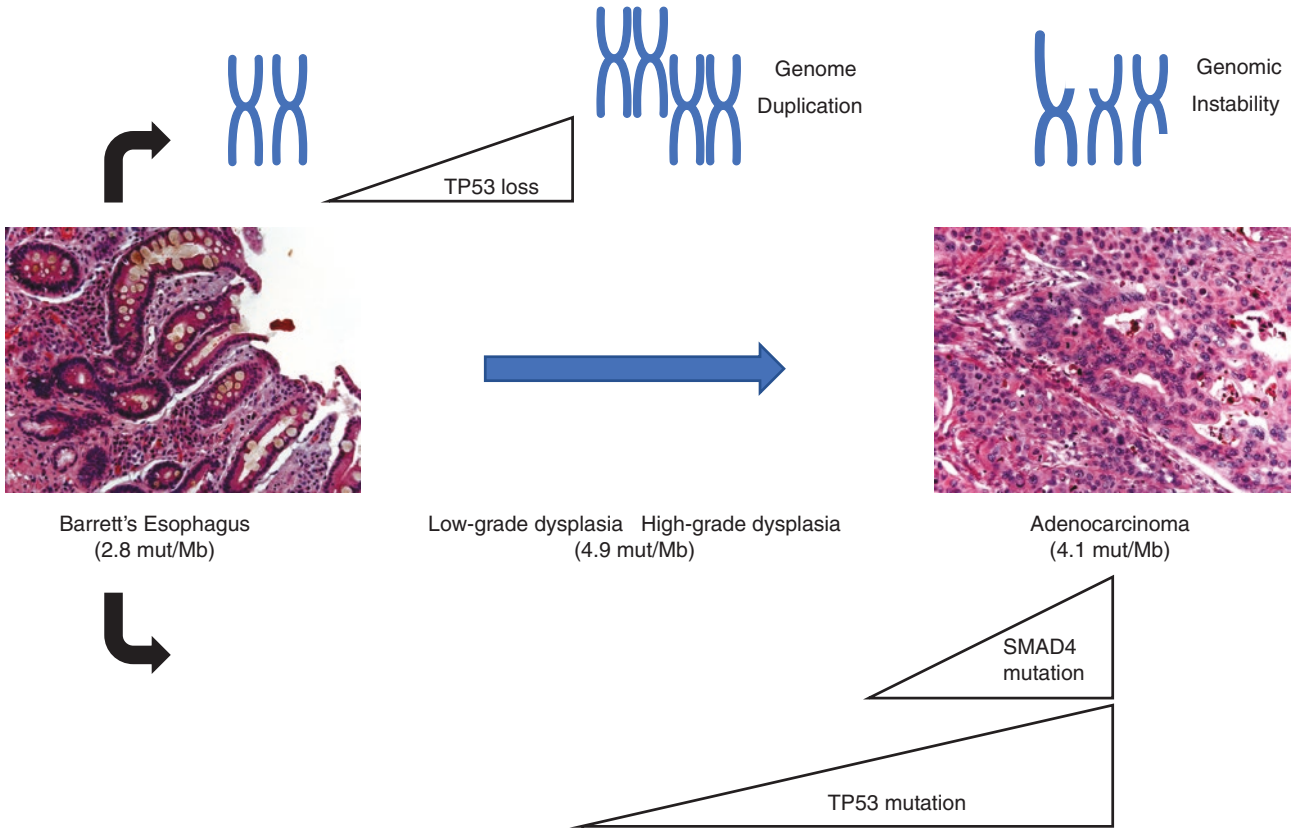

Fig. 21.6 Genetic alterations that occur in the Barrett's esophagus-dysplasia-adenocarcinoma sequence. Mutation rate in dysplasia and carcinoma exceed that in Barrett's esophagus. Transformation can occur through 2 separate pathways: TP53 loss followed by whole genome duplication (top) or accumulation of tumor suppressor gene mutations (bottom)

Table 21.3 Genes involved in esophageal cancer pathogenesis identified through next-generation sequencing

Gene	Function	ICGC	TCGA	Other
ACTL7B	Cytoskeleton			EAC
ADAM29	Male gonad development	ESCC		EAC
AJAP1	Signaling at adherens junctions			EAC
AKAP6	PKA anchoring factor			EAC
APC	Tumor suppressor		EAC	
ARF6	Protein trafficking		EAC	
ARID1A	SWI/SNF (chromatin remodeling)		EAC	EAC
ARID2	SWI/SNF (chromatin remodeling)			EAC
ASCL3	Transcriptional repressor			ESCC
ATR	Ser/Thr kinase			ESCC
BCL6	Transcriptional repressor			ESCC
C6orf118	Uncharacterized			EAC
CCND1	Cell cycle	EAC	ESCC	ESCC
CCND2	Cell cycle			ESCC
CCNE1	Cell cycle		EAC	
CDH1	Cadherin (cell adhesion)		EAC	
CDK14	Cell cycle	EAC		EAC
CDK6	Cell cycle	ESCC	ESCC	
CDKN2A	Tumor suppressor (cell cycle)	EAC/ESCC	EAC/ESCC	EAC/ESCC
CLDN22	Cell adhesion	EAC		EAC
CNTNAP5	Signaling, cell adhesion			EAC
CTNNA3	Cell adhesion	EAC		EAC
DOCK2	Cytoskeleton			EAC

Table 21.3 (continued)

Gene	Function	ICGC	TCGA	Other
EGFR	Receptor tyrosine kinase	EAC	ESCC	EAC
ELMO1	Cytoskeleton			EAC
ERBB2	Receptor tyrosine kinase	EAC	EAC	
EYS	Protein trafficking			EAC
FAM139B	Pseudogene	ESCC		EAC
FAT1	Cell polarization			ESCC
FAT2	Cell mobility			ESCC
FEV	Transcription factor			ESCC
FGFR1	Cell surface receptor	EAC	ESCC	ESCC
FHIT	Regulates apoptosis	EAC		EAC
FOXA	Transcription factor		EAC	
GATA4	Transcription factor	EAC	EAC	EAC
GATA6	Transcription factor	EAC	EAC	EAC
HECW1	E3 ligase			EAC
KAT6A	Histone acetyltransferase			EAC
KCNU1	Potassium channel			EAC
KDM6A	Histone demethylase		ESCC	
KMT2C	Histone methyltransferase		ESCC	
KMT2D	Histone methyltransferase		ESCC	ESCC
MDM2	E3 ligase	EAC	ESCC	EAC
MECOM	Histone methyltransferase			ESCC
MET	Receptor tyrosine kinase	EAC		EAC
MYC	Transcription factor	ESCC	EAC	ESCC
NFE2L2	Transcription factor	ESCC	ESCC	ESCC
NKX2.1	Transcription factor	ESCC	ESCC	
NOTCH1	Receptor	ESCC	ESCC	ESCC
NOTCH3	Receptor			ESCC
NUAK1	Ser/Thr kinase			EAC
PBRM1	Chromatin remodeling	ESCC	EAC	
PIK3CA	Kinase	ESCC	ESCC	EAC/ESCC
PIK3R1	Cell signaling		ESCC	
PTCH1	Receptor		ESCC	
PTEN	Tumor suppressor	ESCC	ESCC	
RB1	Cell cycle	EAC/ESCC	ESCC	EAC/ESCC
RBFOX1	RNA binding	EAC		EAC
RUNX1	Transcription factor	EAC	EAC	EAC
SCN10A	Sodium channel			EAC
SLC39A12	Zinc transporter			EAC
SMAD4	Cell signaling		EAC	EAC
SMARCA4	SWI/SNF (chromatin remodeling)		EAC	EAC
SMYD3	Histone methyltransferase	EAC		EAC
SOX2	Transcription factor		ESCC	ESCC
SPG20	Endosomal trafficking (receptor, BMP, Ub)			EAC
SYNE1	Subcellular spatial organization			EAC
TERT	Replication of chromosomal ends		ESCC	
TGFRB2	Ser/Thr kinase		ESCC	
TLL1	Protease			EAC
TLR4	Innate immune system	ESCC		EAC
TP53	Tumor suppressor	ESCC	EAC/ESCC	EAC/ESCC
TP63	Transcription factor		ESCC	
VEGFA	Growth factor		EAC	
WWOX	Tumor suppressor			EAC
YAP1	Transcription factor		ESCC	ESCC
ZFHX4	Transcription factor			ESCC
ZNF750	Transcription factor	EAC	ESCC	

EAC Esophageal adenocarcinoma, *ESCC* Esophageal squamous cell carcinoma

previously identified mutated genes such as ARID1A, PIK3CA, and SMAD4 were confirmed while 21 new genes were identified. A separate WGS of 129 EAC cases from Europe as part of the ICGC effort reported large-scale structural rearrangements [16]. In genes that were altered in at least 10% of patients, more were rearranged, deleted, or amplified than affected by indels or point mutations. Recurrently rearranged genes included SMYD3, RUNX1, CTNNA3, RBFOX1, CDKN2A/B, CDK14, FHIT, and WWOX. Amplified loci included ERBB2, EGFR, RB1, GATA4/6, CCND1, MDM2, MET, and FGFR while deletions occurred frequently in CLDN22, CDKN2A, and CDKN2B. Genomic catastrophes such as chromothripsis, kataegis, and complex rearrangement events were common. Patients were molecularly classified into three subtypes with potential therapeutic implications: C > A/T dominant, sensitive to chemotherapy and tyrosine kinase inhibitors; DNA damage repair impaired, sensitive to PARP inhibitors combined with cytotoxic or radiation therapy; and mutagenic, sensitive to CHK/MEE1 inhibition or immunotherapy. In total, 158 ESCC and matched normal tissue from Chinese patients underwent WES, WGS, and array CGH analysis as part of the ICGC effort [17]. The somatic mutation rate was less than EAC with CG > TA transitions and CG > GC transversions the most common mutations. Eight genes were significantly mutated: TP53, RB1, CDKN2A, PIK3CA, NOTCH1, NFE2L2, ADAM29, and FAM139B. Further analysis revealed nonsilent mutations in 48 histone-modification-related genes; large-scale chromosome amplifications and deletions; and genomic alterations in Wnt, cell cycle, NOTCH, receptor tyrosine kinase-Ras, and AKT signaling pathways.

The TCGA analysis for esophageal tumors was published in 2017 [18]. In total, 164 untreated tumors (90 ESCC, 72 EAC, 2 undifferentiated carcinomas) from across the world were subjected to WES, SNP array profiling, DNA methylation profiling, and mRNA and miRNA sequencing. EAC had increased CDH1, ARF6, and FOXA signaling, while ESCC had increased Wnt, Syndecan, and p63 pathways. Significantly mutated genes included TP53, CDKN2A, ARID1A, SMAD4, and ERRB2 in EAC and TP53, NFE2L2, MLL2, ZNF750, NOTCH1, and TGFBR2 in ESCC. In EAC, somatic CNA included VEGFA, ERBB2, GATA4, GATA6, and CCNE1 amplification and SMAD4 deletion. Somatic CNA in ESCC included SOX2, TERT, FGFR1, MDM2, NKX2.1 amplification, and RB1 and 3p25 (negative regulator of HIPPO) deletion. Both tumor types had alterations in cell cycle genes. In EAC, CCNE1 was more commonly amplified while CDKN2A was inactivated by mutation, deletion, or epigenetic silencing. For ESCC, CDKN2A and RB1 were inactivated while CCND1 and CDK6 were amplified. In EAC, ERBB2 was frequently mutated or amplified and TGF-beta and Wnt/B-catenin signaling were activated. In ESCC, EGFR was amplified or mutated or downstream PIK3CA, PIK3R1, or PTEN were mutated. ESCC had inactivating mutations of PTCH1, amplification of SOX2, and mutations in NOTCH1. ESCC also had more frequent alterations in histone-modifying factors KDM6A, KMT2D (MLL2) and KMT2C. In contrast, in EAC, alterations affecting SWI/SNF encoding genes ARID1A, SMARCA4, and PBRM1 were more common. The TCGA went on to classify ESCC into three types. The first had alterations in the NRF2 pathway and more frequent amplification of SOX2, P63, and YAP1, resembling squamous carcinomas of the head and neck and lung. The second had higher rates of mutation in NOTCH1 or ZNF750 and higher rates of inactivation of KDM6A/2D, CDK6 amplification, and inactivation of PTEN or PIK3R1. The third had no genetic dysregulation of the cell cycle but had activation of PI3K pathway. The first type correlated with Asians, the second type with Eastern Europeans and South Americans, and the third type with Canadians and Americans. Further, ESCC is associated with C > A substitutions, which themselves are associated with use of chewing and smoking tobacco. The TCGA found that EAC resembled gastric carcinomas, particularly the chromosomal instability subtype, but EAC has higher mutation rates of SMARCA4, amplification of VEGFA and MYC, deletion of RUNX1, and lower APC mutation rates compared to gastric carcinomas.

Conclusions

Esophageal cancer remains a significant health problem worldwide, with ESCC the predominant histological type. In Western countries, EAC has become the predominant type. This difference is due to disparate risk factors that predispose to ESCC and EAC. Chemoprevention may be effective in selected patients. ESCC arises from squamous dysplasia and transformation occurs through DNA damage leading to genomic instability and activation of squamous pathways and oncogenes. EAC arises from BE with dysplasia and frequently involves early whole-genome duplication.

Questions

1. Which medications have been shown in a randomized trial setting of patients with Barrett's esophagus to decrease the composite risk of death, esophageal cancer, and high-grade dysplasia?
   A. Statins and aspirin
   B. Celecoxib and aspirin
   C. Statins and proton pump inhibitors
   D. Aspirin and proton pump inhibitors

Answer: D. Statins have not been studied in randomized trials in patients with Barrett's esophagus. Celecoxib compared to placebo did not prevent progression to esophageal adenocarcinoma in patients with Barrett's esophagus following 48 weeks of therapy. Proton pump inhibitors (PPIs) decreased the risk of death, esophageal cancer, and high-grade dysplasia in the AspECT trial. Patients who received both PPIs and aspirin in the trial experienced even lower rates of the primary composite endpoint. Patients who received aspirin monotherapy in the trial were less likely to progress to the primary endpoint if they were not already on NSAIDs, suggesting that NSAIDs as a group were favorable in patients with Barrett's esophagus.

2. What genes are commonly altered in both esophageal squamous cell carcinoma and esophageal adenocarcinoma pathogenesis?
   A. TP53 and CDKN2A
   B. TP63 and SOX2
   C. FOXA and GATA4
   D. NOTCH1 and NOTCH3

Answer: A. TP63, SOX2, NOTCH1, and NOTCH3 are altered in esophageal squamous cell carcinoma while FOXA and GATA4 are altered in esophageal adenocarcinoma. TP53 and CDKN2A are altered in both esophageal squamous cell carcinoma and esophageal adenocarcinoma.

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Screening Technologies for Barrett's Esophagus and Esophageal Adenocarcinoma

22

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Objectives

1. To understand the population at risk of Barrett's esophagus and esophageal adenocarcinoma and describe the rationale for screening for Barrett's esophagus
2. To review traditional screening techniques for Barrett's esophagus and their limitations in clinical practice
3. To summarize the state of novel technologies for Barrett's esophagus screening and future directions of the practice

Introduction

A variety of novel screening technologies for Barrett's esophagus (BE) now under development have the potential to address limitations of current screening strategies that rely on performing sedated esophagogastroduodenoscopy (EGD), including cost, tolerability, and acceptability. This chapter summarizes the current state of novel emerging technologies undergoing study for BE screening with an emphasis on potential advantages and disadvantages over traditional screening techniques.

Rationale for Screening for Barrett's Esophagus

Barrett's esophagus (BE) is a premalignant condition that develops from aberrant healing of the normal esophageal squamous mucosa following injury caused by chronic gastroesophageal reflux. The exact prevalence of BE in Western society is difficult to ascertain given that the condition is often asymptomatic. In the general population, the prevalence of BE is estimated to be approximately 1.6% and varies from 7 to 14% in patients with symptomatic gastroesophageal reflux in Western countries.

Screening for BE is advocated by all gastroenterology professional societies, despite the lack of high-quality evidence to support this practice. The rationale for screening stems from a number of factors, including the rising incidence of esophageal adenocarcinoma (EAC) in Western countries, the poor 5-year survival (10–20%) associated with advanced disease, and the observation that the overwhelming majority of cases of adenocarcinoma are not found in current endoscopic surveillance programs. In addition, several randomized controlled trials have demonstrated the safety and efficacy of BE endoscopic eradication therapy. In this context, screening for BE followed by surveillance would in theory allow for detection of early-stage disease that can be managed endoscopically, a practice associated with reduced morbidity and mortality when compared to esophagectomy.

Risk Factors for Barrett's Esophagus and Who to Screen

All professional society guidelines recommend against the practice of screening for BE in the general population. On the contrary, screening is advocated in individuals with symptoms of chronic gastroesophageal reflux in conjunction with multiple other risk factors for BE including age greater than 50 years, male gender, white race, central obesity, history of smoking, first-degree relative with BE or EAC, and presence of hiatal hernia. However, the presence of symptomatic gastroesophageal reflux is notably unreliable for identifying patients with BE and EAC, and the current guideline recommendations that require GERD symptoms to perform screening have a low sensitivity. It is precisely for this reason that there is growing interest in the use of clinical risk prediction tools to identify individuals that would benefit

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from screening for BE. The practice of screening for BE carries significant economic burden and a diagnosis of BE is associated with increased life insurance premiums and decreased quality of life. Careful selection for screening is therefore imperative and should take into consideration patient comorbidities and estimated life expectancy.

Conventional (Video-Based) Screening Techniques

Video-based screening techniques are capable of directly visualizing the gastroesophageal junction and distal esophagus and include EGD and transnasal endoscopy (TNE). Video capsule devices have also been adapted for esophageal imaging, but performance characteristics are suboptimal and their use is currently not recommended for screening. Next-generation esophageal video capsule devices with improved viewing angles and higher capture rate are currently under study. This includes a magnetically assisted capsule endoscopy device that can be stationed in the distal esophagus by means of an external magnet. Further studies are warranted to determine the clinical impact of these emerging video-based technologies.

Esophagogastroduodenoscopy

Esophagogastroduodenoscopy is considered the gold-standard screening test for BE and should be used as a reference when comparing emerging technologies discussed in this chapter. Endoscopy is typically performed under conscious sedation or monitored anesthesia care. The procedure involves a careful examination of the BE segment with targeted biopsies of areas of mucosal irregularity followed by a systematic four-quadrant biopsy protocol at 1–2 cm intervals (Seattle Protocol). The advantage of BE screening by endoscopy is the ability to perform a comprehensive examination to properly characterize the Barrett's segment with tissue sampling that allows for appropriate risk stratification. However, this approach is hampered by the need for sedation along with considerable direct and indirect costs. The quality of the examination is also operator dependent with the risk of missing a diagnosis of dysplasia when not performing an adequate examination or tissue sampling, or with inappropriate biopsies of the gastroesophageal junction that can lead to overdiagnosis of BE.

Transnasal Endoscopy

Transnasal endoscopy involves the use of an ultrathin endoscope (diameter <6 mm) that is passed through the nares without the need for sedation (Fig. 22.1). Several randomized controlled studies demonstrate the safety, high tolerability, and high patient acceptance rate for TNE compared to conventional endoscopy. TNE can be performed in an ambulatory setting by a trained physician or ancillary healthcare staff (physician assistants, nurse practitioners), with technical competency achieved after an average of 45 supervised procedures. In a meta-analysis of seven studies (613 patients), TNE demonstrated a pooled sensitivity of 98% and specificity of 100% in detecting BE when compared to endoscopy. Although the image quality of TNE is inferior to high-definition white light endoscopy, this does not appear to have a direct impact on the diagnosis of BE. Most TNE devices have an instrument channel that allows passage of a pediatric biopsy forceps for tissue sampling. However, the histological sensitivity of detecting BE with TNE appears to be somewhat lower (66.7%) compared to conventional endoscopy. Second-generation TNE devices have been designed to minimize or eliminate the need for device reprocessing by using a disposable sheath (EndoSheath Technology, Vision Sciences Inc., NY) or a disposable probe (EG Scan II, Intromedic Ltd., Seoul, South Korea). Although TNE is considered a safe and cost-effective alternative to standard endoscopy for screening, this technology has not been widely adopted by gastroenterology and primary care practices. Barriers to adoption are likely multifactorial including both physician and patient attitudes toward the technology.

Fig. 22.1 Transnasal endoscopy. (**a**) PrimeSight TNE-5000 transnasal flexible esophagoscope (length 650 mm, field of view 110°, outer diameter of EndoSheath protective barrier (not shown) 1.5 mm or 2.1 mm. (**b**) PrimeSight Video System with integrated monitor and air insufflation tubing

Emerging Screening Techniques

The implementation of a BE screening program using conventional techniques is limited by the availability of endoscopy, patient acceptability, and cost. Growing interest in minimally invasive screening has led to the development of novel screening techniques, including swallowable tissue sampling devices, tethered imaging capsules, and electronic nose technologies.

Swallowable Tissue Sampling Devices

Swallowable devices are used to sample the mucosa of the esophagus without the need for endoscopy or patient sedation. The first device developed for BE screening was the Cytosponge (Medtronic, Minneapolis, MN), which consists of a 30-mm-diameter porous sponge attached to a tether (Fig. 22.2). The sponge is housed within a gelatin capsule that is swallowed by the patient and dissolves in the stomach. The device is then retrieved after 5–8 min by gentle traction,

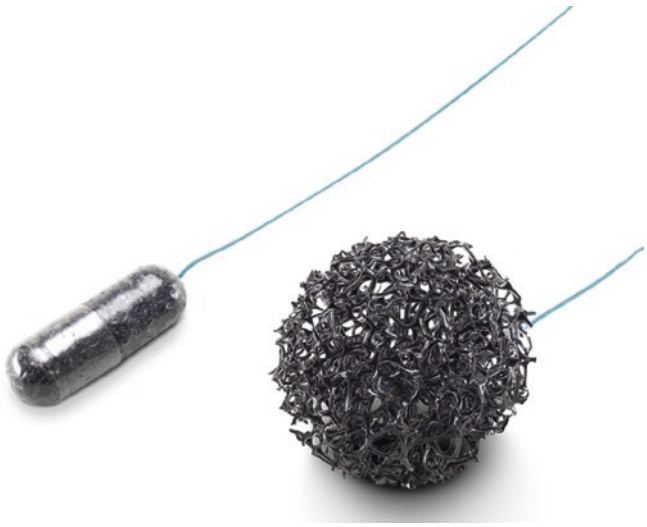

Fig. 22.2 Cytosponge device. A tissue sampling sponge is housed within a dissolvable capsule that is attached to a tether. The capsule is swallowed by the patient and dissolves in the stomach exposing a 30 mm diameter porous sponge. The sponge is retrieved by means of the tether and samples the gastroesophageal junction and esophagus by gentle abrasion. (Image courtesy of Medtronic, Minneapolis, MN)

and in doing so, samples the mucosa of the gastroesophageal junction, entire esophagus, and oropharynx by gentle abrasion. The sampling method is akin to performing soft esophageal mucosal brushings. The EsophaCap (Capnostics, Doylestown, PA) is a similar device that consists of a 25-mm-diameter sponge of 10 pores per inch (Fig. 22.3). A limitation of both capsule sponge devices is that sampling is not limited to the area of interest, which in the case of BE screening should be confined to the gastroesophageal junction and distal esophagus. The EsoCheck Balloon (Lucid Diagnostics, New York, NY) consists of a textured balloon with ridges that is attached to a thin silicon catheter (Fig. 22.4). The balloon measures 16 mm × 19 mm and is inflated in the stomach with 5 cm^3 of air to expose the abrasive ridges. Following sampling of the luminal surface of the distal esophagus, the balloon is deflated and inverted back into its casing before being retrieved. This technique allows targeted sampling while protecting the collected cells from sample dilution and contamination in the proximal esophagus and oropharynx during device retrieval. Swallowable tissue sampling devices are designed to be administered by a physician or ancillary healthcare staff.

Several studies have measured the safety, acceptability, and tolerability of these swallowable devices. In a patient-level review of five prospective trials (2672 procedures in 2418 individuals), the use of the Cytosponge was associated

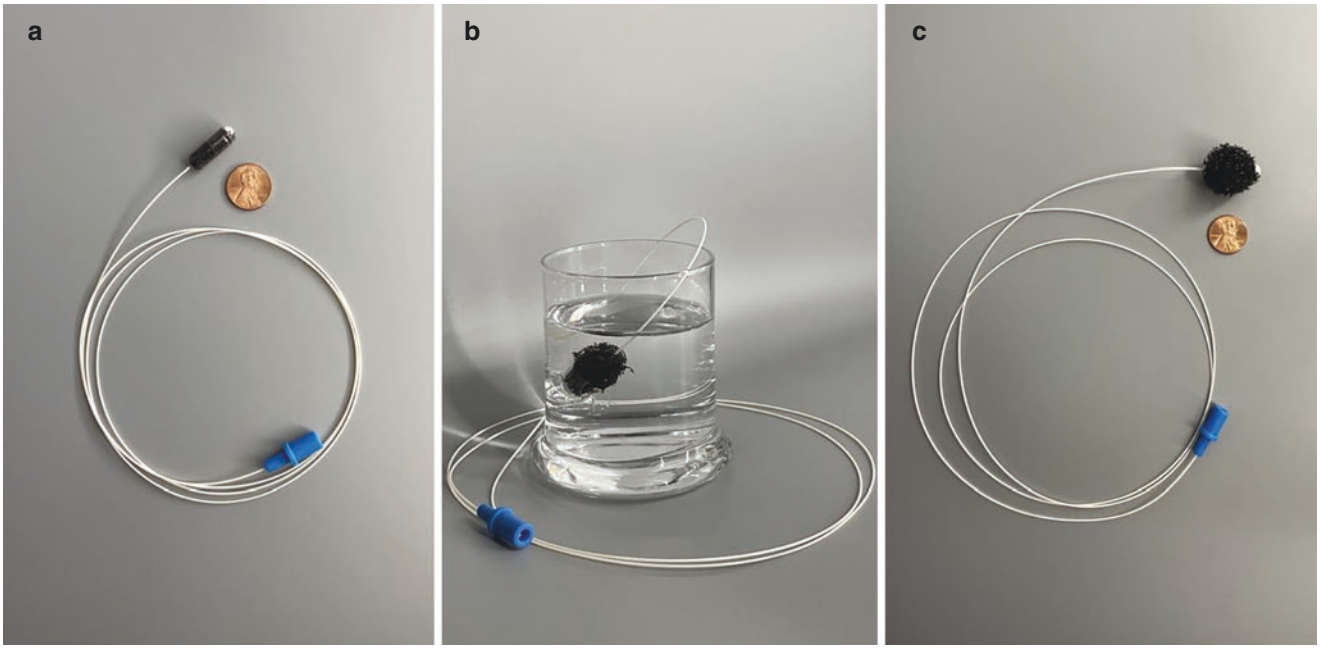

Fig. 22.3 EsophaCap device (**a**) A tissue sampling sponge is housed within a dissolvable capsule (length 23.4 mm, diameter 8.56 mm) that is attached to a tether. The capsule is swallowed by the patient and dissolves in the stomach, represented by (**b**) the capsule dissolving in a glass of water. (**c**) Once fully expanded the sponge measures 25 mm in diameter and is retrieved by means of the tether to sample the gastroesophageal junction and esophagus. (Image courtesy of Prasad Iyer MD, Division of Gastroenterology and Hepatology, Mayo Clinic)

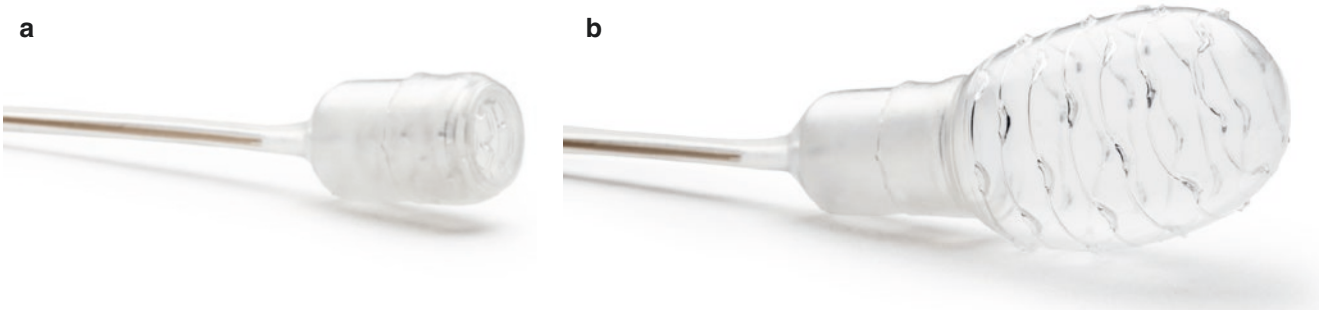

Fig. 22.4 EsoCheck Balloon. (**a**) A silicone capsule houses the deflated tissue sampling balloon. The capsule is swallowed by the patient and once in the stomach the (**b**) tissue sampling balloon (16 mm by 19 mm) is exposed by injecting 5 cm^3 of air through the capsule tether. The inflated balloon is pulled back by means of the tether to sample the distal esophagus. Following sample acquisition, the balloon is deflated and inverted back into its casing before being retrieved. (Image courtesy of Lucid Diagnostics, New York, NY)

with only two minor adverse events, including self-limited pharyngeal bleeding and a single case of device detachment. More than 90% of participants were able to swallow the capsule, with most of them doing so on the first attempt. Similar data on the EsophaCap device showed a high swallowing success rate (98%) and tolerability with 85% of participates willing to use the device again. The EsoCheck Balloon was tested in 152 patients of which 128 (82%) successfully swallowed the device with excellent tolerance in 72% of cases.

The cytological sample obtained using these devices is preserved and submitted for biomarker analysis. Biomarkers studies to date are outlined below.

Trefoil Factor 3

Trefoil factor 3 (TFF3) is a marker of intestinal cells seen in BE but not from columnar cells of the cardia or upper airway, making it a suitable biomarker for nonendoscopic screening. The diagnostic performance of TFF3 in conjunction with the Cytosponge device has been examined in several studies performed in the United Kingdom. A large multicenter case–control study of 1042 patients in 2015 demonstrated an overall sensitivity and specificity of 79.9% and 93.8%, respectively, for TFF3-Cytosponge for detection of BE. The sensitivity of the test increased to 87.2% in patients with a BE segment length ≥3 cm and in patients who swallowed the device twice (89.7%). A subsequent landmark multicenter randomized controlled trial enrolled 13,514 patients in 109 general practice clinics aged 50 years or older who were taking acid suppressants for symptoms of gastroesophageal reflux for more than 6 months and had not undergone an upper endoscopy within the past 5 years. Participants were then randomized to receive either TFF3-Cytosponge followed by endoscopy if positive for TFF3 cells or standard management of reflux disease with endoscopy only if required by their general practice physician. A total of 6834 patients were offered the Cytosponge procedure of which 1750 agreed to undergo the procedure and 95% swallowed the device successfully and produced a sample. During 12 months of follow-up, 2% of patients in the Cytosponge group and <1% in the usual care group were diagnosed with BE. Furthermore, nine patients in the intervention group and no patients in the usual care group were diagnosed with dysplastic BE or stage 1 adenocarcinoma. This study demonstrates that TFF3-Cytosponge leads to improved detection of BE and diagnosis of early neoplasia but could potentially lead to increased number of endoscopic procedures in the context of false-positive results.

Methylated DNA Biomarkers

Alterations in DNA methylation have a direct impact on gene expression and can lead to silencing of tumor suppressor genes and overall chromosomal instability. Aberrant DNA methylation occurs in BE prior to neoplastic progression, making this a promising target for the purpose of screening. An advantage of DNA methylation analysis compared to TFF3 is that DNA methylation is a quantitative test that does not require manual histopathological analysis. Several methylated DNA markers (MDMs) that distinguish between BE and neighboring normal squamous and gastric epithelium have been studied. Using esophageal biopsies, Chettouh et al. described 10 hypermethylated genes associated with BE of which *TFPI2, TWIST1, ZNF345,* and *ZNF569* were used to detect BE using Cytosponge samples. In this study, the tumor suppressor gene, *TFPI2,* was determined to be the best candidate marker with an AUC of 0.88 and sensitivity of 78.5% and specificity of 96.9%. A discovery and validation study by Iyer et al. described 19 MDMs that differentiate BE from squamous epithelium with an AUC >0.85. Using EsophaCap samples, a two-marker panel (VAV3, ZNF682) yielded an AUC of 1.0 for the detection of BE. In a marker elimination study, a 5 MDM panel was identified (*VAV3, ZNF682, NDRG4, FER1L4, ZNF568*) with a sensitivity of 92% and specificity of 94% for the detection of BE in a multicenter study that enrolled 295 patients (112 cases with BE and 89 controls). The diagnostic performance was not affected by age, gender, smoking history, or grade of histological dysplasia but appeared to be influenced by BE segment length. Further validation of the 5 MDM panel was performed in a multicenter case–control study that included 199 patients (110 cases with BE and 89 controls in the training set) and 89 patients (60 cases with BE and 29 controls) in the test set. The 5 MDM panel had a sensitivity of 93% and specificity of 90% in the training set and 93% and 93%, respectively, in the test set. The 5 MDM panel is currently undergoing further study in an at-risk primary care screening population. In another discovery and validation study by Wang et al. described five candidate MDMs (*p16, HPP1, NELL1, TAC1, AKAP12*) with samples obtained using the EsophaCap. A lasso model using four biomarkers and age showed an AUC of 0.93, sensitivity of 78.6%, and specificity of 92.8% for the diagnosis of BE in an independent test set. A study of 86 patients using the EsoCheck Balloon in combination with *VIM* and *CCNA1* MDMs showed a sensitivity of 90.3% and specificity of 91.7% for the diagnosis of BE and related neoplasia.

MicroRNA

MicroRNAs are noncoding RNA molecules responsible for gene expression that have shown promise as molecular biomarkers for cancer diagnosis. A meta-analysis of 11 studies that examined microRNA expression between normal esophageal squamous epithelium and BE showed increased MIR192, MIR194, MIR215, and reduced MIR203 and MIR205 expression between tissue types. Using samples collected by Cytosponge, a 6-miRNA panel (*MIR7, MIR30a, MIR181a, MIR192,* and *MIR196a, MIR199a*) was shown to

have similar accuracy for the diagnosis of BE compared to TFF3 [sensitivity of 86.2% vs. 83.9% and specificity of 91.6% vs. 93.7%, respectively] when applied to the same sample set. BE is a polyclonal and highly mutated disease, even in the absence of dysplasia. As such, microRNAs appear to have a more limited role in differentiating between BE and EAC.

Swallowable tissue sampling devices in combination with biomarker analysis are a promising minimally invasive strategy for BE screening. Despite great advancements in this field, the use of these devices continues to be investigational.

Tethered Capsule Endomicroscopy

Tethered capsule endomicroscopy (TCE) incorporates principles of optical coherence tomography into a tethered capsule device that allows high-resolution cross-sectional imaging of the esophagus. The TCE capsule has a diameter of 11 mm and a length of 25 mm with a tether comprised of a 1 mm diameter sheath that encloses an optical fiber (Fig. 22.5). A swept-source infrared laser beam is focused on a 45° prism attached to a micromotor at the distal end of the device. The capsule device is swallowed by the patient into the stomach and slowly retrieved by gentle traction of the tether. Rotation of the micromotor allows for circumferential imaging while longitudinal imaging is controlled by the speed of tether pullback. TCE imaging (7 μm axial resolution, 10 μm depth) allows direct observation of microarchitectural characteristics that distinguish BE from normal squamous epithelium and gastric tissue. An advantage of TCE over swallowable tissue sampling devices is the capability of directly interrogating the Barrett's epithelium by means of an "optical biopsy" that provides information on segment length and presence and distribution of early neoplasia. In this regard, TCE could potentially be used for both screening and risk-stratification of BE. The feasibility, safety, and tolerability of TCE have been investigated in a multicenter study that enrolled 147 patients with BE of which 116 (79%) successfully swallowed the device. High-quality imaging was obtained in 93.7% of patients who completed the procedure. The average imaging duration was 5.55 ± 1.92 min. A blinded comparison of maximum extent of BE measured by TCE and EGD showed a strong correlation (r = 0.77–0.79). A similar device using ultra-high-speed swept-source optical coherence tomography and capable of en face cross-sectional imaging demonstrated feasibility of use in a pilot study of 16 patients. TCE can be administered by ancillary healthcare staff, but quality of imaging remains operator-dependent and can be improved by multiple TCE passes and tether manipulation. The TCE device is reusable following reprocessing with an enzymatic detergent. A portable TCE imaging system has been designed for point-of-care use, but at present the system is not commercially available.

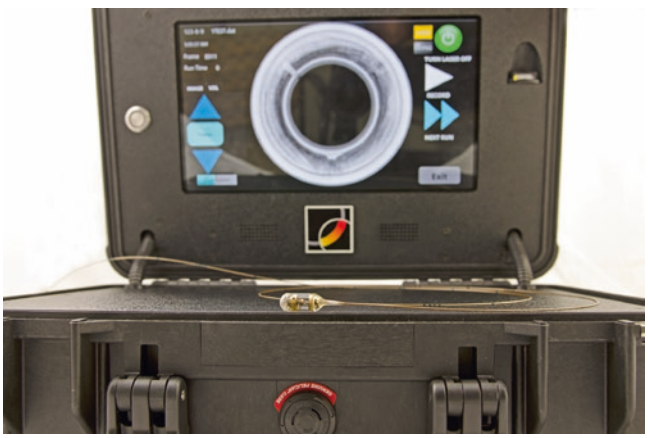

Fig. 22.5 Tethered capsule endomicroscopy (TCE). The portable console consists of an optical coherence tomography system with a touch screen that controls and displays the TCE scan. The reusable capsule device is connected to the imaging console and measures 25 mm in length and 11 mm in outer diameter. Circumferential imaging is generated by an infrared laser focused on a rotating prism located at the distal end of the capsule device. The capsule device is swallowed by the patient and retrieved by manual pullback of the tether. (Image courtesy of Guillermo Tearney, MD PhD, Wellman Center for Photomedicine at the Massachusetts General Hospital)

Exhaled Volatile Organic Compounds

Volatile organic compounds (VOCs) are gaseous products arising from normal metabolic processes in the body, the microbiome, and inflammatory processes that can be detected in various types of samples, including exhaled breath. Analyses of VOCs have the potential to detect patients with BE. Chan et al. were the first to describe the use of exhaled VOCs for the diagnosis of BE using an electronic nose device (Aeonose, Zutphen, the Netherlands). The electronic nose is a noninvasive device that consists of an array of metal oxide sensors, which when in contact with VOCs produce a unique signal representative of the VOC composition in a breath sample (Fig. 22.6). This cross-sectional study evaluated breath VOCs in a cohort of patients with a history of dysplastic BE (n = 122) undergoing endoscopic eradication therapy. VOC profiles of patients with and without BE were compared using principles of artificial intelligence and showed a sensitivity of 82% and specificity of 80% for the diagnosis of BE. These findings were followed by a multicenter proof-of-principle cross-sectional study by Peters et al. that performed exhaled VOC analysis in 402 patients (129 patients with BE, 141 patients with gastroesophageal reflux, and 132 controls) that found a sensitivity of 91% and specificity of 74% (AUC

Fig. 22.6 Electronic nose device. The Aeonose is a handheld device that consists of an array of metal oxide sensors, which when in contact with volatile organic compounds (VOC) produce a unique signal representative of the VOC composition of a breath sample. To generate a VOC signal, a patient breathes into a mouthpiece for several minutes

of 0.91) for the diagnosis of BE. The VOC signal appeared to be independent of proton pump inhibitor use, presence of hiatal hernia, and presence of gastroesophageal reflux symptoms. A limitation of this technology is that it is unable to identify individual VOC biomarkers at a molecular level. A study using mass spectrometry techniques analyzed VOCs in patients with esophageal ($N = 48$) and gastric ($N = 33$) adenocarcinoma in comparison to patients without malignancy ($N = 62$). Twelve VOCs derived from fatty acids, phenol, and aldehyde compounds were present at significantly higher concentrations in the cancer groups. The AUC to discriminate esophageal and gastric cancer was 0.97 and 0.98, respectively. The authors of this study advocate that these chemical targets can be used to develop noninvasive point-of-care sensors for the diagnosis of gastroesophageal cancer. The application of VOCs to BE screening remains investigational despite the commercial availability of electronic nose devices.

Cost-Effectiveness of Screening

Screening for BE with sedated upper endoscopy is associated with significant direct and indirect costs and is currently recommended only for populations at increased risk including patients with chronic symptoms of gastroesophageal reflux with additional risk factors. In the absence of symptoms of gastroesophageal reflux, screening for BE with upper endoscopy is not considered cost-effective. However, a significant number of patients with BE do not experience chronic symptoms of gastroesophageal reflux and are missed when applying a symptom-driven screening strategy. The emerging minimally invasive technologies have the potential to provide cost-effective screening even when applied to a population without symptoms of gastroesophageal reflux.

Compared to upper endoscopy, the improved cost-effectiveness of screening with TNE has been demonstrated in both a randomized controlled study and cost-effectiveness modeling studies. Swallowable tissue sampling devices are associated with very high patient acceptability and their cost-effectiveness as a complementary screening tool to endoscopy has been explored in various studies. A simulation model screening 50-year-old men with symptoms of gastroesophageal reflux with the Cytosponge device found this strategy to be cost-effective and associated with reduced mortality from EAC compared with no screening. The model found that Cytosponge followed by endoscopic therapy for patients with BE neoplasia reduced the number of incident cases of EAC by 19% compared with 17% for screening by endoscopy alone, with the premise that patients are more likely to undergo Cytosponge as a screening test. In a similar study by Herbele et al. comparative modeling analysis of various screening strategies for BE in patients with gastroesophageal reflux favored the use of Cytosponge with endoscopic confirmation as a cost-effective strategy. This strategy was associated with a lower false-positive rate compared to a single-screening endoscopy, leading to a reduction in the number of people requiring surveillance endoscopy.

Conclusions and Future Directions

The practice of screening for BE followed by surveillance in combination with endoscopic eradiation therapy in selected patients is advocated as a strategy to decrease mortality from EAC. Medical guidelines recommend screening patients with chronic gastroesophageal reflux and associated risk factors. However, this practice misses a significant number of patients who are otherwise asymptomatic. As such, the use of clinical risk prediction tools in combination with emerging technologies promises to identify patients who would benefit from screening and offer them a minimally invasive, effective, and acceptable alternative to endoscopy. The emerging screening technologies discussed in this chapter are all designed for ease of use in the primary care setting and are considered to be cost-effective with an excellent tolerability profile. Adoption of these technologies will largely depend on physician and patient attitudes toward

performing and undergoing these tests, respectively. As in the case of TNE, the availability of a good screening test does not guarantee its use. Future studies will provide insight regarding the real-world experience of these technologies and highlight their true impact in the practice of screening for BE.

Questions

1. Which of the following screening techniques can be considered as an alternative to conventional upper endoscopy for BE screening?
   A. Cytosponge-TTF3
   B. Tethered capsule endomicroscopy
   C. Transnasal endoscopy
   D. EndoCap—methylated DNA biomarkers

Answer: C

ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus

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2. Which of the following novel screening techniques was the first to be validated by a multicenter randomized controlled trial in a primary care setting?
   A. Tethered capsule endomicroscopy
   B. Cytosponge with trefoil factor 3
   C. Exhaled volatile organic compounds
   D. EsophaCap with methylated DNA markers

Answer: B

Fitzgerald RC, di Pietro M, O'Donovan M, et al. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. Lancet. 2020 Aug 1;396(10247):333–344

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Staging Endoscopic Ultrasound

23

Eun Ji Shin and Shruti Mony

Objectives

1. Staging in gastric and esophageal cancer
2. Role of endoscopic ultrasound (EUS) with and without fine needle aspiration (FNA) in staging
3. Technical and special considerations while using EUS
4. Impact of EUS on patient survival and economic impact
5. Limitations of EUS

Introduction

The role of endoscopic ultrasound (EUS) has evolved since its conception in the 1980s for not only diagnostic but also therapeutic purposes. It continues to be instrumental in the diagnosis, staging, and management of gastrointestinal malignancies. For esophageal and gastric cancers, it plays a crucial role in evaluating tumor invasion and lymph node metastasis. This, in turn, assists with overall diagnosis, prognosis, and treatment planning. In this chapter, we will discuss the role of EUS in esophageal and gastric cancer, with a focus on staging.

Esophageal Cancer

Epidemiology and Risk Factors

Esophageal cancer (EC) carries a poor prognosis due to its aggressive nature and late-stage diagnosis. Globally, it is the sixth leading cause of cancer death and the eighth most common cancer worldwide [1]. The 5-year survival is only 15–25% given its late-stage diagnosis and limited treatment options [2]. The incidence, prevalence, and risk factors vary by geographical location [3, 4].

Among its subtypes, esophageal squamous cell carcinoma (SCC) is prevalent in Asia, South Africa, and Eastern Europe while esophageal adenocarcinoma (EAC) has a higher prevalence in North America, Australia, the United Kingdom, and Western Europe [4–7]. The risk factors for SCC include black race, genetics, diet low in fruits and vegetables, and alcohol and tobacco use. The risk factors for EAC include white race, male gender, gastroesophageal reflux disease (GERD), Barrett's esophagus, history of tobacco smoking, and obesity [4, 6, 8, 9].

Classification

The tumor–node–metastasis (TNM) system is the most widely used cancer staging system and is based on primary tumor invasion depth (T), regional lymph nodes (N), and distant metastasis (M), which was established by the eighth edition of the American Joint Committee on Cancer (AJCC) [10] as detailed in Table 23.1. This edition is different from its predecessor in that it incorporates the newly constructed clinical (c) and post-neoadjuvant pathological (yp) stage groups. The TNM components for staging EAC and SCC are similar; however, there are slight variations in the anatomical stage due to differences in mortality between the histological subtypes.

The esophagus is divided into five main layers: the superficial and deep mucosa, submucosa, muscularis propria, and adventitia. The mucosal layer is further divided into the epithelium, lamina propria, and muscularis mucosae. The T stage is classified as follows: T1a cancers are confined within the mucosa and are often called intramucosal cancers (M1—within epithelium, M2—limited to lamina propria, M3—involving muscularis mucosae); T1b cancers invade submucosa (Sm1—invasion less than 200 μm or invasion of the first 1/3rd of submucosa, Sm2—invasion more than 200 μm or second 1/3rd of submucosa, Sm3—reaching the muscle layer); T2 tumors

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Table 23.1 AJCC eighth edition staging for esophageal cancer [10]

Category	Criteria
Tumor category (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades adjacent structures such as the aorta, vertebral body, or airway
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups, adenocarcinoma			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
Stage III	T3	N0 or N1	M0
Stage III	T4a	N0 or N1	M0
Stage IVA	T1–4a	N2	M0
Stage IVA	T4b	N0, N1, or N2	M0
Stage IVA	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Anatomic stage/prognostic groups, squamous cell carcinoma			
Stage 0	Tis	N0	M0
Stage I	T1	N0 or N1	M0
Stage II	T2	N0 or N1	M0
Stage II	T3	N0	M0
Stage III	T3	N1	M0
Stage III	T1, T2, or T3	N2	M0
Stage IVA	T4	N0, N1, or N2	M0
Stage IVA	Any T	N3	M0
Stage IVB	Any T	Any N	M1

invade the muscularis propria, T3 the adventitia, and T4 denotes invasion of adjacent structures (Fig. 23.1a) [11].

These layers are reflected on EUS that can be used to delineate T-staging (Fig. 23.1b). Advanced esophageal cancers are those extending beyond T2 stage while superficial esophageal cancers are those localized to Tis and T1 stage.

The absence of serosal layer in the esophagus and extensive lymphatics in the muscularis mucosae results in faster local spread of the tumor [12]. Understanding the depth of invasion is pivotal as the risk of lymph node metastasis increases from M1 and M2 layers (<5%) to M2 and Sm1 layers (12–27%) and Sm2 and Sm3 (36–46%). This, in turn, helps decide between endoscopic and surgical therapy for curative intent.

Pretreatment Evaluation

The preoperative evaluation as outlined by the National Comprehensive Cancer Network Guidelines [JNCCN V2.2019] for esophageal cancer [13] is shown in Table 23.2.

Pretreatment Staging

The most critical factor affecting cancer prognosis is the depth of tumor invasion and presence of lymph node or distant metastasis. While surgical pathology yields the most accurate staging, advances in endoscopic techniques (EGD/EUS) and imaging modalities such as CT and 18-fluorodeoxyglucose [FDG]-PET/CT have greatly improved the accuracy of clinical staging [14].

Staging begins with assessment of distant metastasis, for which contrasted CT (chest/abdomen) or PET scans are employed. Tumoral extension below the diaphragm warrants the addition of CT pelvis. If there is evidence of metastatic disease, further investigations to evaluate the T and N status are not required. If CT is negative for metastatic disease, FDG-PET/CT is performed as it can detect previously unsuspected metastatic disease in 15–20% of cases [15].

EUS in Staging

EUS should be performed if noninvasive imaging of the abdomen and pelvis excludes distant metastases. It provides an in-depth view of the acoustic layers of the esophageal wall and surrounding tissues (Fig. 23.1b) allowing precision with TNM staging [8, 13]. Not only is EUS considered to be the most sensitive tool for locoregional staging in EC, its use with fine needle aspiration (EUS-FNA) further assists with confirming diagnosis of lymph node metastasis [16].

EUS Examination Technique

For initial endoscopic diagnosis, the clinician should describe tumor location, extent, circumferential involvement, presence of obstruction, and obtain targeted tissue biopsies.

Staging EUS examination begins at the stomach and GE junction, followed by slow withdrawal of the echoendoscope while examining the esophageal layers. The report should include the details of the endoscopic and echoendoscopic features of the tumor.

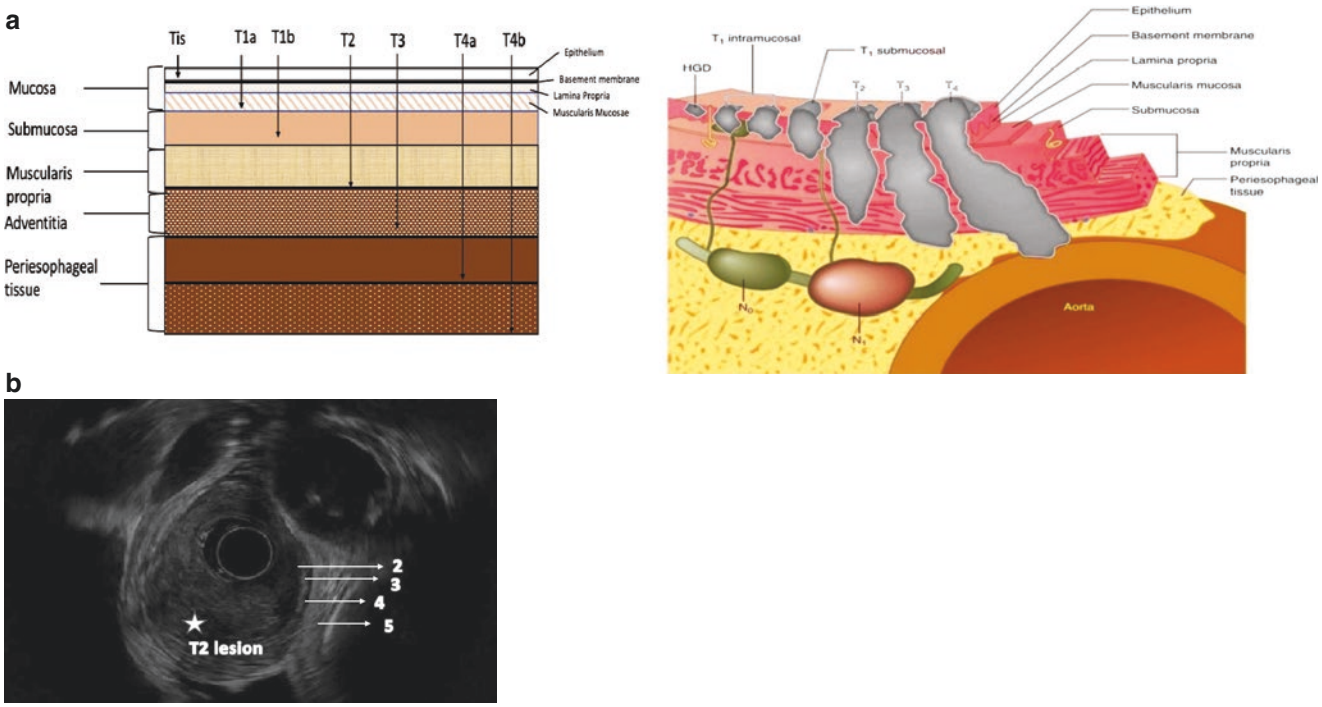

Fig. 23.1 (**a**) Layers of the esophagus (T-staging). (**b**) Layers of the esophagus: radial EUS view. Radial EUS showing uT2N0 esophageal adenocarcinoma: *T* tumor; 2, muscularis mucosa; 3, submucosa; 4, muscularis propria; 5, adventitia

Table 23.2 Initial workup of esophageal and esophagogastric junction cancers

- History and physical examination
- Upper GI endoscopy and biopsy
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT with contrast as clinically indicated
- FDG-PET/CT evaluation [skull base—mid thigh] if no evidence of M1 disease
- Complete blood count and comprehensive chemistry profile
- EUS if no evidence of M1 disease
- ER is essential for the accurate staging of early-stage cancers (T1a or T1b)
- Biopsy of metastatic disease as clinically indicated
- If metastatic disease is documented or suspected
  - MSI-H/dMMR and PDL-1 testing
  - HER2 testing
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated
- Screen for family history

Source: National Comprehensive Cancer Network Guidelines V2.2019, Esophageal and Esophagogastric Junction Cancers

Three different types of EUS scopes can be used

- Radial echoendoscope provides a circumferential 360° view of the visceral wall and surrounding tissues, similar to axial images obtained by CT [14, 17] (Fig. 23.1b).
- Curvilinear array echoendoscope has the added benefit of tissue acquisition with fine needle aspiration (FNA) or biopsy [18, 19, 20].
- Miniature probes carry a higher frequency (20–30 MHz) than standard EUS and yield increased superficial anatomic resolution, but lack deeper sonographic tissue penetration, limiting regional assessment [21].

T-Staging

In the past decade, the overall accuracy of EUS for T-staging has been reported ranging from 71 to 92% [22, 23] depending on the stage, with some studies challenging the accuracy of EUS for superficial cancers [19].

Thosani et al. [24], in their meta-analysis, reported an overall accuracy for superficial EC of 94% but pooled sensitivity and specificity of 85% and 86% for both T1a and T1b stages. They concluded its best use is in detecting T2 lesions that are not amenable to EMR or ESD. Luo et al. [16] reported an overall EUS accuracy of 79% for T-staging and 71% for N-staging.

Qumesya et al. [20] highlighted the 9% risk of overstaging to T1b with EUS, making it a suboptimal choice in superficial T-staging. A recent meta-analysis by Klamt et al. for EAC and EGJ tumors showed a low EUS accuracy (65.5%) for T-staging but a higher accuracy for subcatego-

ries—T1 (89.1%) and T2 (87.1%), T3 (87%), and T4 (66.4%). A plausible explanation for EUS overstaging is likely due to peritumoral inflammatory changes [25, 26].

Given these controversies with EUS, endoscopic resection (ER) with either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is considered the best method for determining early T-staging. ER is curative in T1a lesions with a 5-year survival of 98% and excellent long-term results [27, 28–31].

N-Staging

The presence of malignant lymph nodes is an important prognostic indicator that influences therapy. EUS is the preferred modality for locoregional nodal assessment with sensitivity and specificity rates approaching 72–80% [16, 22, 32]. The addition of EUS-FNA improves the sensitivity for N-staging from 84.7 to 96.7% [22].

A malignant lymph node on EUS is classically described as round, hypoechoic with smooth borders, measuring >10 mm [16, 33] (Fig. 23.2).

M-Staging

EUS is seldom required in the setting of distant metastasis as it will not alter management options of palliative chemoradiotherapy. However, EUS may still be used in some settings to eliminate nodal involvement and calculate the field of radiation [34]. PET and/or CT is preferable for patients with invasive disease or presence of metastasis. CT has an accuracy of 90% compared to 70% for EUS [15].

Comparison Among Different Modalities for Staging Esophageal Cancer

Superficial Cancers: EUS and ER are preferable for superficial cancers. CT and FDG-PET may not be accurate in differentiating T1 versus T2 due to poor soft-tissue resolution and concern for overstaging [35].

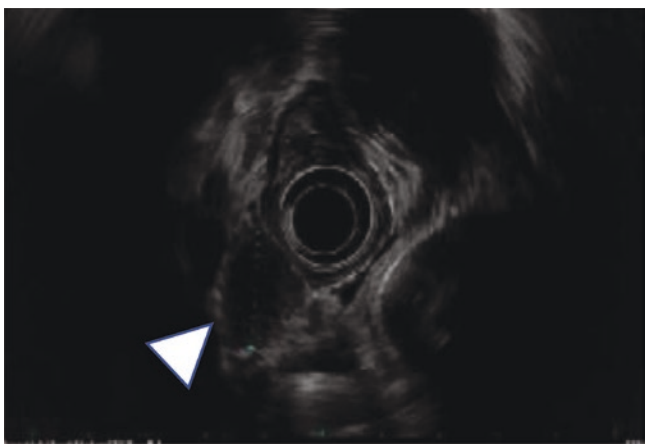

Fig. 23.2 EUS malignant lymph node. Malignant lymph node (arrowhead) seen on radial EUS in a patient with uT3N1 esophageal cancer

Locoregional Disease: van Vliet et al. found the sensitivities of EUS, CT, and FDG-PET to be 80%, 50%, and 57%, respectively, and the specificities were 70%, 83%, and 85%, respectively [36]. Sihvo et al. showed EUS to be more accurate in the diagnosis of nodal disease compared to PET and CT [37] and using EUS in addition to CT and PET increased the nodal staging accuracy from 70 to 91% (P = 0.008). FDG-PET and FDG-PET-CT are less accurate for N-staging [38–40].

Metastatic Disease: PET-CT has a higher accuracy than CT alone for distant and locoregional metastases but is inferior to EUS for locoregional metastases [36]. In a systematic review, FDG-PET for the detection of locoregional metastases had a 51% sensitivity and 84% specificity. For distant metastases, pooled sensitivity and specificity were 67% and 97%, respectively [41].

EUS in Restaging After Therapy

Neoadjuvant chemoradiation therapy (nCRT) is recommended for locally advanced diseases [42], which can downstage patients to become candidates for curative resection.

EUS has unfortunately yielded less-than-optimal results for the assessment of tumor response following nCRT [43–47]. This could be attributed to the regional wall changes in response to inflammation and healing following CRT, which causes hypoechoic wall thickening on EUS, resulting in overstaging. This was demonstrated in a meta-analysis by Sun et al. [48], who evaluated the staging accuracy of EUS after preoperative chemotherapy. EUS was most sensitive in localized staging of T3 lesions at 81%, but the sensitivity in stages T1, T2, and T4 was poor (23–43%). For N-staging, EUS had a sensitivity of 69% and specificity of 52%. The authors concluded that EUS was moderately accurate after neoadjuvant therapy for T- and N-staging, and in their subgroup analysis the results did not improve with time following neoadjuvant chemotherapy. Another meta-analysis evaluated cases where EUS was performed after neoadjuvant chemotherapy in 593 patients for reevaluation of primary tumor status and in 602 patients for reevaluation of locoregional lymph node status. They reported EUS sensitivity and specificity of 96.4% and 10.9% for residual cancer at the primary tumor site and 62.0% and 56.7%, respectively, for malignant locoregional lymph nodes [49].

Other modalities, including endoscopic biopsies, CT, and PET-CT, have yielded inconsistent results in evaluating pathological response following nCRT [32, 44–46]. Kroese et al. reported that while PET-CT following CRT detected true distant interval metastases in 8% of patients, false-positive findings occurred in 5% of patients, cautioning providers on the need for pathological confirmation for suspected lesions [50]. On the contrary, with improvements in diffusion-weighted MRI, early studies have shown better predictive performance following CRT with pooled sensitivity and

specificity of 93% and 85% [51]. Despite these advances, we need more accurate diagnostic tests to restage patients with esophageal cancer after nCRT.

A summary of the staging modalities is shown in Table 23.3 and Fig. 23.3.

Special Considerations

Stenotic Lesions

Since the caliber of echoendoscope is larger than gastroscope, it may not be able to traverse all malignant obstructions. EUS mini-probe can be used, but as stated previously they are limited in regional assessment. A multicenter study suggested that routine EUS examinations may not be required in such cases as the inability to advance a diagnostic gastroscope through a malignant stricture correlated 100% with locally advanced disease [52, 53]. Endoscopic dilation balloon could be considered in lesions above stage T2 to assist echoendoscope passage; however, it can compress the esophageal wall and surrounding tissues, resulting in abnormal ultrasound images.

Table 23.3 Comparison of different modalities for staging esophageal cancer

	Modality				
Stage	EUS	CT	PET	PET-CT	DW-MRI
Superficial esophageal cancers	+++ (If distant metastasis has been ruled out by cross-sectional imaging)	+	+	+	+
Locoregional/ lymph node	+++	++	++	++	+
Distant metastasis	+	++	+++	+++	+++
Post-neoadjuvant therapy	+	+	+	++	+++

Outcomes

Impact on Patient Management and Survival

EUS can play a clinically significant role in altering patient management with locoregional disease evaluation [54, 55]. EUS changed patient management in over a third of cases (38%) from being surgically resectable to requiring chemoradiotherapy [56]. A retrospective analysis by Hulshoff et al. found that EUS following FDG-PET for resectable disease influenced treatment planning in 29% of the patients, assisting with delineation of radiotherapy target volumes of mediastinal lymph nodes metastases [34]. In a prospective study of surgically resectable patients with mediastinal lymph nodes, EUS-FNA changed the management in 11 of 48 patients (23%) from planned trans-hiatal esophagectomy to transthoracic esophagectomy [57].

In a British randomized trial of 223 participants with non-metastatic gastroesophageal cancer, EUS not only signifi-

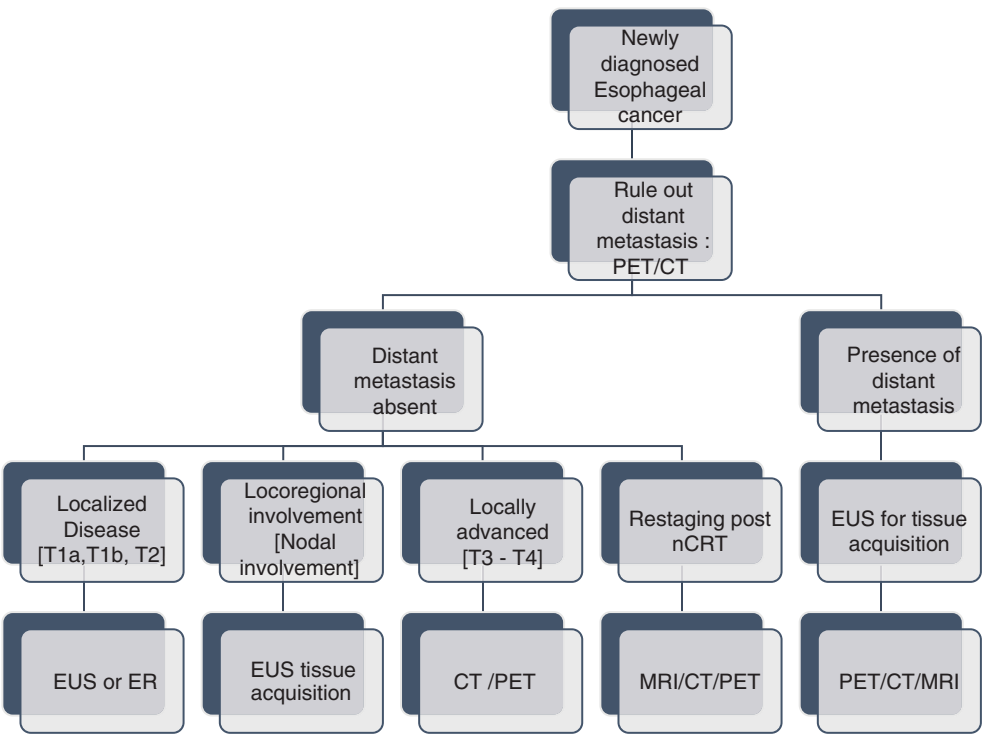

Fig. 23.3 Flow diagram for staging esophageal cancers

cantly improved survival but also reduced healthcare resource use and was cost-effective. The crude survival hazard ratio was 0.706 (95% CI 0.501–0.996), and the median survival was increased by 121 days when comparing the group with standard workup (1.63 years) versus the group that underwent EUS (1.96 years). There was also a net saving of £2800 per trial participant, resulting in a 96.6% probability of being cost-effective by the National Institute for Health and Care Excellence (NICE) criteria. EUS also augmented the proportion of tumors being completely resected from 80 to 91% ($P > 0.05$) [58].

Using the Surveillance, Epidemiology, and End Results (SEER) registry, Wani et al. reported that patients undergoing EUS, CT-PET, and EUS + CT-PET had improved overall survival for all stages relative to those not undergoing these procedures, with the exception of stage 0 disease. The receipt of either EUS or CT-PET alone was a significant predictor of improved 1-, 3-, and 5-year survival. EUS increased the odds of undergoing endoscopic therapies, esophagectomy, and chemoradiation. Similar results were noted when results were stratified based on histology, as well as for CT-PET and EUS + CT-PET groups [59].

Cost-Effectiveness and Economic Impact

A national database analysis done on 188 EUS procedures as part of preoperative staging showed that EUS incurs an average cost savings of $3443 per patient by identifying patients with stage I and IV disease and obviating the need for neoadjuvant therapy or surgery, respectively [60]. In cases of advanced disease, a cost minimalization analysis done by Hadzijahic et al. showed that while CT remains the initial test to rule out metastasis, in certain settings and large referral centers, EUS found a statistically significant number of advanced diseases (T4 and/or M1) more frequently compared to CT (44% vs. 13%) and was the least costly strategy [61]. Chang et al. performed a prospective analysis among 60 patients with esophageal cancer and found that the medical decisions favoring surgical or medical therapy correlated significantly with their EUS staging and EUS-guided therapy decreased the cost of care by $740,424 ($12,340/patient) by reducing the number of thoracotomies [55]. A recent systemic review looking at cost-effectiveness analyses reported that the use of EUS as a complementary staging modality provided more QALYs (0.0019–0.1969 more QALYs) and saved costs (by £1969–3364 per patient, 2017 price year) compared to staging strategy without EUS [62]. Lastly, a targeted approach of EUS for suspicious LN further assists in reducing costs [63].

Gastric Cancer

Epidemiology and Risk Factors

Worldwide, gastric cancer (GC) ranks as the fifth most common type of malignancy and third most common cancer-related death, reaching 784,000 deaths in 2018 [1, 64]. Its incidence is declining in the United States; however, countries like Central and South America, Eastern Europe, and East Asia (China and Japan) continue to see a high prevalence of GC.

Helicobacter pylori infection is a recognized risk factor for non-cardia gastric cancer [65]. Other risk factors for GC include advanced age, high salt intake, low fruit and vegetable intake, low socioeconomic status, cigarette smoking, alcohol abuse, familial predisposition, previous gastric surgery, and living in a population at high risk [66]. Due to organized screening and surveillance programs, prognosis is improving in East Asia, but in the United States and Europe, the 5-year relative survival rate is between 10 and 30% [67, 68], underscoring the importance of early diagnosis and management.

Classification

There are several ways to classify GC as depicted in Fig. 23.4.

Pretreatment Evaluation

Initial workup of gastric cancer is detailed in Table 23.4, adapted from the National Comprehensive Cancer Network Guidelines [71].

The goal of staging is to appropriately classify patients into stages I–III (locoregional or potentially resectable) versus stage IV (metastatic, unresectable). The various modalities used for staging with intended approach are summarized in Fig. 23.5.

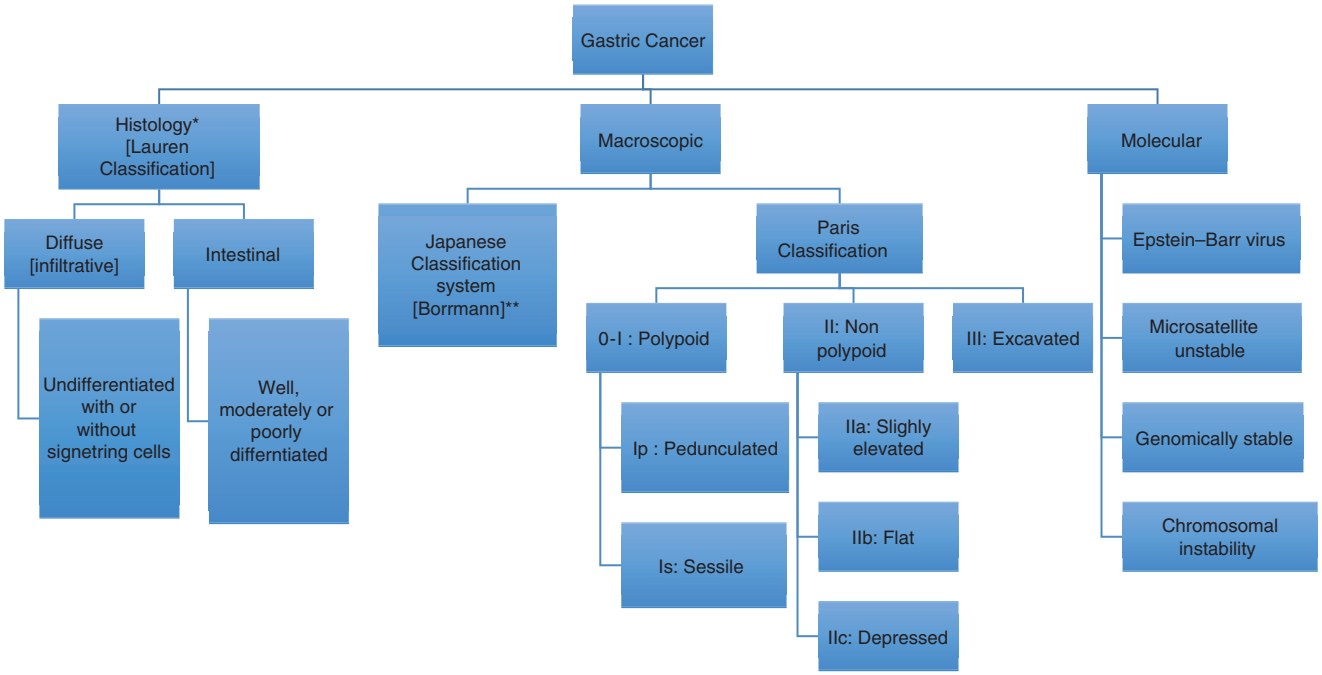

Fig. 23.4 Gastric cancer classification, *Lauren classification is the most commonly used system [69]. Additionally, there are discrepancies in Western and Japanese Classifications among pathologists with disagreement on characterization of high-grade dysplasia and intramucosal cancer [70]. There are other classification systems, including Vienna, Padova, and WHO systems, which are not the focus of this chapter. **East Asia uses classification systems specifically for early gastric cancer, rarely used in the United States. This includes the Japanese Macroscopic Classification of Superficial Gastric Carcinoma

Table 23.4 Initial workup of gastric cancer

- History and physical examination
- Upper GI endoscopy and biopsy-target lesion and for *H. pylori* testing
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT with contrast as clinically indicated
- FDG-PET/CT evaluation (skull base—mid thigh) if no evidence of M1 disease
- Complete blood count and comprehensive chemistry profile
- EUS if no evidence of M1 disease
- ER is essential for the accurate staging of early-stage cancers (T1a or T1b)
- Biopsy of metastatic disease as clinically indicated
- If metastatic disease is documented or suspected: HER2 testing
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated
- Screen for family history

Source: National Comprehensive Cancer Network Guidelines V1.2017

Pretreatment Staging

Surgery and endoscopic therapies are the backbone of curative treatment for early-stage gastric cancer, making accurate staging critical to choosing appropriate therapy. Cross-sectional imaging with CT, PET, and invasive modalities such as EUS and laparoscopy are commonly employed for staging GC.

The most widely used staging system, based on the TNM staging and developed jointly by the AJCC and the Union for International Cancer Control (UICC) Staging System, is detailed in Table 23.5 [72]. The eighth edition differs from previous versions by (1) revising the anatomical distinction between esophagus and stomach, (2) categorizing N3 disease by number of involved nodes, (3) reclassification of T4aN2 and T4bN0 tumors as stage IIIA disease, and (4) separate prognostic stage groups for clinical and pathological staging, including pathological staging after neoadjuvant therapy [73].

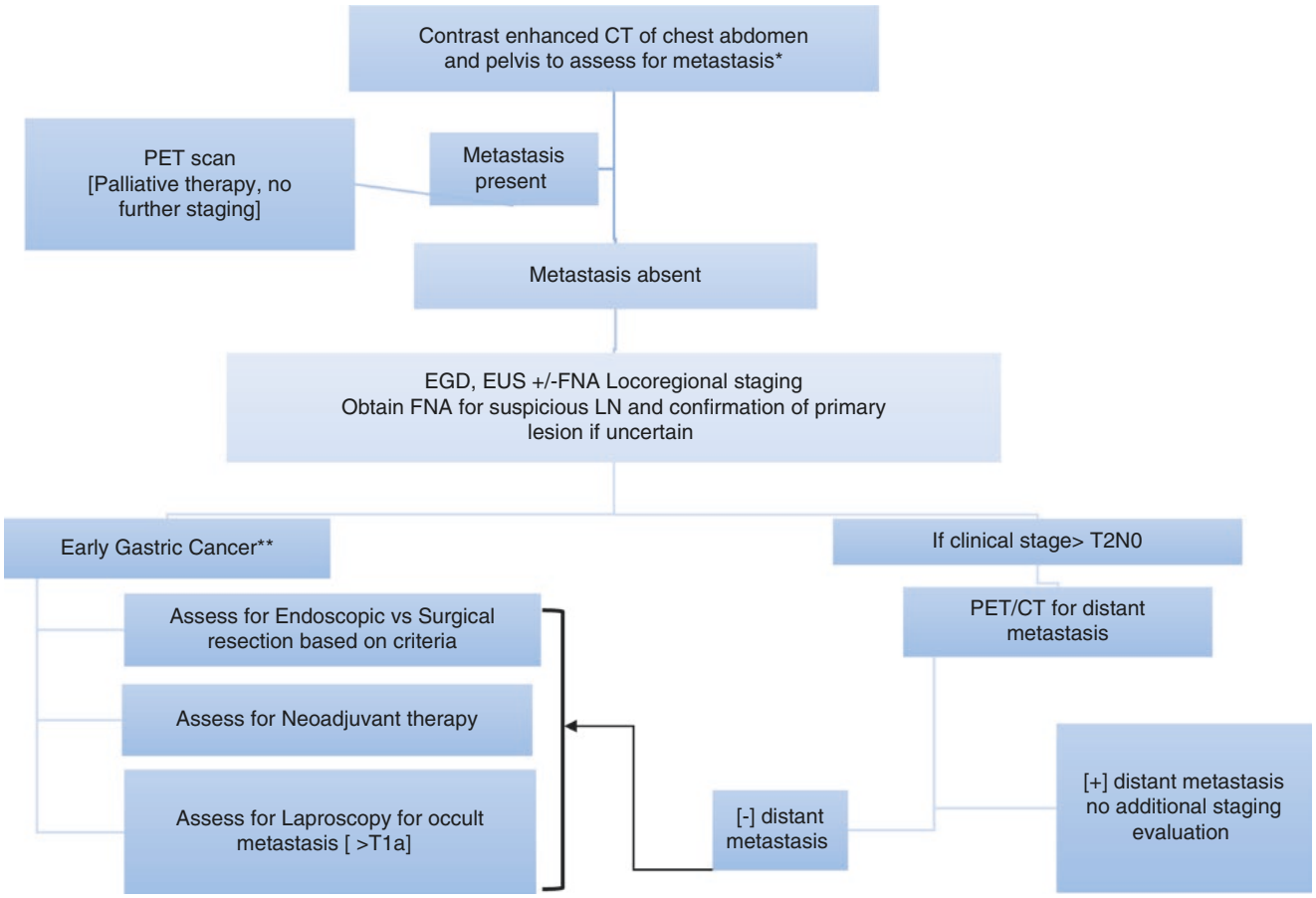

Fig. 23.5 Approach to staging. *Visceral, peritoneal lesions warrant biopsy for confirmation. Ascites when present should be sent for fluid analysis. **Early gastric cancer is defined as lesions localized to the mucosa or submucosa regardless of lymph node (LN) status. For endoscopic resection, absolute and expanded criteria are utilized [74, 75]

Table 23.5 AJCC/UICC TNM eighth edition staging for gastric cancer

Category	Criteria
Tumor category (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates the sub-serosal connective tissue without invasion of the visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic group			
Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage IIA	T1 or T2	N1, N2, or N3	M0
Stage IIB	T3 or T4a	N0	M0
Stage III	T3 or T4a	N1, N2, or N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

EUS in Staging

EUS plays a pivotal role in GC staging and is considered the most attested tool for assessing the depth of invasion (T-staging) and presence of malignant lymph nodes (N-stage) and less often for metastasis or presence of ascites (M-staging). This distinction is paramount as it helps navigate patients to endoscopic resection (EMR or ESD) over surgical therapy or palliative therapy [76].

EUS Examination Technique

T-Stage

The layers of the gastric wall are clearly defined on EUS as shown in Fig. 23.6a and their corresponding T-stage is depicted in Fig. 23.6b. The layers appear with alternating echogenicity starting and ending with the echo-rich mucosal layer and serosal layer, respectively. A gastric wall thickness of 2–4 mm is considered normal with a 1:1:1 relation between the mucosa, submucosa, and muscularis propria [77].

In cases of small or flat lesions, a high-frequency (20 Hz) miniature probe can be more useful, providing a higher resolution and less penetration compared to conventional EUS.

The examination begins at the antrum, and the layers of the stomach are carefully evaluated circumferentially. The key principles to keep in mind during scanning of the gastric lumen with EUS in order to achieve accurate T-staging are as follows:

- Acoustic coupling is optimized by application of fluid as an interface between transducer and the gastric wall, achieved by using a water-filled balloon at the tip of the echoendoscope or by water instillation (200–400 mL) in the lumen while constantly suctioning air.
- Tangential imaging and thus misdiagnosis should be avoided by placing the transducer perpendicular to the lesion.
- Appropriate focal distance (up to 1 cm) should be maintained.
- Higher-frequency echoendoscopes assist with better visualization of the lesion.

N-Staging

Perigastric and regional lymph node stations are surveyed and, as previously described, malignant lymph nodes can be sampled via FNA.

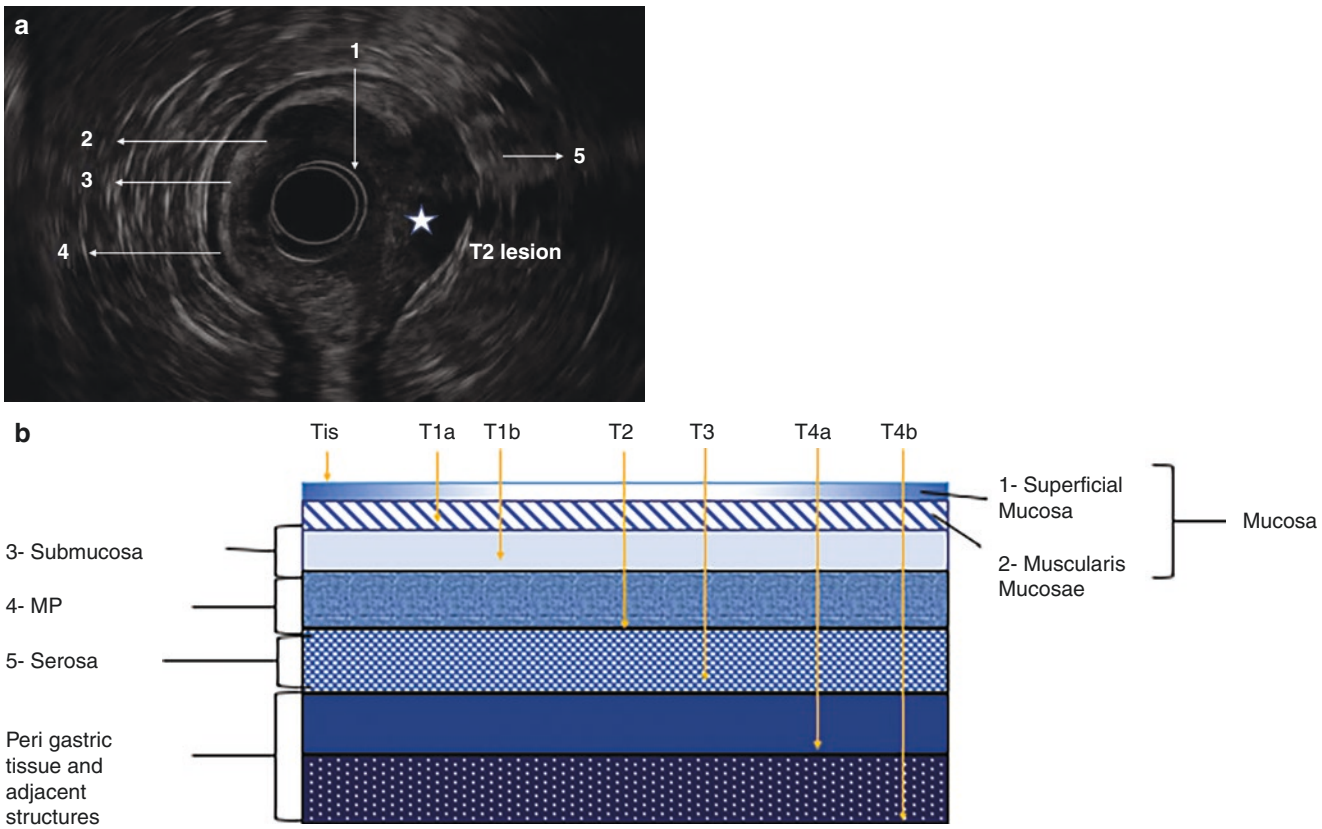

Fig. 23.6 (**a**) Radial EUS layers of the gastric wall showing T2 N0 Mx gastric cancer. Radial EUS showing uT2N0 gastric adenocarcinoma. *Tumor, 1, mucosa; 2, muscularis mucosa; 3, submucosa; 4, muscularis propria; 5, serosa. (**b**) T-stage corresponding with EUS layers

M-Staging

Surrounding structures and organs are evaluated, including the left lobe of liver, pancreatic body/tail, peritoneum, pleural layers of the lung, and mediastinum, including vascular structures.

EUS Accuracy

EUS is considered the most accurate tool for locoregional staging in gastric cancer and is recommended by both the NCCN and European Society for Medical Oncology (ESMO) for pretreatment evaluation of all patients with gastric cancer who have no radiographic evidence of metastasis and potentially resectable disease [71, 78, 79]. Several studies have noted the high-frequency mini-probe being the most suitable for assessing depth of invasion [70, 80].

The reported accuracy of EUS ranges from 67 to 92% for T-stage [81–85] and from 66 to 90% for N-stage [86–89]. A meta-analysis by Mocellin et al. evaluated EUS for staging GC using histology as a reference. The pooled accuracy, sensitivity, and specificity of EUS in discerning T1–T2 versus T3–T4 gastric carcinomas were 88%, 86%, and 90%, respectively. For distinguishing T1 from T2 cancers, the pooled accuracy, sensitivity, and specificity were 86.5%, 85%, and 90%, respectively. For distinguishing T1a from T1b cancers, the pooled accuracy, sensitivity, and specificity were 83.4%, 87%, and 75%, respectively. For N-staging, the pooled accuracy was 75%. The authors reported EUS to be clinically useful for guiding physicians in locoregional staging; however, they emphasized using these results with caution in the setting of high heterogeneity [88].

For N-staging, while EUS is clinically useful, its use as a sole modality is not optimal and should be used in conjunction with other modalities. The EUS characteristics for a malignant lymph node were previously described (Fig. 23.2). A recent meta-analysis by Chen et al. reported that EUS is sensitive for N-staging (82%) but not as specific (68%) [89]. The addition of EUS-FNA for staging further adds to its accuracy [34, 90].

Early Gastric Cancer (EGC)

It is paramount to accurately identify EGC given the criteria for endoscopic versus surgical resection differ. EUS has not shown promising results in EGC for assessing depth of invasion in superficial gastric cancer. The T-stage accuracy for EUS in EGC ranges from 41.4 to 87% [91, 92]. There have been conflicting data favoring conventional endoscopy with white light or chromoendoscopy over EUS for EGC [93]. This could be attributed to several factors, including the presence of ulceration, tumor size, and grade of differentiation. Due to these factors, in East Asia, endoscopic resection rather than EUS is considered the primary staging procedure for EGC [94], but in Western countries, EUS is still recommended for patients without evidence of metastatic disease in assessing for submucosal invasion [85, 95, 96].

Ding Shi et al. reported a moderate diagnostic value for T-staging in EGC with sensitivity (87%), specificity (67%), positive likelihood ratio (2.90), negative likelihood ratio (0.17), and diagnostic dominance ratio (18.25) of EUS. EUS resulted in overstaging of mucosal and submucosal lesions in 13.1% and 32.8%, respectively, while the overall understaging of submucosal lesions was 29.7%. Subgroup analysis revealed tumor size, shape, differentiation, and type of probe used were the factors affecting the accuracy of EUS [97].

The risk of lymph node metastasis guides management options, wherein a negligible risk favors endoscopic resection over surgery. The risk of lymph node metastasis is 1% in pT1a lesions and <3% in pT1b (pathological [p] stage) and endoscopic resection is comparable to surgical resection in early disease, achieving similar outcomes and long-term survival [11, 98–100]. In EGC, endoscopic resection serves the dual purpose of staging and curative resection. ESD is favored over EMR in EGC as it achieves higher en bloc resection, histological complete resection, and lower recurrence rate [98, 101, 102].

M-Staging

The overall sensitivity for EUS in M-staging is 72.2% [86] and is mainly indicated for assessment of malignant ascites, pleural effusion, or metastasis in distant nodes, which can be missed on staging CT [77, 90, 103].

Comparison with Other Modalities

In addition to EUS, other staging modalities include multidetector CT (MDCT), FDG-PET, and MRI. There is no gold standard for staging as each has its limitations, and thus should complement one other to formulate a therapeutic plan.

MDCT is the primary tool for evaluating metastatic burden [104–106]. For detecting distant peritoneal metastasis, CT showed a pooled sensitivity and specificity of 33% and 99% compared to EUS (34%, 96%), FDG-PET (28%, 97%), and conventional ultrasound (9%, 99%), respectively [107].

EUS with or without FNA is more accurate than conventional CT for locoregional staging (T-stage and N-stage) [108]. With increased use of MDCT, there has been improved tumor delineation and thus overall accuracy compared to conventional CT, showing an overall accuracy of 80% and stage-specific accuracy of 75–84.5% for MDCT [92, 109]. Kwee et al. reported diagnostic accuracy range of T-staging with EUS (65–92.1%), CT (77.1–88.9%), and MRI (71.4–82.6%), respectively [106]. Thus, the accuracy of EUS and MDCT in recent studies is comparable and should be utilized on a case-by-case basis [110].

PET-CT is used in cases of distant lymph node metastases when the findings of CT are equivocal as it carries a high positive predictive value (>90%) but low sensitivity (41–80%) for nodal involvement [111, 112]. MDCT and PET further assist in diagnosis of visceral metastasis and are preferred over EUS [113].

The role of MRI in gastric cancer staging has been limited by the small number of studies and technical challenges. However, with technological improvements, MRI shows promise in the near future as a potent imaging modality [114].

EUS After Neoadjuvant Chemotherapy

Following neoadjuvant chemotherapy, EUS is not considered as reliable. Prior studies report accuracy for T-staging ranges from 47 to 63% and for N-staging from 39 to 53% [115, 116]. A prospective study by Bohle et al. with 67 patients who underwent EUS for TN-staging before and after neoadjuvant therapy showed a poor concordance between endosonographic and pathological TN stage. However, they identified findings on sequential EUS that could be used for the prediction of prognosis—low endosonographic tumor stage (T0–2) and a maximal tumor thickness of <15 mm after chemotherapy [117].

Special Considerations

Linitis Plastica

Linitis plastica (LP) is an aggressive subtype of gastric cancer with an ominous prognosis. It is known to affect deeper gastric layers (submucosal or muscle layers), and endoscopically presents as diffusely thickened gastric folds, with inability to expand the stomach on insufflation. Endoscopic biopsies carry a high false-negative rate up to 30% due to the aforementioned factors and absence of obvious endoluminal lesion [118, 119]. Some of these limitations are overcome by the use of EUS, which can accurately assess the thickness of gastric layers in staging and surveillance. EUS accuracy in LP is 64–92% for T-staging and 50–90% for N-staging [120, 121]. EUS examination shows loss in demarcation between normal gastric layers, which is replaced by homogeneous thickening of all layers. This is more prominent in the second to fourth layers.

Limitations of Staging EUS

- Differences in technology and EUS equipment across centers with interobserver variability in interpreting EUS findings may lead to inaccurate diagnosis, resulting in over- or understaging.
- Difficulty in differentiating malignant from benign inflammatory lymph nodes.
- Stenotic esophageal lesions carry a higher risk of esophageal perforation [122] and inability to traverse beyond the lesion with echoendoscope, thus limiting T-staging.
- Less sensitive in superficial tumors or cases of isolated mucosal thickening, [16] and may result in overstaging in early disease [24, 27]. This may be overcome by using high-frequency catheter probes, but these are not as accurate in locoregional staging.
- Limited accuracy after nCRT due to mucosal changes following therapy and inability to differentiate tumor from inflammatory tissue.
- Inability to visualize distant lymph nodes and metastases.

Conclusion

EUS is a useful tool for locoregional staging in gastric and esophageal cancer. Clinicians must be cognizant of its indications, advantages, and diagnostic performance limitations in order to maximize its use and complement other modalities when necessary.

Chapter Questions

1. All of the following patient characteristics have been associated with increased risk of esophageal adenocarcinoma except:
   A. White race
   B. Male gender
   C. Obesity
   D. Diet low in fruits and vegetables

Answer: D. White race, male gender, and obesity all have been associated with increased risk of esophageal adenocarcinoma. A diet low in fruits and vegetables has not been shown to increase the risk of esophageal adenocarcinoma.

2. All of the following patient characteristics have been associated with increased risk of gastric cancer except:
   A. Male gender
   B. High salt intake
   C. Helicobacter pylori infection
   D. Previous gastric surgery

Answer: A. High salt intake, previous *H. pylori* infection, and previous gastric surgery all have been associated with increased risk of gastric cancer. Male gender has not been shown to increase the risk of gastric cancer.

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Minimally Invasive Esophagectomy

24

Navjit Dharampal, Michael N. Tran, Ninh T. Nguyen, and Brian E. Louie

Objectives

1. Review brief history of minimally invasive esophagectomy (MIE)
2. Outline indications for MIE
3. Understand technical operative steps for completing MIE
4. Review variations of MIE
5. Review outcomes of MIE

Introduction

Esophageal resection via an open approach was first described in 1913; however, the conduit was constructed with a rubber tube rather than with native tissue [1]. From this historic operation, there has been significant progress in the surgical management of esophageal cancer, including the advent of minimally invasive techniques. There are three main surgical approaches to complete the objectives of resecting and reconstructing the esophagus: transhiatal, Ivor Lewis, and McKeown esophagectomies. Each of the components of these operations can be performed minimally invasively, which constitute a minimally invasive esophagectomy (MIE) [2]. Furthermore, the thoracoscopic and laparoscopic approaches can be completed on the robotic platform. The narrowest definition of MIE is one that removes part or all of the esophagus, and does not retract, lift, spread, or remove any part of the chest or abdominal wall; and the surgeon's and assistant's vision of the operative field is via a monitor, with the patient's tissue only manipulated by instruments that are controlled by the operating surgeon or team, except when a neck incision is used [2].

The history and evolution of minimally invasive esophagectomy (MIE) have been described elsewhere and are beyond the scope of this chapter. With the progress in thoracic surgery, the postoperative mortality following esophagectomy has dropped dramatically. Overall mortality following esophagectomy was reported at 29% in 1960–1979, 13% in 1980–1988, and 6.7% in 1990–2000 [3, 4]. More recent studies have reported a perioperative mortality less than 2% [5, 6]. Some of this decline in perioperative mortality has been associated with the wider application of minimally invasive techniques, earlier detection of perioperative complications, and improved critical care management. This chapter will focus on the techniques and outcomes of minimally invasive Ivor Lewis esophagectomy as it is the most performed operation and discuss other MIE variations.

Indications

The indications for esophagectomy, including MIE, can be divided into two general categories: benign and malignant disease. Esophagectomy for benign disease is often due to end-stage disease in which other treatments have failed and/or the patient has lost esophageal function. Benign esophageal diseases requiring resection can be further divided into three major categories: obstruction, perforation, and dysmotility [7]. MIE for malignant disease is predominantly for esophageal or gastric cardia malignancy with esophageal involvement. The most common malignant indication is cancer of the lower third of the esophagus with or without involvement of the gastroesophageal junction.

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Preoperative Evaluation

Preoperative evaluation for MIE involves two components. The first component is when the indication is malignant disease. The preoperative evaluation includes endoscopic ultrasound (EUS) and PET-CT scan. Additional oncological studies may include bronchoscopy if the tumor is near the left or right main stem bronchus, MRI of the brain when neurological symptoms are present, and diagnostic laparoscopy when the bulk of tumor is contained in the gastric cardia. In patients with benign disease, a CT chest and abdomen is usually sufficient to provide anatomic detail of the areas impacted by surgery. Occasionally, an anatomic variant such as a retroesophageal innominate artery or right-sided aortic arch will be revealed. The second component involves the assessment of the patient's physiologic status. This includes pulmonary function testing, cardiac evaluation with stress testing, and/or echocardiogram and laboratory testing to include nutritional parameters to ensure the patient's nutritional status is satisfactory. Beyond these studies, any additional studies will depend on the patient's history of comorbidities. In patients with a limited performance status, prehabilitation with a physiatrist and physical therapist is encouraged since outcomes are improved when this aspect of care is included [8].

Operative Technique

There are two phases for the minimally invasive Ivor Lewis esophagectomy: laparoscopy and thoracoscopy. Each of these can be completed via laparoscopy or the robotic platform. The port placement will vary but the operative steps remain the same. A McKeown esophagectomy will require first thoracoscopy followed by laparoscopy and a third phase through the left neck where proximal esophageal dissection and the cervical anastomosis are completed.

Laparoscopic Phase

Positioning

The patient is placed in either supine or lithotomy depending on surgeon preference. If supine positioning is used, the surgeon operates from the patient's right side. If lithotomy is chosen, the surgeon operates from between the legs of the patient.

Port Placement

An array of port configurations can be utilized for the laparoscopic component of MIE. In short, the port placement depends on surgeon preference and the patient's body habitus. Most commonly, five ports are used for the laparoscopic portion of the MIE. If necessary, an additional sixth port is often placed at the right lower quadrant for passing an endo-GIA stapler for conduit creation. The ports used by the authors are depicted in Fig. 24.1. Following the insertion of the initial port, all subsequent ports are placed under direct visualization, each at least a hand's breadth from each other for favorable ergonomics. A Nathanson liver retractor is used by some of our authors to reflect the left lobe of the liver away and obtain clear exposure of the diaphragmatic hiatus, which is placed through a 5 mm subxiphoid incision. A snake liver retractor is also utilized by some authors and is placed through a right lateral 5 mm port and secured to the table with Martin's arm device. Other liver retractors may also be used (fan, LiVac) to achieve exposure of the hiatus. The abdomen is insufflated to a pressure of 15 mmHg with a flow of 40 L/min during the laparoscopic phase.

Diagnostic Laparoscopy

The abdominal cavity should be adequately evaluated to identify any contraindications to resection following insufflation even if done during staging. Specifically, the presence of peritoneal, omental, or other metastatic diseases (with particular focus on diaphragmatic and hepatic surface implants) should be ruled out. Other areas to examine include the celiac axis and gastrohepatic ligament to evaluate for fixated nodal involvement. Examination of the gastroepiploic artery should be performed early to establish its position relative to the greater curve of the stomach and ensure an adequately visible pulse.

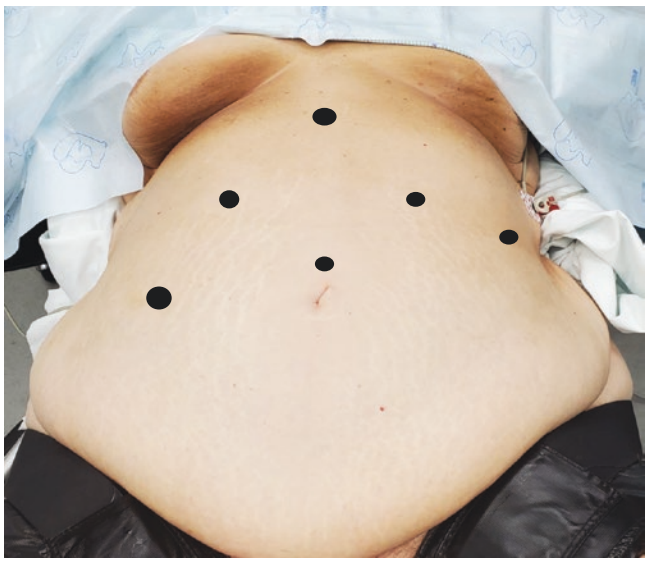

Fig. 24.1 Ports for laparoscopic stage of minimally invasive esophagectomy

Hiatal Dissection and Lymph Node Dissection

Opening of the gastrohepatic ligament at the pars flacida from near the anterior aspect of the right crura inferiorly to just above the right gastric artery is the initial step necessary to expose the right crus and celiac axis. This dissection is carried out close to the liver to include all pertinent fibrofatty, perigastric tissue as the right crus is approached, specifically when completing an oncological resection. The mobilization is typically continued anteriorly, working in a clockwise manner circumferentially around the anterior hiatus, and then down the left crus. A Penrose drain can be used to encircle the esophagus to provide traction. The phrenoesophageal ligaments are also divided. Some authors argue the phrenoesophageal ligaments should be kept intact to maintain pneumoperitoneum; however, in our experience this has not proven to be an issue prohibitive to the conduct of the operation in a minimally invasive fashion.

Following the initial hiatal dissection, the left gastric artery and vein pedicle are identified. Using a blunt-tipped laparoscopic grasper from the lateral-most assistant port (on the patient's left side), the lesser curve is elevated laterally and toward the anterior abdominal wall. This maneuver places the left gastric artery on adequate tension and allows the base to be easily visualized. At this point using an appropriate energy device or careful monopolar electrocautery, the abdominal lymphadenectomy is started by incising the peritoneum along the superior border of the pancreas at the base of the left gastric vein. This lymphadenectomy is typically continued first, along the splenic artery, and includes the fatty tissue along the superior border of the pancreas out to the superior aspect of the splenic and second along the common and proper hepatic artery to resect the nodes along these vessels, and the celiac nodes around the left gastric and the tissue between the right crura and the left gastric artery. Once the left gastric artery and vein are skeletonized of surrounding tissue and circumferentially dissected, they are divided with a laparoscopic vascular staple load (Fig. 24.2). We routinely ensure a visible pulse is present in the hepatic and splenic artery before the stapler is fired. We prefer to perform this portion of the gastric mobilization prior to addressing the greater curvature dissection as some of the CO_2 insufflation is introduced into the lesser sac facilitating entry into the correct plane during the subsequent step. Dissection along the splenic artery to the hilum of the spleen is often facilitated by division of the left gastric artery and vein.

If the hiatal dissection has not been completed above due to tumor and exposure, dissection after division of the left gastric artery will continue cephalad to expose the entirety of left crus and then the decussation of the left and right crus. Further dissection toward the spleen is often helpful to release the retrogastric attachments along the left crus. If the periesophageal plane does not develop due to either tumor involvement or post-induction fibrosis, there should be no hesitancy to resect some hiatal crural muscle fibers to ensure an R0 resection. At this point, the entire esophagus should be free and encircled, usually with a Penrose drain. Further dissection into the mediastinum is not performed at this time as inadvertently entering the pleural space may lead to laxity of the hemi-diaphragm(s) and lead to suboptimal visualization and, potentially, cardiopulmonary effects.

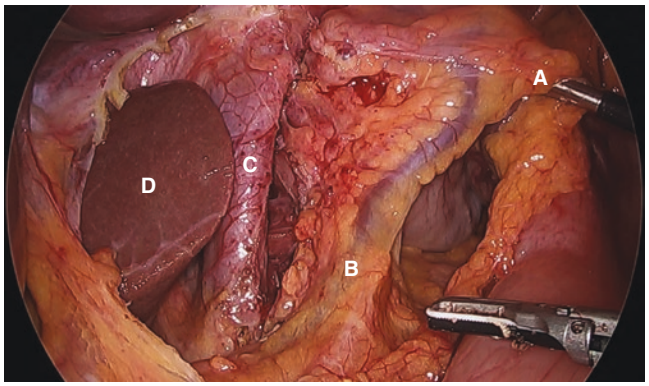

Fig. 24.2 Lesser curve retraction (**a**) laterally and anteriorly toward the abdominal wall. This maneuver places the left gastric artery (**b**) on tension and allows its base to be easily visualized. Right crura (**c**) and caudate lobe of liver (**d**)

Gastric Mobilization

Next, attention is moved toward the greater curvature dissection. Using a "minimal touch" technique, a window in the gastrocolic ligament (greater omentum) adjacent to the colon is created to enter the lesser sac. Entry into the correct plane can be difficult during this step in obese patients who have a large amount of omental fat. Care must be taken to ensure the transverse mesocolon is not violated. It is crucial during this step to protect the right gastroepiploic artery from any trauma as it forms the sole blood supply to the gastric conduit. We aim to stay at least 3–4 cm away from the gastroepiploic vessel by staying adjacent to the colon, which serves the dual purpose of protecting the feeding vessel from trauma as well as preserving omentum to be used as a buttress for the esophagogastric anastomosis. Once the lesser sac is entered, the greater curvature dissection is carried cranially toward the inferior tip of the spleen. Eventually the gastroepiploic artery fades out and the short gastric vessels are reached at this landmark. The short gastric vessels are similarly divided with the energy device staying close to the hilum of the spleen. After this dissection is completed, the stomach is atraumatically retracted toward the patient's right and anteriorly. Often a second Penrose drain is placed around the body of the stomach and retracted using the low right-sided port. This places the retrogastric attachments on tension and allows them to be divided. Dissection is then carried through the gastrocolic ligament toward the pylorus. One must be exceedingly careful during this portion of the dissection as

injury to the proximal right gastroepiploic artery may completely devascularize the gastric conduit. The latter part of this dissection can be particularly difficult in patients with a history of pancreatitis or prior biliary tract procedures, most commonly a cholecystectomy.

Adequate mobilization can be estimated by ensuring the pylorus easily reaches the hiatus. A Kocher maneuver is rarely required. At this point, the stomach should be completely mobilized and gastric conduit creation proceeds.

Conduit Creation

We begin our conduit creation at the level of the crow's foot on the lesser curvature. The initial staple fire is a vascular load to divide the lesser curvature fat pad coming across the "crow's foot" toward the lesser curve edge (Fig. 24.3). The next staple fire will be onto the gastric cardia with an appropriately sized tissue staple load. During the initial gastric staple fire, the stomach is put on stretch to ensure a straight conduit and prevent spiraling of the conduit. This is facilitated by having the assistant grasp the top of the fundus (preferably an area that will be resected) and retract toward the left upper quadrant. At the same time, countertraction toward the patient's right lower quadrant is applied via the second Penrose drain placed around the stomach (Fig. 24.4). With the stomach on appropriate tension, the gastric conduit staple line is continued with serial staple fires toward the fundus, with each fire being parallel to the greater curvature. We aim to create a conduit approximately 4–5 cm in width, which is estimated by placing marks 4 cm from the greater curve to the lesser curve all along the greater curve (Fig. 24.3). The retraction and countertraction needs to be adjusted throughout the conduit creation to maintain a straight, nonspiraled conduit and prevent "accordioning" of the stomach.

Some surgeons prefer to incompletely transect the conduit from the specimen to facilitate transposition of the conduit into the chest during the next phase of surgery. Alternatively, the conduit can be divided from the specimen and loosely reattached with interrupted sutures. The staple line along the gastric conduit can be oversewn with a running suture at the discretion of the surgeon.

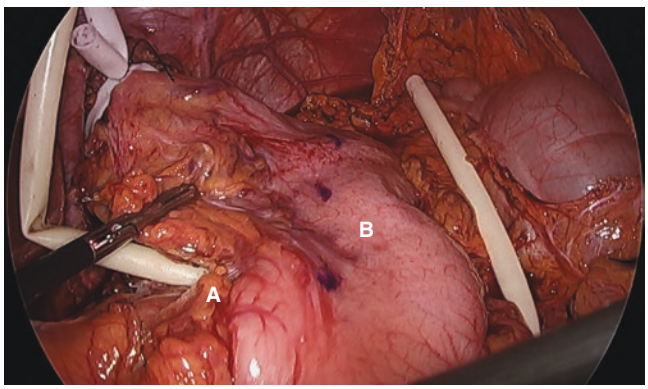

Fig. 24.3 Conduit creation begins at the level of the Crow's foot (**a**) on the lesser curvature after 4 cm marks (**b**) from the greater curve are made along the stomach as our planned staple line

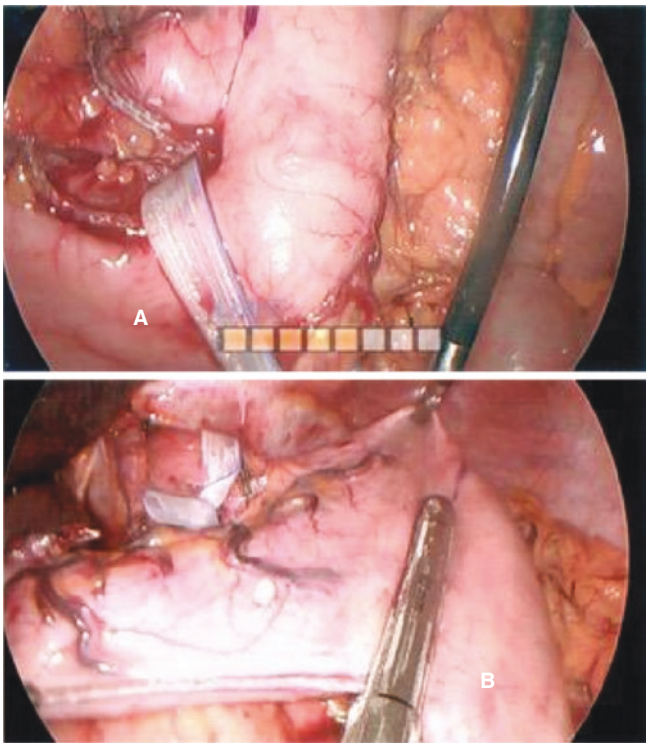

Fig. 24.4 A Penrose drain is looped around the conduit (**a**) and used to hold traction down to the patient's RLQ, to straighten the conduit (**b**) during stapling

Pyloric Drainage Procedure

Pyloric drainage (pyloroplasty, pyloromyotomy, Botox) at the time of esophagectomy is controversial and remains the choice of the operating surgeon as the authors here use varying approaches including pyloromyotomy (BL) and no drainage procedure (NN/MT).

Placement of Feeding Jejunostomy Tube

Routine placement of a feeding jejunostomy tube at the time of esophagectomy has previously been the standard of care due to concerns regarding anastomotic leak due to early feeding and complications relating to total parenteral nutrition [9]. If the surgeon elects to create a feeding jejunostomy, this can be completed via laparoscopy or small (<5 cm) access incision. We routinely place a feeding jejunostomy tube with a Witzel tunnel during esophagectomy and have found them to be beneficial.

Mediastinal Dissection

With most of the abdominal portion of the operation complete, downward retraction on the Penrose surrounding the esophagus to perform a lower mediastinal dissection is done.

We aim to include within our specimen all fibrofatty and lymph node tissue anterior to the aorta and spine posteriorly to the posterior aspect of the pericardium. Similarly, the associated left and right pleural envelopes are included in this dissection.

Conclusion of Laparoscopic Component

Prior to closing the abdomen, it is crucial to evaluate and maintain proper orientation of the conduit. The Penrose drain is placed in the mediastinum for later retrieval during the thoracoscopic portion. A JP drain is placed through the hiatus into the left pleural space if that was inadvertently entered during the mediastinal dissection. The hiatus is assessed to ensure it can accommodate the removal of the specimen. If the hiatus is enlarged, then it can be closed with one or two sutures. If the hiatus is too small for the specimen, then partial division of the right crus may be needed to ensure adequate pull-through without resistance or kinking of the conduit. Hemostasis is checked and ensured. The liver retractor is removed, and the abdominal ports are closed.

Thoracoscopic Phase

Positioning and Port Placement

Once the abdominal portion of the procedure is complete, the single-lumen endotracheal tube, if present, should be exchanged for a double-lumen endotracheal tube (DLT) in preparation for single-lung ventilation and confirmed its position with fiberoptic bronchoscopy. The patient is placed in the lateral decubitus position with the right side up. The patient is tilted slightly anteriorly to expose the posterior mediastinum. The patient should be adequately secured while preventing pressure points.

The arrangement of port placement depends on surgeon preference with some using four or five ports. An example of one of our author's configurations is presented in Fig. 24.5.

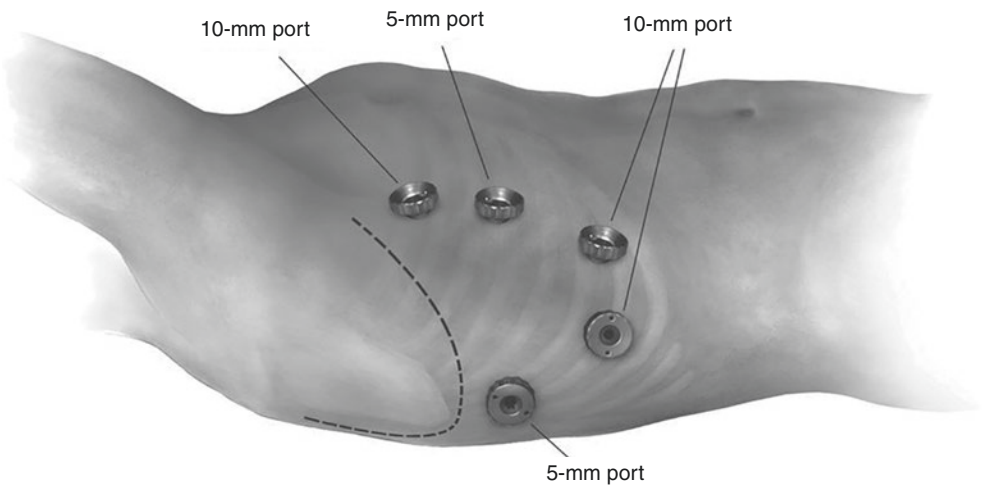

Fig. 24.5 Thoracoscopic port placement for MIE. (From Tsai WS, Levy RM, Luketich JD. Technique of minimally invasive Ivor Lewis esophagectomy. Oper Techn Thorac Cardiovasc Surg 2009;14:176–92)

Esophageal Dissection

Prior to mobilization of the intrathoracic esophagus, a retraction suture can be placed through the tendinous portion of the diaphragm to allow downward retraction and subsequent exposure of the distal esophagus when visualization is limited. The inferior pulmonary ligament is divided into the inferior pulmonary vein and level 9 lymph nodes are harvested. With adequate mediastinal dissection previously completed from within the abdomen, the Penrose drain is often easily identified once the inferior pulmonary ligament is taken down. The lung is retracted anteriorly while the esophagus is retracted posteriorly to allow this dissection to continue along the pericardium (Fig. 24.6). The posterior mediastinal pleura is opened superiorly until the inferior border of the azygos vein. Dissection of the pleura overlying the esophagus is then transitioned inferiorly within the posterior groove of the esophagus just anterior to the azygos vein, leaving some pleura adherent to the specimen. A subcarinal lymph node dissection should be performed at this point. Next, the azygos vein is divided with a 45-mm vascular staple load. The thoracic esophagus is completely mobilized circumferentially to a level just cephalad to the divided azygos vein.

Several areas of caution during the intrathoracic esophageal dissection deserve special mention. Firstly, care must be taken regarding the position of the airway to prevent injury to the membranous portions of the right and left mainstem bronchi. Secondly, dissection posterior to the esophagus and adjacent to the thoracic aorta can cause an injury to the thoracic duct. While it is not our practice to routinely perform thoracic duct ligations, it is completed by en mass ligatures at the aortic hiatus when the duct is seen and chyle is identified. Generous use of metal clips is recommended to clip large lymphatics especially near the azygous arch where the thoracic duct crosses the mediastinum and any aortoesophageal vessels. Lastly, the vagal nerves are identified and divided below the carinal level to minimize postoperative cough.

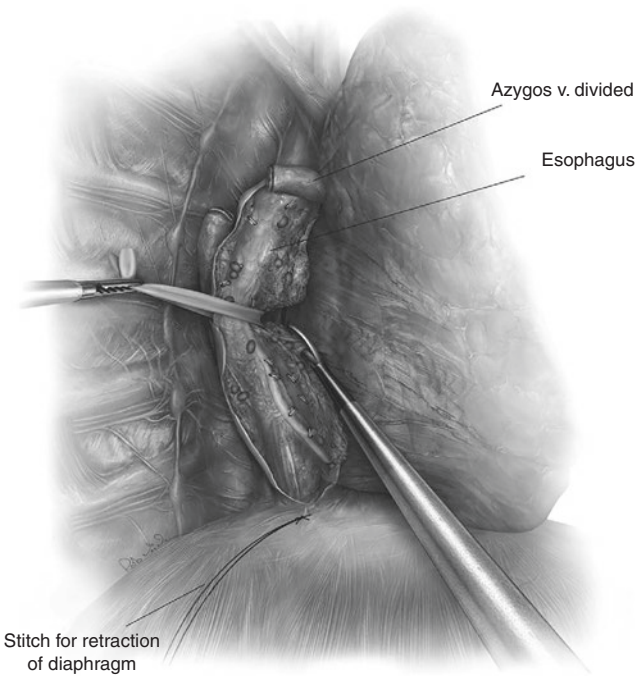

Fig. 24.6 Thoracoscopic esophageal mobilization. (From Tsai WS, Levy RM, Luketich JD. Technique of minimally invasive Ivor Lewis esophagectomy. Oper Techn Thorac Cardiovasc Surg 2009;14:176–92)

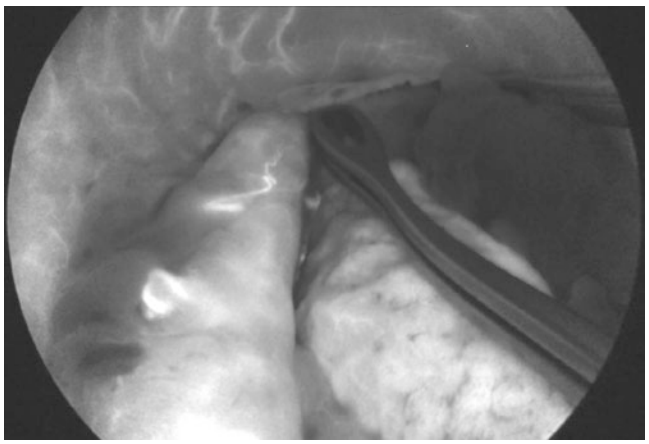

Fig. 24.7 Indocyanine green (ICG) showing the adequate vascular supply of the conduit

Once the intrathoracic esophagus has been adequately mobilized, the gastric conduit and the esophageal specimen are gently brought into the chest and the remaining gastric bridge or sutures between the specimen and the conduit are divided. The conduit is then laid next to the mobilized thoracic esophagus. The surgical team must be vigilant in maintaining proper orientation of the conduit to prevent torsion. The staple line of the gastric conduit should be facing laterally (toward the ceiling of the operating room).

The vascularity of the conduit is assessed. This can be completed by visual inspection or perfusion imaging using indocyanine green (ICG). The authors prefer to use fluorescence imaging by injecting ICG to assess the conduit vascularity (Fig. 24.7). Multiple studies have shown visual inspection may underestimate the extent of conduit ischemia compared to ICG imaging. A systematic review and meta-analysis of ICG for esophagectomy showed a 25% rate of change in the management of the anastomosis with this technology when used intraoperatively [10].

Areas of decreased vascularity are noted on the gastric conduit and the site of the anastomosis selected based on vascularity. It is important to balance a tension-free anastomosis without bringing too much conduit into the chest. A redundant conduit should be avoided as it tends to lead to functional and emptying issues in the postoperative course. If there is redundant conduit, it is best to remove the excess tip of the conduit, which would minimize emptying issues and remove the most ischemic portion of the conduit. The proximal esophagus is divided with an endo GIA stapler ideally above the level of the azygos vein and as high in the chest as the gastric pull-up will allow based on the vascularity assessment taking into consideration that the proximal extent of dissection is dependent on the indication for esophagectomy. The esophagogastric specimen is removed through the low anterior access incision using a bag or through a wound protector. The proximal and, if needed, distal margins are sent for frozen section.

Thoracic Anastomosis

Once adequate margins are confirmed by pathology, the esophagogastric anastomosis is constructed. Two of the more common techniques used are the circular anvil stapler or hand-sewn end-to-side esophagogastrostomy with or without linear stapler.

When a circular stapler is used, it is completed using the OrVil 25-mm anvil and the EEA XL circular stapler (25-mm with 4.8-mm staples) to complete the intrathoracic anastomosis. Briefly the anvil-orogastric tube device is passed transorally by the anesthesiologist until the surgeons can visualize it abutting the esophageal staple line. A small esophagotomy is made and the attached orogastric tube is retrieved. With careful coordination between the surgeon and anesthesiologist, the Orvil is seated within the proximal esophageal stump. A purse string may be used to tighten the esophagotomy around the Orvil if necessary. The staple line is incised and removed around the tip of the conduit through which the EEA stapler is placed into the conduit and positioned for the anastomosis (Fig. 24.8). The stapler spike should be brought out through the greater curve of the stomach, again maintaining appropriate orientation of the conduit to prevent twisting. After the stapler spike and anvil are connected, the stapler is fired and donuts from the anvil should be assessed for completeness. Once the anastomosis has been created, the excess

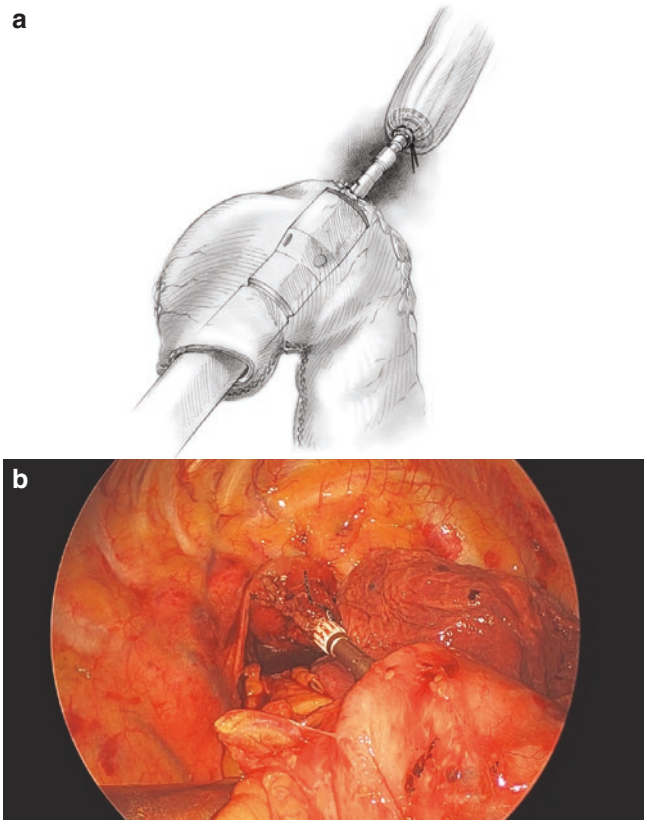

Fig. 24.8 Creation of esophagogastric anastomosis: (**a**) schematic from Levy RM, Trivedi D, Luketich JD. Minimally invasive esophagectomy. Surg Clin North Am. 2012 Oct;92(5):1265–85; (**b**) intraoperative photo

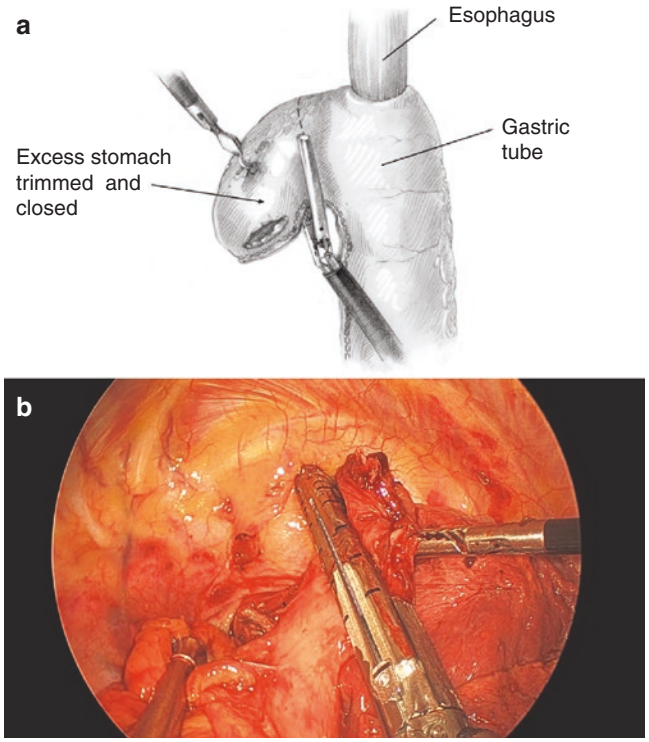

Fig. 24.9 Resection of gastric fundic tip: (**a**) schematic from Levy RM, Trivedi D, Luketich JD. Minimally invasive esophagectomy. Surg Clin North Am. 2012 Oct;92(5):1265–85; (**b**) intraoperative photo

gastric fundus should be trimmed using an Endo GIA stapler (which will include the gastrotomy) as seen in Fig. 24.9. It is important to mention that this staple line should not be too close to the anastomotic staple line as the small bridge of interposing stomach can be at risk for ischemia. We aim to have a minimum of 1 cm of tissue between these staple lines. We recommend reinforcing the anastomotic staple line with four interrupted imbricating 2–0 silk sutures at the intersecting staple lines and anterior and posterior.

When a hand-sewn anastomosis is performed, it can be completed in an end-to-side fashion with interrupted horizontal mattress or Connell sutures using the Endostitch and 2-O Surgidac. The sutures are then tied down with the Ti-KNOT device (LSI solutions). After completion of the posterior row of sutures, the nasogastric tube is placed across the anastomosis and into the conduit under direct visualization. The anterior row of sutures is then placed but not immediately tied down. Once all the sutures for the anterior row are placed, the sutures are then tied down the Ti-KNOT device. A hybrid option is to use a linear stapler between the esophagus and greater curve of the stomach with closure of the esophagogastrostomy with interrupted sutures. The final configuration of the neo-esophagus and anastomosis is shown in Fig. 24.10.

Finally, the anastomosis is wrapped with the omental flap mostly to interpose tissue between the conduit and the airway (Fig. 24.11). Endoscopic evaluation is often used to confirm patency of the anastomosis. Air is insufflated via the endoscope with the anastomosis submerged under irrigation fluid to confirm no areas of leakage. A nasogastric tube is passed through the anastomosis during endoscopy. Two drains are placed within the pleural cavity: a chest tube within the pleural space as well as a soft round Blake drain adjacent to the gastric conduit.

Variations of Minimally Invasive Esophagectomy

There are several permutations that may constitute MIE. A recent paper has attempted to provide a nomenclature for these various options and is shown in Table 24.1 [2]. In the strictest of definitions, hybrid approaches such as open thoracotomy and laparoscopy are not considered as MIE and are not included.

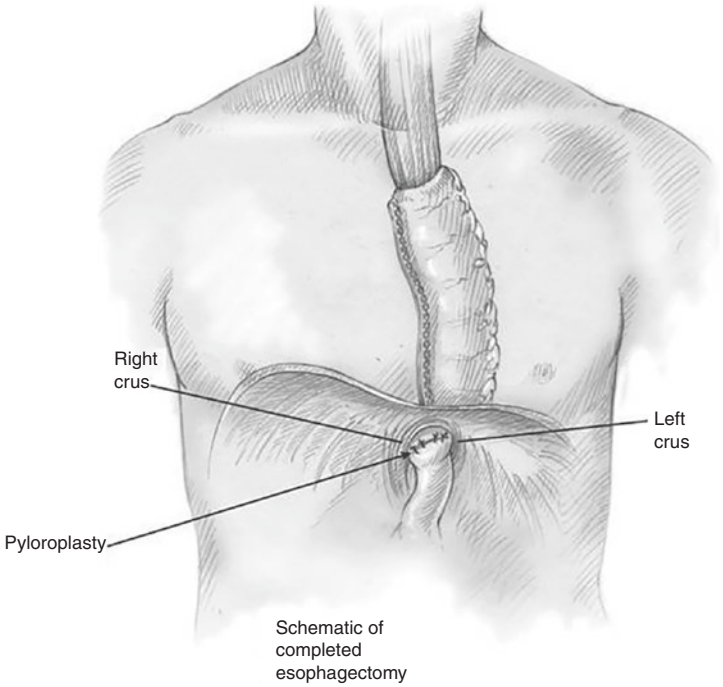

Fig. 24.10 Completed Ivor Lewis reconstruction. (From Levy RM, Trivedi D, Luketich JD. Minimally invasive esophagectomy. Surg Clin North Am. 2012 Oct;92(5):1265–85)

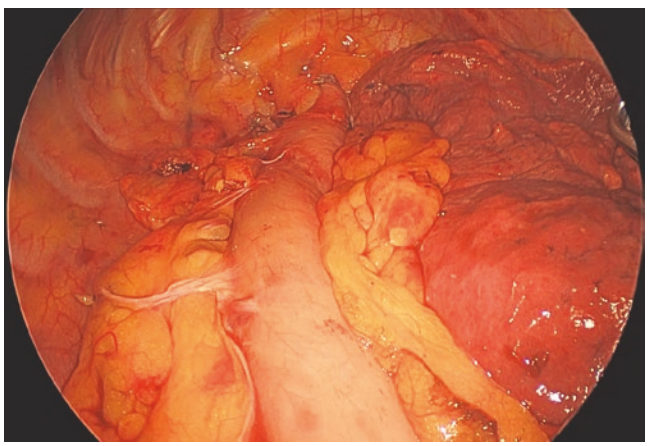

Fig. 24.11 Portion of omental placed between conduit and airway

Table 24.1 Versions of minimally invasive esophagectomy

Transhiatal using laparoscope in abdomen
Transhiatal using robot in abdomen
Ivor Lewis using a robot in abdomen and VATS in chest
Ivor Lewis using robot in abdomen and robot in chest
Ivor Lewis using laparoscope in abdomen and VATS in chest
McKeown using laparoscope in abdomen and robot in chest
McKeown using laparoscope in abdomen and VATS in chest
McKeown using robot in abdomen and robot in chest

Minimally Invasive Ivor Lewis Esophagectomy

The operation described above is a completely minimally invasive Ivor Lewis esophagectomy with an intrathoracic esophagogastric anastomosis. Variations of this operation can be a combination of laparotomy with thoracoscopy or laparoscopy with thoracotomy. These techniques are referred to as hybrid MIE. The advantages of Ivor Lewis MIE are lower rate of anastomotic leak and recurrent laryngeal nerve injury compared to operations with a cervical anastomosis. The disadvantages include requirement for single-lung ventilation.

Minimally Invasive Three-Field McKeown Esophagectomy

In this version of MIE, the thoracoscopic dissection described above is completed first in the left lateral decubitus position with a double-lumen endotracheal tube. Esophageal mobilization is completed up to the thoracic inlet proximally and to the hiatus distally. Once the intrathoracic phase of the operation has been completed, the patient is placed in supine position and the double-lumen tube is exchanged for a single-lumen tube. The abdominal phase of the procedure is completed as described above. The specimen is extracted from left neck incision and the conduit is also brought up to the neck through this incision. A stapled or hand-sewn anastomosis is completed through the left neck as has been described previously by Orringer [11].

Minimally Invasive Transhiatal Esophagectomy

This version of the MIE begins similarly to Ivor Lewis MIE with laparoscopy. The esophageal dissection is continued through the hiatus under direct visualization to the level of the left mainstem bronchus. If further mediastinal dissection is required, a Gel-hand port can be placed in the upper abdomen to facilitate adequate esophageal mobilization [12]. The specimen is again brought to a left neck incision where the

anastomosis is created (hand sewn or stapled). This option is also considered as a hybrid MIE.

Two-Stage Procedures

Some surgeons elect to complete the laparoscopic portion of the MIE in two procedures. During the first operation, the patient undergoes diagnostic laparoscopy, staging, hiatal dissection, and laparoscopic insertion of feeding jejunostomy. The surgeon then proceeds with the resection and reconstruction on a separate date.

Special Considerations

The most common approach to the reconstruction aspect of esophagectomy involves utilizing the stomach as a conduit. Patients with previous gastric surgery present a unique technical challenge that needs attention during resection and reconstruction. Two patient populations in which this issue may arise are those with previous antireflux or bariatric surgery.

A previous antireflux operation is not a contraindication to MIE. Several reports and series have been published, which indicate the stomach can still be used as a conduit even if it has previously been incorporated into an antireflux procedure. The rate of postoperative morbidity, including pulmonary complications, anastomotic leak, and need for reoperation, may be higher in these patients compared to esophagectomy without previous ARS [13]. This is likely since patients undergoing esophagectomy following ARS have had significant complications, which render the esophagectomy more complex. Due to potential disruption of gastric vascular supply during ARS, experts would argue ICG imaging should be used routinely in these patients to ascertain the viability of the conduit [14].

The two most common bariatric procedures performed in the United State are laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB). Obesity is a risk factor for the development of esophageal cancer, and thus patients requiring esophagectomy may present with altered gastrointestinal anatomy.

In an LSG, a lateral gastrectomy is performed, and the remaining gastric sleeve is reliant on the right and left gastric arteries. As the left gastric artery is divided during an esophagectomy, the altered blood supply poses significant risk to the gastric conduit that would be solely dependent on the right gastric artery. In most circumstances, however, the stomach should be considered an inadequate conduit due to compromised vascular supply; this necessitates an alternative conduit choice, such as colon or jejunum, and would likely require an open approach.

In patients with a prior Roux-en-Y gastric bypass, the gastric remnant can be isolated and be used as the gastric conduit. The Roux limb is transected immediately above the jejunojejunostomy and removed. The entire gastrojejunal complex is also removed with the surgical specimen. The gastric remnant should be fashioned to the appropriate conduit size and diameter. The gastric remnant can be sutured to the esophageal specimen in preparation for gastric pull-up.

Postoperative Management

Most high-volume centers performing MIE have site-specific pathways for postoperative management of these patients. The pillars of postoperative care of these patients include early mobilization, adequate pain control, thorough pulmonary toilet, and timely enteral nutrition. The principles of management of esophagectomy patients have been well described and summarized into an enhanced recovery after surgery (ERAS) protocol [15]. The protocol includes evidence-based recommendations regarding the preoperative, intraoperative, and postoperative periods. Implementation of an ERAS protocol for esophagectomy has been shown to decrease length of stay, pulmonary complications, and cost [16].

Complications

MIE is a complex surgical procedure that is performed in patients who can be subclinically malnourished or have recently completed induction chemoradiotherapy, and thus complications can occur. Postoperative complications following MIE have been difficult to quantify due to the variability in surgical technique and the heterogeneity of what constitutes an MIE. According to the Esophageal Complications Consensus Group, the most common complications of MIE are pneumonia, arrhythmia, anastomotic leakage, conduit necrosis, chylothorax, and recurrent laryngeal nerve palsy [17].

Anastomotic leak rates have improved over time especially with the use of fluorescence imaging and resection of the gastric tip during Ivor Lewis MIE. However, they still occur. The vast majority of options for managing these are now endoscopic with endoluminal stents, vacuum therapy, and other endoscopic techniques. When there is sufficient conduit necrosis that endoluminal therapy is not an option, resection of the necrotic portion, bringing the gastric conduit back down to the abdomen and creation of an esophagostomy, is the appropriate choice with delayed reconstruction when the patient has sufficiently recovered.

Outcomes

Due to the heterogeneity of approaches utilized in completing a minimally invasive esophagectomy, it can be difficult to compare short- and long-term outcomes. Multiple single-arm studies, however, have demonstrated the feasibility and safety of minimally invasive approaches with a length of stay ranging from 5 to 14 days, mortality between 1 and 4% and an anastomotic leak rate between 4 and 12% (Table 24.2).

A 3-year follow-up study of the TIME (Traditional Invasive vs. Minimally Invasive Esophagectomy) trial established minimally invasive esophagectomy as oncologically sound with the overall survival (OS) and disease-free survival (DFS) equivalent to open esophagectomy [18]. A systematic review and meta-analysis of MIE compared to open suggested that MIE may be associated with superior long-term survival; however, it was unclear whether this was due to postoperative events rather than oncological differences [19]. A randomized trial (MIRO) comparing hybrid minimally invasive esophagectomy (laparoscopic abdominal approach with right thoracotomy) and open esophagectomy found slightly improved long-term oncological survival for the minimally invasive approach [20]. In this study, however, this difference was attributed to decreased perioperative complications in the minimally invasive group, specifically pulmonary morbidity.

Table 24.2 Summary of outcomes in large series of MIE

Authors	Year of publication	Number of patients	Years included	Operative technique	Outcomes
Fernando et al	2002	27	1996–2001	– Laparoscopic and thoracoscopic esophagectomy with cervical anastomosis	Mortality rate = 3.7% LOS = 5 days Anastomotic leak = 3.7%
Luketich et al	2003	222	1996–2002	– Laparoscopic transhiatal esophagectomy with cervical anastomosis ($n = 8$) – Laparoscopic and thoracoscopic with cervical anastomosis	Mortality rate = 1.4% LOS = 7 days Anastomotic leak = 11.7%
Nguyen et al	2008	104	1998–2007	– Thoracoscopic/laparoscopic esophagectomy with a cervical anastomosis ($n = 47$) – Minimally invasive Ivor Lewis esophagectomy ($n = 51$) – Laparoscopic hand-assisted blunt transhiatal esophagectomy ($n = 5$) – Laparoscopic proximal gastrectomy ($n = 1$)	Mortality rate = 1.9% LOS = 8 days Anastomotic leak = 9.6%
Ben-David et al	2012	100	2007–2011	– Laparoscopy/thoracoscopy cervical anastomosis – Laparoscopy/thoracoscopy or mini-thoracotomy with intrathoracic anastomosis	Mortality rate = 1% LOS = 7.5 days Anastomotic leak = 4%
Luketich et al	2012	1033	1996–2011	– Laparoscopic and thoracoscopic with cervical anastomosis ($n = 481$) – Laparoscopic and thoracoscopic with thoracic anastomosis ($n = 530$)	Mortality rate = 1.7% LOS = 8 days Anastomotic leak* = 5% *Requiring surgery
Mariette et al	2019	103	2009–2012	– Laparoscopic and right open thoracotomy with thoracic anastomosis	Mortality = 1% LOS = 14 days Anastomotic leak = 11%* *Requiring surgery
Yoshida et al	2020	12,711	2012–2016	– Esophagectomy performed using only thoracoscopy, abdominal portion completed laparoscopically or open	Mortality rate = 0.7% Anastomotic leak = 12.7

Conclusions

Minimally invasive esophagectomy, particularly the Ivor Lewis approach, has rapidly become one of the more common approaches to esophagectomy for distal third and gastroesophageal junction cancers. The switch to a minimally invasive approach has reduced length of stay and allowed patients to recover quicker, while maintaining similar oncological outcomes to open surgery.

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Endoscopic Management of Anastomotic Leaks

25

James M. Ackerman, Ryan M. Levy, and Inderpal S. Sarkaria

Objectives

1. Identify patients suitable for endoscopic management of anastomotic leak
2. Explore common endoscopic therapies
3. Describe postprocedural management

Introduction

Unfortunately, esophagogastric anastomoses sit atop the rest of the alimentary tract, both literally and figuratively, regarding anastomotic complications. In addition to the inherently high-risk nature of a deserosalized and extraperitoneal anastomosis, a multitude of factors, including neoadjuvant therapy, nutrition, medical comorbidities, type of conduit, length of conduit, conduit perfusion, location of anastomosis, anastomotic technique, anastomotic tension, anastomotic adjuncts, and postoperative management, contribute to the 0–53% reported anastomotic leak rate. This highly variable rate prompted multiple groups to create leak classification systems (Tables 25.1 and 25.2). Modern series report leak rates of approximately 5–17% for cervical anastomoses and 2–16% for thoracic anastomoses. No advantage in leak rate has ever been consistently identified between hand-sewn, stapled, or hybrid (stapled and hand-sewn) techniques. Anastomotic leaks are associated with increase in morbidity, length of hospitalization, stricture rate, postoperative dysphagia, and mortality more so if operative intervention is required. As such, a high index of suspicion and vigilance for anastomotic leak is required in the postoperative period to best ensure prompt diagnosis and treatment of these complications.

Table 25.1 Anastomotic leak classification system proposed by Schuchert et al. [6]

Class 1	Radiographic leak only	No intervention
Class 2	Small (<10%) leak	Cervical and/or percutaneous drainage
Class 3	Disruption of anastomosis (10–50%) with perianastomotic abscess and pleural or mediastinal collection	VATS or thoracotomy
Class 4	Gastric tip necrosis with anastomotic separation (>50%)	Surgical resection and drainage

Table 25.2 Anastomotic leak classification system proposed by Esophagectomy Complications Consensus Group (ECCG) 2015

Type 1	Local defect	No change in therapy, Medical treatment, Dietary modification
Type 2	Local defect	Interventional but not surgical therapy
Type 3	Local defect	Surgical therapy

Indications

Any patient suspected of having an anastomotic leak should be further evaluated. In the absence of salivary, bilious, or purulent drainage from wounds or tubes, or radiographic evidence of extraluminal contrast extravasation, the signs of anastomotic leak can be more challenging. Although not directly diagnostic of anastomotic dehiscence, the level of suspicion should be heightened in the setting of new-onset supraventricular arrhythmias, worsening oxygenation, altered mental status, fever, hypotension, oliguria, and/or sepsis. New onset of pneumothorax, hydrothorax, or increase in measured salivary amylase from drainage tubes is also indicative of anastomotic leak.

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Patient Selection and Preoperative Evaluation

When approaching a patient with a possible anastomotic complication, the overall clinical picture and presence of organ failure provide the first branchpoint of the management decision tree (Fig. 25.1). In unstable patients with progressive multiorgan failure, the goal of treatment is to prevent imminent mortality. These patients require emergent, aggressive surgical management and are frequently not candidates for endoscopic management alone. Specific scenarios may exist, however, where endoscopic techniques are used in combination with surgical drainage to stabilize an unstable patient.

Similarly, it is worth briefly mentioning conduit necrosis, which is a separate but related entity that often results in anastomotic leak. Conduit necrosis occurs in 2–13% of patients but is a rapidly progressive and potentially fatal surgical emergency with reported mortality rates as high as 90%. These patients are generally not candidates for endoscopic management of their conduit and often require aggressive surgical resection of devitalized tissue with wide drainage of the mediastinum and pleura. This is frequently a staged, damage-control scenario ultimately resulting in bipolar esophageal exclusion and delayed reconstruction after a significant period of recovery.

In the stable or semi-stable patient, further workup is begun to better characterize the anastomotic complication. Laboratory tests, including hematological and metabolic panels, should be analyzed and blood cultures can be considered. Fluoroscopic esophagram is often utilized to assess the location and size of leak in addition to extraluminal flow of contrast. Computed tomography (CT) scanning aids to identify discrete and/or undrained fluid collections, although the addition of oral contrast can provide similar information to fluoroscopic esophagram. The routine use of endoscopy is institution dependent, but it can offer valuable information about conduit perfusion, presence and extent of necrosis, visualization and quantification of leak, and leak communication with existing drains.

The advent of endoscopic interventions provides a chance to control soilage while salvaging the conduit. Clinically asymptomatic patients with a small, contained radiographic leak may not require specific invasive interventions. In patients with clinical presentation ranging from asymptomatic to symptomatic but not unstable, the role of endoscopic management of anastomotic leak may have the greatest benefit in avoiding the morbidity of more invasive surgical interventions. In patients presenting with a highly unstable clinical picture, the surgeon must use careful judgment in utilizing endoscopic therapies in lieu of surgical options, although combined strategies may have significant value. Regardless, the outcome of the highly unstable and high-risk patient will often be dependent on definitively controlling ongoing sources of sepsis at the time of first intervention.

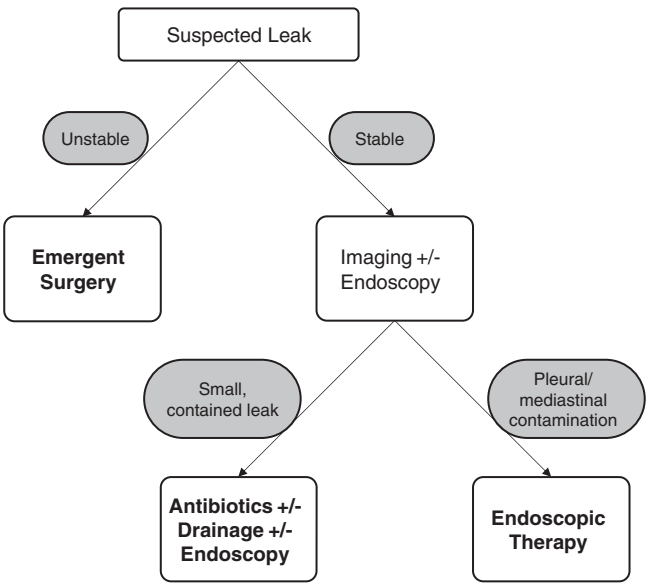

Fig. 25.1 Clinical decision tree on endoscopic-specific management of esophagogastric anastomotic leak. Of note, potential surgical and/or interventional therapy with or without addition of endoscopic management is assumed at all points of the pathway, and should be liberally utilized at the discretion of the surgeon to control foci of ongoing sepsis

General Principles

Some tenets of managing anastomotic leak hold true regardless of the specific treatment strategy. Sepsis should be aggressively managed with broad-spectrum antibiotics, antifungals, and volume resuscitation. The use of vasopressors should be used cautiously, and hypoxia treated aggressively as perfusion to the conduit should be maximized. Caution should be used with noninvasive positive pressure ventilation both due to aspiration risk and conduit distension.

Limiting oral intake with or without nasogastric decompression can be utilized to minimize flow through the anastomotic defect. Nutrition should be optimized, ideally with enteral feeding over parenteral nutrition. If a feeding tube was not placed at the time of esophagectomy, consideration of postanastomotic feeding tube placement should occur at the time of leak diagnosis.

Finally, all leaks and contaminated spaces should be drained. Although intrathoracic anastomoses have a lower leak rate, they are relatively inaccessible compared to cervical anastomoses. For this reason, prophylactic drains are more commonly placed near an intrathoracic anastomosis at the time of index operation in hopes of controlling a potential leak. On the contrary, cervical anastomoses are generally

accessible simply by opening the cervical incision at bedside. In either case, image-guided percutaneous drainage or surgical drainage can be added to control soilage of undrained spaces or collections.

Specific Techniques and Outcomes

Endoscopic Dilation

Early anastomotic dilation is directed at lowering impedance of flow to promote antegrade passage of enteric contents into the conduit rather than through the anastomotic defect. Despite the long history of its use, there has been surprisingly little published about this technique. In small case series, it has been shown to be a safe and effective method of managing leak with a 100% success rate and a 0% mortality rate when combined with adequate drainage. This method has never been directly compared to other treatment options.

Endoscopic Stents

Increasingly used in the contemporary management of anastomotic leak, endoscopic stenting allows for local control of ongoing soilage from the GI tract defect while potentially allowing for continued oral intake. A wide variety of endoluminal stents are commercially available. Stents can be self-expanding or balloon-expandable, plastic or metal, fully covered, partially covered, or uncovered. Each variety of stent is available in multiple diameters and lengths. Balloon-expandable stents have largely been replaced by self-expanding stents at most centers (Fig. 25.2). No difference in healing rate has been shown between self-expanding plastic stents (SEPS), fully covered self-expanding metal stents (fcSEMS), or partially covered self-expanding metal stents (pcSEMS), although SEPS have been demonstrated to have a higher rate of migration and longer duration of placement. Overall, the clinical success rate of endoluminal stenting is 77–86% in modern series.

Stent migration is the most common complication of endoluminal stenting, which occurs in 16–62% of patients. To mitigate this risk, some centers have described securing the stent to the nasopharynx via bridle, or to the luminal mucosa with clips or endoluminal sutures. Stents placed in an intrathoracic position have a higher rate of migration over the cervical position. Cervical stents, however, pose their own placement challenges. Proximal stents at or above the level of the cricopharyngeus can cause significant patient discomfort with dysphagia, odynophagia, or globus sensation, occasionally interfering with the swallowing mechanism and leading to aspiration. Alternative soft silicone-based solid stents (Montgomery Salivary Bypass Tube, Boston Medical products, USA) may provide an effective option in this position (Fig. 25.3). These stents are generally better tolerated in this position due to their relative lack of rigidity, slimmer profile, and simple non-self-expanding design. Due to the nature of the stent and position, Montgomery Salivary Bypass Tubes tend to be less occlusive leading to increased rate of salivary leakage

Fig. 25.3 Examples of Montgomery Salivary Bypass Tubes in a variety of sizes

Fig. 25.2 Example of fully covered self-expanding metal stent

around the stent. Some advocate that self-expanding stents can result in increased tissue loss due to ischemia from the radial force of the stent. Conversely, it could be argued that this radial force may decrease stricture rate from continuous luminal dilation.

Perhaps the most feared complication of endoluminal stenting is stent erosion into local structures, namely, the aorta or tracheobronchial tree. Occurring in approximately 1.5% of patients, stent erosions are rare but potentially life-threatening. The risk of stent erosion is significantly heightened in the placement of dual airway and conduit stents when airway-enteric fistulae are involved. This is generally not recommended, except in cases of palliation for late and/or terminal stage cancer patients.

After stent deployment, fluoroscopic esophagram may be used to confirm adequate seal and patency of the stent, although clinical observation may suffice. Generally, stents are left in place for 2–8 weeks prior to repeating endoscopic evaluation of healing. Repeat stenting can be performed if the anastomotic defect persists.

Endoluminal Vacuum Therapy (EVAC)

Negative pressure wound therapy has been long established in the management of soft-tissue defects but remains in its infancy when applied to the gastrointestinal tract. Conceptually, a porous material is placed in a wound and connected to a vacuum via a closed system. In doing so, the wound environment is altered. The resultant debridement of the wound, fluid removal, and traction on wound edges increase neurogenesis, angiogenesis, hemostasis, and inflammation modulation. The ultimate effect is fibrin deposition, epithelialization, and eventually secondary wound closure.

When considering a patient for EVAC, essentially the only requirements are that the leak is accessible endoscopically and the proceduralist is comfortable with the procedure. The leak must not communicate with the atmosphere to maintain a seal. Caution should be used with placing an EVAC on or near a visible vessel or the tracheobronchial tree. The utilization of EVAC in the setting of conduit ischemia is controversial. Some propose EVAC to promote healing and will even place prophylactic EVACs before a leak occurs, while others avoid EVAC due to concern about the pressure pushing the conduit distally and propagating the leak.

At present, there are no commercially available endoluminal vacuum therapy devices in the United States. The device must be "homemade" by the operator prior to use. First, a nasogastric (NG) tube is inserted through the nose and brought through the patient's mouth. A section of readily available wound VAC foam is cut to the size of the defect, placed over the tip of the NG tube, and secured to the NG tube with large permanent sutures (Fig. 25.4). The apparatus is dragged by the endoscope to the desired location and released. EVAC can be placed either intracavitary or intraluminal at the site of leak depending on the size of the cavity and/or leak (Fig. 25.5). The NG tube is secured at the nose by tape or a bridle. The main channel of the NG tube is connected to a standard wound VAC-negative pressure system and, if present, the sump port of the NG tube is occluded to achieve a complete seal. The optimal amount of continuous negative pressure is yet to be established, but pressures of 125–175 mmHg have been reported. Like soft-tissue VAC dressings, EVAC requires serial sponge changes to debride tissue and prevent tissue ingrowth into the sponge. The optimal interval of EVAC changes is also yet to be determined. While the early reports of EVAC changed the device every 3–5 days, recently, some have advocated extending the interval to 7–10 days. If required for a protracted period of time, some advocate exit of the nasogastric tube through the neck in a manner similar to a pharyngostomy tube to avoid patient discomfort associated with a foreign body in the nose and

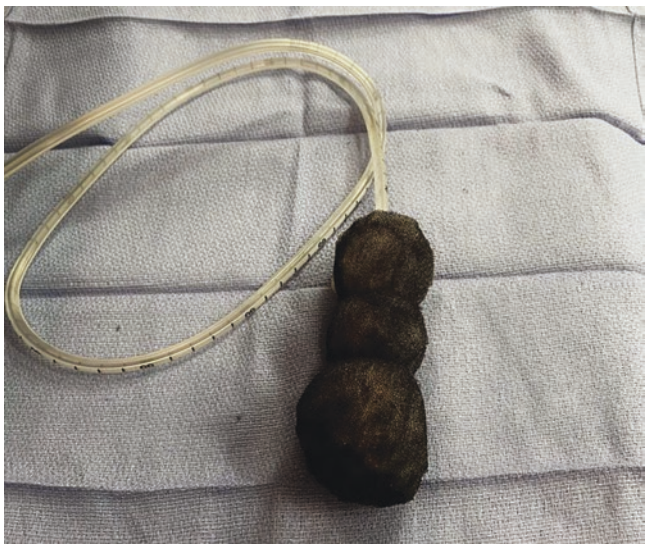

Fig. 25.4 Example of EVAC setup. Of note, the nasogastric tube needs to be passed through the nose prior to application of foam in vivo

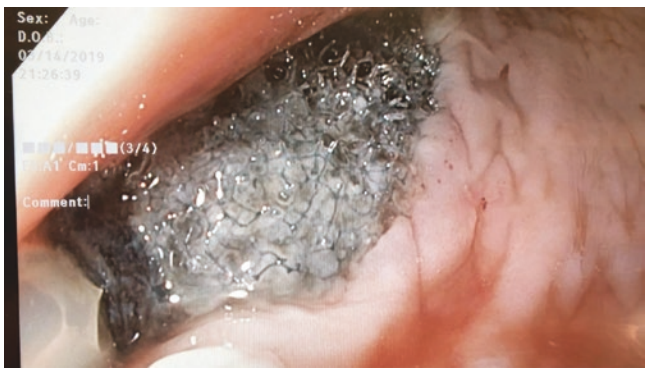

Fig. 25.5 Endoscopic placement of EVAC into anastomotic defect

oropharynx (practitioner experience with this method is critical to avoid complications of these procedures).

While trials are currently underway, there are no prospective randomized data on EVAC as yet. The data from retrospective studies, however, are quite promising. The overall healing rate has been reported to occur in 67–100% of patients. Several studies have suggested EVAC results in increased leak closure rate and a lower stricture rate with no difference in length of hospitalization or mortality when compared to esophageal stents. The most common complication of EVAC is anastomotic stricture, which occurs in 7–9% of patients. There have been reports of massive hemorrhage during EVAC changes. Even with encouraging results, the repeat endoscopic EVAC changes can be burdensome to both the proceduralist and the patient. Time to leak healing is 8–40 days requiring 2–10 EVAC changes.

Endoscopic Clips and Suturing

Unlike other endoscopic methods of managing leaks that rely on secondary wound healing, direct closure of the anastomotic defect has been reported using commercially available endoscopic suturing and endoscopic clipping devices. As with any primary closure of a wound, the local environment is critical for success. At minimum, the wound edges need to be viable and well-perfused, and ideally without inflammation.

Endoscopic clipping of anastomotic defects has been reported since 1995 and can be performed using through-the-scope clips (TTSC) or over-the-scope clips (OTSC). Endoscopic clipping can be attempted on defects of any size, although the average size of successful closure is 0.8 cm with increased rates of failure on defects greater than 1.3 cm. As they are not required to fit through the working channel of the scope, OTSCs can be larger with a stronger closing force. Defects up to 3 cm have been reported to be closed with OTSCs in the lower GI tract. Clips will generally remain affixed for 2–4 weeks before dislodging and being excreted in the stool. When comparing TTSCs and OTSCs for iatrogenic esophageal perforations, there is a decreased failure rate with OTSCs. Clip closure of the leak results in an overall success rate of 60–92% for healing anastomotic leaks without further surgery. The ideal lesion for endoscopic clipping is small with healthy wound edges and minimal inflammation. There is an increased risk of failure with chronic fistulae, local inflammation, or when clips are used as a secondary strategy after trial of another intervention. Complications of endoscopic clipping are rare and mostly minor, self-limited processes, including clip malfunction during deployment, contralateral esophageal mucosal ulceration from clips, and tongue laceration. Enlargement of perforation during attempted clipping requiring operative repair has been reported. Overall, endoscopic clipping of anastomotic leaks is feasible, but its utility is limited by the frequently encountered inflammation or nonviable tissue at the anastomotic mucosal edges.

Endoscopic suturing employs similar concepts to clipping albeit with a different delivery system. Commercially available devices are available for full-thickness suturing. The data on these devices are limited aside from case series demonstrating feasibility. Most attempts at endoscopic suturing to close esophagogastric anastomotic leaks were in conjunction with endoscopic stenting. While endoscopic clips can interfere with stent placement, a sutured defect is amenable to stenting either at the time of suturing or at a later procedure.

Postoperative Considerations

Endoscopic local control of the GI tract defect does not represent the definitive or final mode of therapy for many patients. The same principles of leak management previously described remain of utmost importance. The clinician should remain alert to the clinical status of the patient and have a low threshold to repeat diagnostic or therapeutic efforts. Until the leak is healed or surgically resected, all endoscopic treatment modalities have the potential for persistent or repeat uncontrolled soilage, resulting in ongoing sepsis. Some centers routinely perform radiographic or endoscopic evaluation to document healing of the anastomotic defect, while others rely on the clinical status of the patient.

After healing the anastomotic defect, the most common sequela is anastomotic stricture. In all patients undergoing esophagectomy, anastomotic stricture occurs in 9–40%. The presence of an anastomotic leak increases the risk of subsequent stricture two- to threefold. Endoscopic evaluation and dilation should be strongly considered in the patient who develops dysphagia after esophagectomy, especially after a known leak.

Conclusions

Endoscopic management of anastomotic leak after esophagectomy can be successful in the appropriately selected patients. The potential morbidity of this complication is such that the “conservative” option is invasive surgical resection, and the “aggressive” option is conduit preservation with potentially less-invasive adjuncts. The invasiveness of the treatment can be tailored to the illness of the patient coupled with the extent of the anastomotic dehiscence. Although the technical aspects of these endoscopic procedures can be challenging, they may provide less invasive and lower-risk

options for the management of anastomotic leak in appropriately selected patients.

Questions

1. Which of the following is an absolute contraindication to endoscopic management of anastomotic leak?
   A. 50% anastomotic dehiscence
   B. Cervical anastomosis
   C. Conduit necrosis with sepsis and hemodynamic instability
   D. Small, contained, asymptomatic leak

Answer: C. Conduit necrosis in the setting of sepsis and an unstable patient is rapidly progressive with a high mortality if left untreated. Definitive endoscopic management is not appropriate in these unstable patients who require surgical debridement with bipolar esophageal exclusion. The size, location, and symptoms of the leak are certainly factors in the management of leaks, but are not absolute indications or contraindications.

2. After successful endoscopic management of anastomotic leak, which of the following complications is the patient at greatest risk of developing?
   A. Anastomotic stricture
   B. Chronic abdominal pain
   C. Local recurrence of cancer
   D. Paraconduit hiatal hernia

Answer: A. Anastomotic stricture occurs in up to 50% of patients with anastomotic leak. Although the other choices are possible complications, they are generally unrelated to anastomotic leak in the perioperative period.

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Palliative Therapy in Esophageal Cancer

26

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Objectives

1. Identify patients with advanced esophageal cancer who would benefit from palliative endoscopic therapy
2. Discuss different modalities of endoscopic palliation of dysphagia in advanced esophageal cancer
3. Discuss surgical palliative techniques for advanced esophageal cancer

Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, and global predicted mortality is expected to rise up to 85% by 2035. Early esophageal cancer can be cured by endoscopic eradication therapy (ETT), a combination of endoscopic resection followed by ablation. For more advanced esophageal cancers, curative treatment requires surgical resection with lymphadenectomy, but this is only possible in a small subset of patients with local tumor invasion. Definitive chemoradiation may be offered for patients who are not surgical candidates, but its survival benefit is controversial and it has shown more utility in squamous cell carcinoma (SCC) than adenocarcinoma. As EC has a notoriously low 5-year survival rate of under 20%, in patients who are not surgical candidates due to tumor location or metastatic disease, the recommended approach to treatment is palliative rather than curative.

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Disease Staging

Accurate disease staging at the time of diagnosis of esophageal cancer is necessary for disease prognostication. The American Joint Committee on Cancer (AJCC) published the eighth edition of its guidelines for EC and esophagogastric junction cancers in 2017. The guidelines stage EC by three schemas, all of which incorporate TNM categories (where T describes tumor size and local invasion, N describes lymph node involvement, and M describes degree of metastasis). The classifications include pathological staging (pTNM) and clinical staging (cTNM), both divided by EC subtype due to the impact of histopathological cell type on prognosis. The third schema is a new addition to prior guidelines, post-neoadjuvant staging (ypTNM), and addresses the histopathological changes that can occur in patients who have completed or are currently undergoing neoadjuvant therapy. This classification is not affected by histopathological cell type and thus not differentiated by subtype.

pTNM is based on histology and depth of invasion of resected tumors and is considered superior to cTNM for determining prognosis. Superficial SCC invades the mucosa and submucosa only. Advanced histological features in SCC include invasion into the muscularis propria, ulceration, exophytic lesions, and intramural invasion. Adenocarcinoma severity is characterized by the proportion of the tumor that contains glands. Consensus guidelines recommend a minimum of 10 lymph nodes resected for superficial T-staged tumors. Resection margins are considered positive if the tumor is within 1 mm of the margin.

Another change in the eighth edition is that EC location was previously reported by the upper edge of the cancer, but now is based on the epicenter of the tumor as calculated from upper and lower border measurements. Adenocarcinomas that have their epicenters 2 cm or less into the gastric cardia are now considered ECs, and those that spread 2 cm or more into the cardia are classified as stomach cancers.

N. T. Nguyen et al. (eds.), *The AFS Textbook of Foregut Disease*, https://doi.org/10.1007/978-3-031-19671-3_26

Initial staging of EC starts with noninvasive imaging, commonly multidetector contrast-enhanced computed tomography (CT) of the chest and abdomen. If there are no metastases seen, fluorodeoxyglucose positron emission tomography (FDG-PET) or endoscopic ultrasound (EUS) should be performed to determine the depth of tumor involvement and evaluate the extent of locoregional metastasis if the cancer is not amenable to endoscopic resection or there is concern for invasion into the submucosa or beyond. EUS has a high degree of accuracy for T staging, though it has potential to overstage more superficial tumors. Additionally, diagnostic surgical laparoscopy should be performed for tumors involving the gastric cardia.

The depth of invasion of tumors determines the T staging. T1 tumors do not invade beyond the muscularis propria. These are further divided into T1a (involves the lamina propria or muscularis mucosa only) and T1b (invades the submucosa). T1b is further divided by which third of the submucosa the mass has spread to, with T1b SM1 invading the upper third, T1b SM2 invading the middle third, and T1b SM3 invading the deepest third. These divisions are relevant for prognosis in SCC particularly as T1b SM3 staging or vascular involvement are the highest risk factors for spread to the lymph nodes. T2 tumors involve the muscularis propria. Tumors that invade the adventitia are T3 and those with invasion into adjacent structures are T4. This staging is important because for early-stage esophageal tumors endoscopic resection alone may be curative. Tumors that are staged as T3 and T4 have a high probability of at least locoregional metastasis. Advanced EC is associated with a poor prognosis and thus the intent of treatment shifts from curative to palliation of symptoms.

Medical palliative therapy in EC patients focuses on pain control and management of nausea and emesis. The major symptom that impacts patients' quality of life is dysphagia from tumor obstruction or malignant stricture. Endoscopic approaches are the primary method of treating this, although external beam radiation therapy may also be used. Due to the high morbidity of surgical interventions, surgical palliation is typically reserved for specific cases in which endoscopic therapies have failed. Endoscopic approaches can be grouped into mechanical interventions, administration of oncological therapies, and introduction of thermal energy.

Endoscopic Mechanical Interventions

Stenting

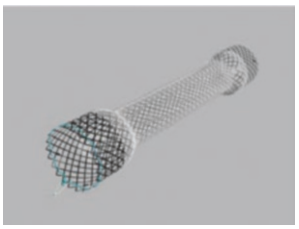
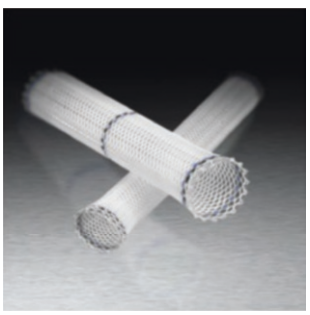
Esophageal stenting has been in use since the nineteenth century. The technology has advanced from rigid stents to self-expanding ones, with a variety of materials currently available (Table 26.1). Self-expanding metallic stent (SEMS) placement is the most common palliative therapy in EC. Currently, guidelines recommend SEMS placement for patients with a life expectancy under 3 months as it is associated with rapid relief of dysphagia but can become obstructed with food bolus and/or tumor ingrowth. Stent insertion is often performed with fluoroscopy to guide placement. Alternatively, visualization with an endoscope alone may be used for guidance. If a stricture is present, dilation may be required prior to placement of a SEMS. A stent diameter of at least 16–24 mm is associated with improved swallowing. Interestingly, studies on optimal stent sizing do not indicate a decreased rate of adverse effects in smaller diameter metal stents compared to larger diameter ones.

Images taken from manufacturer websites

Complications from esophageal stent placement may occur immediately or may have a delayed presentation. Immediate adverse events include bleeding, retrosternal/atypical chest pain, stent migration, and incomplete stent expansion. Patients may also experience persistent dysphagia despite SEMS, particularly with proximal esophageal stents. Chest pain may require analgesics, such as acetaminophen with codeine suspension or benadryl-maalox-xylocaine suspension. Late complications include stent migration, which has been reported more frequently in patients receiving adjuvant chemotherapy or chemoradiation. Covered stents were developed to reduce the growth of granulation tissue over the stent and prolong duration of symptom relief. They had been associated with higher rates of migration, resulting in the development of techniques to prolong stent durability such as stent fixation with endoscopic sutures or clipping. Partially covered stents are designed so that the distal ends are uncovered, thereby encouraging tissue ingrowth to anchor the stent. This may lead to less stent migration, although efficacy of this is unclear. Recent analyses suggest no significant difference in rate of stent migration between partially or fully covered stents. In situations where the stent may need to be removed, such as refractory pain after placement, partially covered and uncovered stents may not be able to be retrieved endoscopically due to tissue growth embedding them in the mucosa. Stent in-stent placement may be required in such cases. Another major complication is stent obstruction, either secondary to granulation tissue or tumor ingrowth into the stent, food impaction, or a combination. A rare but serious complication of SEMS placement is development of an esophageal-airway fistula, which has been reported in up to 3.4% of patients following SEMS placement.

Self-expanding plastic stents (SEPS) have been studied for EC dysphagia palliation as well. Dysphagia relief is similar between SEMS and SEPS, but adverse event rates are higher with the latter. Notably, more stent migration is reported for SEPS than SEMS as a late side effect in multiple studies. One SEPS is currently available (Table 26.1).

Table 26.1 Sample of commercially available esophageal stent types

Stent Type	Complications	Strengths	Example
Uncovered Self Expanding Metallic Stents (SEMS)	Migration, Tumor Ingrowth, Difficult to Remove, Tissue Necrosis	Single Use, Lower Cost	 Ultraflex Single Use Noncovered Esophageal NG Stent System, Boston Scientific
Partially Covered SEMS (pcSEMS)	Obstruction, Higher Risk of Tumor Ingrowth than FCSEMS, Difficult Endoscopic Removal	Possibly lower rates of Migration than fcSEMS	 Evolution Esophageal Controlled-Release Stent Partially Covered, Cook Medical
Fully Covered SEMS (fcEMS)	Obstruction, Possibly Higher rates of migration than pcSEMS	Less Tissue Ingrowth than pcSEMS	 ALIMAXX-ES Esophageal Stent, Merit Medical
Self Expanding Plastic Stents (SEPS)	Higher rates of Migration, Higher risk of Tumor Ingrowth than FCSEMS	May reduce reactive tissue growth	 Polyflex Stent, Boston Scientific
Biodegradable Stents	Corrosion, Loss of Structural Integrity	Does not need to be removed	 SX-Ella Biodegradable Stent, ELLA -CS

Images taken from Manufacturer Websites

Additional stent varieties are actively being studied. Biodegradable stents have been investigated for their potential in reducing granulation tissue development, but their inherent structural instability appears to reduce their utility in dysphagia treatment. Drug-eluting SEMS have been developed as well. Specifically, films loaded with paclitaxel and 5-fluorouracil have been deployed over the metal framework, and results in animal models suggest they may slow tumor growth.

Dilation

Esophageal dilation alone is not an effective treatment modality for the management of dysphagia secondary to a malignant mass or stricture due to its high rate of recurrence and the availability of other superior treatment options, such as SEMS. Dilation of a malignant esophageal stricture may however be required during initial staging to facilitate safe passage of the echoendoscope or prior to placement of a SEMS. Dilator types include through-the-scope (TTS) balloons, over-the-wire bougies, or mercury-/tungsten-filled bougies. The latter group is associated with a higher risk of esophageal perforation.

Endoscopic Ablation Therapy for Esophageal Cancer

Photodynamic Therapy (PDT)

The earliest endoscopic ablation therapy was photodynamic therapy. In this treatment, a photosensitizing agent (porfimer solution, talaporfin sodium) is administered systemically. Several days later, an endoscope with a light source that emits a specific wavelength is passed adjacent to the tumor to initiate a chemical reaction, leading to release of free radicals and reactive oxygen species in the tumor cells. Theoretically, this specifically targets and destroys the EC cells due to their hypervascularity causing increased rates of uptake of the photosensitization agent. Due to its high cost, limited availability, and serious adverse events such as photosensitivity, chest pain, and post-ablation esophageal strictures, and with the advent of newer safe and effective ablation techniques (see Table 26.2), PDT has fallen out of favor.

Cryoablation

Cryoablation is a newer modality that is available as a spray or a balloon-based system. Spray cryotherapy uses a catheter that is inserted through the working channel of an endoscope to deliver liquid nitrogen at a temperature of −196 °C (−320 °F) (Fig. 26.1). Treatment is directed at the target lesion(s) for up to 30 s per cycle. Balloon-based cryoablation performs direct ablation of targeted tissue through a balloon using nitrous oxide. Several treatments, performed at frequent intervals (i.e., every 2–4 weeks), are required for best results. Cryoablation is generally well tolerated; however, chest pain, bleeding, perforation, and post-ablation strictures have been reported. Early studies evaluating the efficacy of cryoablation with and without concurrent systemic chemotherapy have not demonstrated any significant improvement in dysphagia in patients who receive concurrent therapy; however, large prospective studies are needed to further evaluate combination therapy versus cryoablation alone.

Table 26.2 Comparison of endoscopic ablative techniques

Therapy	Weaknesses	Strengths
Argon plasma coagulation	High recurrence rates, requires multiple treatments	Low risk of perforation due to superficial depth
Cryoablation	Requires multiple treatments at consistent intervals, stricturing	Safety, efficacy
Endoscopic laser ablation	High recurrence rates, requires multiple treatments	Rapid symptom relief, good for bulky tumors
Photodynamic ablation	Systemic complications due to photosensitization agent, high cost	Increased uptake of photosensitizer by tumor cells should lead to preferential destruction

Argon Plasma Coagulation (APC)

APC uses ionized argon gas to deliver a noncontact tissue coagulation. It has been used in patients with superficial EC who are unable to undergo endoscopic resection secondary to technical issues such as significant fibrosis from prior treatment attempts or significant stricturing. APC has also been applied for debulking of esophageal masses with variable effect. Tumor regrowth has been reported relatively quickly and multiple sessions are required; however, its widespread availability and ease of use increase its usability.

APC has also been studied in combination with SEMS with some reports suggesting prolonged symptom relief in patients treated with APC prior to placement of SEMS. Additionally, APC has been studied as combination therapy (APC/high-dose brachytherapy and APC/PDT) for relief of dysphagia with greater symptomatic improvement and longer duration of symptom relief in patients who received combination therapy versus APC alone.

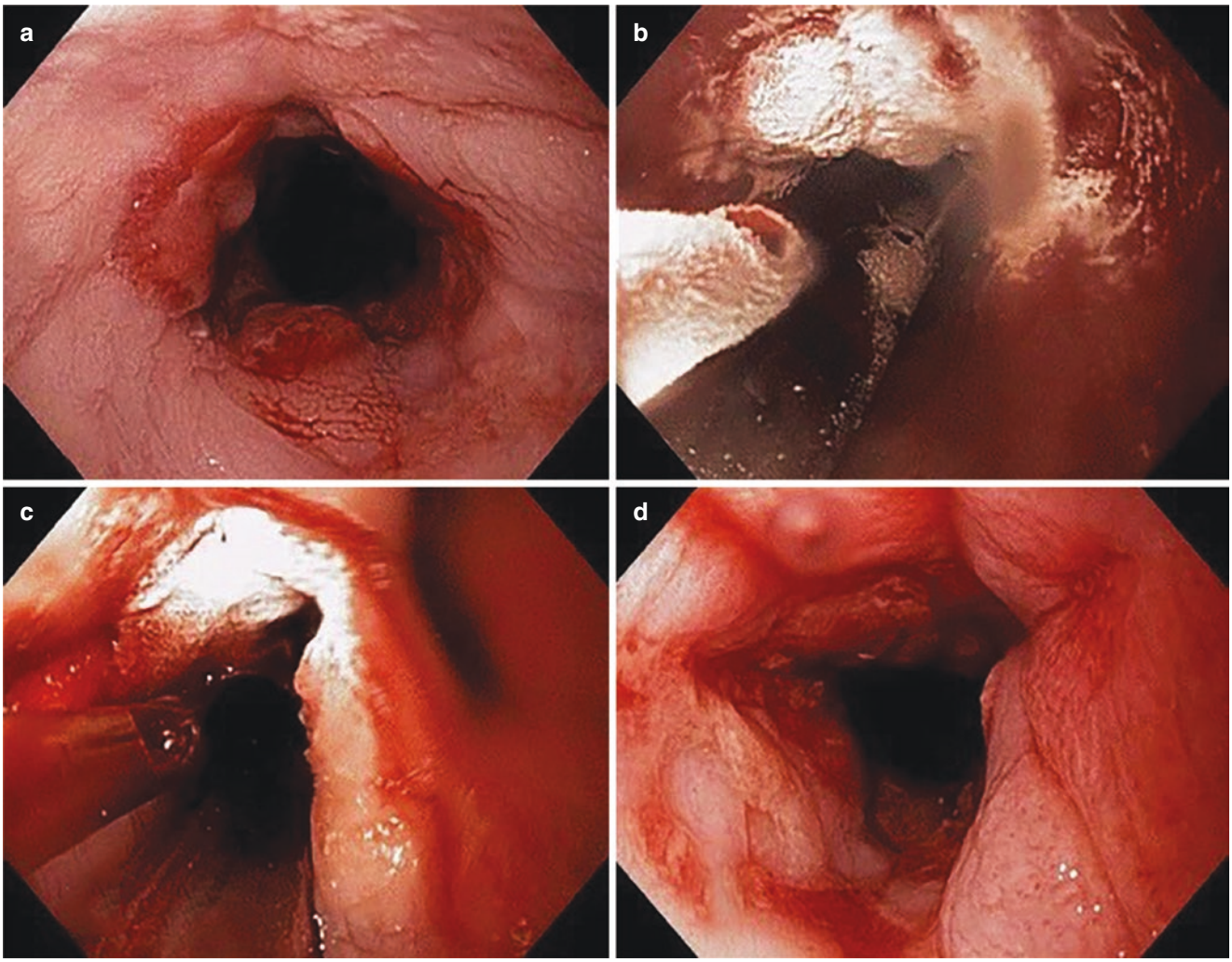


Fig. 26.1 Cryotherapy for treatment of esophageal cancer. (**a**) The tumor at the GE junction. (**b**) Spray cryotherapy being applied. (**c**) An image immediately after application of the spray cryotherapy as it is starting to melt. (**d**) An image of the GE junction after the therapy was completed. (Image courtesy of Michael Smith, Temple University Hospital)

Endoscopic Laser Ablation

Neodymium–yttrium–aluminum–garnet (Nd–YAG) laser ablation was first used in the 1980s for esophageal cancer palliation. It is administered endoluminally and utilizes high-energy lasers at a wavelength above 1000 nm to incinerate tumor tissue directly. As with APC, laser treatments generally require repeat sessions due to tumor regrowth and dysphagia recurrence. Its use has decreased in recent years as newer alternative endoscopic palliative therapies have become available.

Endoscopic Oncological Therapies

External Beam Radiation Therapy (EBRT)

EBRT is the second most common palliative therapy in EC after SEMS placement. Fiducial markers can be placed at the margins of the esophageal tumor with the guidance of endoscopic ultrasound to facilitate radiation therapy. This has been shown to improve targeted therapy.

Notably, stenting is often accompanied by EBRT. Early studies indicated that the combination may produce a reduc-

tion in dysphagia symptoms compared to SEMS alone. However, a recent stage 3 randomized controlled trial suggested that the combination did not impact reduction in dysphagia symptoms compared to stenting alone. The study did note a statistically significant decreased risk of bleeding in the group receiving SEMS plus EBRT compared to SEMS alone. A second large-scale retrospective study reported equivalent efficacies between the same groups and confirmed lower rates of hemorrhage in the radiation group. It also noted lower rates of perforations and esophageal-airway fistulas in the EBRT/SEMS cohort.

Less data exist on the utility of EBRT as monotherapy. One group assessed treatment schedules and found that the ideal EBRT schedule should be determined based on a patient's life expectancy. Outcomes were comparable between radiation doses of 20, 30, and 39 Gray (Gy). A longer time to second intervention was seen in the two higher dose groups, with second intervention defined as stenting, brachytherapy, or repeat EBRT. Short-course EBRT (20 Gy in five sessions) appears to have similar utility to brachytherapy in the management of dysphagia.

Endoluminal Brachytherapy

Multiple guidelines recommend the use of intraluminal brachytherapy for palliation of malignant dysphagia. Studies have compared the efficacy of SEMS placement with brachytherapy and found that for patients with longer life expectancy (greater than 3 months), brachytherapy is superior due to its longer efficacy in relieving dysphagia. Intraluminal brachytherapy involves radiation administered via an endoscopic catheter adjacent to the tumor, which theoretically decreases radiation exposure to surrounding organs and resultant organ toxicity. The radiation source is usually high-dose-rate iridium-192. Brachytherapy can be administered in a single session or multiple sessions, and mean dose per fraction is often between 4 and 8 Gy. Higher doses are associated with increased rates of radiation toxicity in adjacent structures. However, one meta-analysis indicated that high doses (18 Gy or 21 Gy) administered in 2–3 sessions provided greater symptom relief than low doses or single sessions. Potential complications of brachytherapy include stenosis, fistulas, perforation, and hemorrhage. Brachytherapy is contraindicated if the tumor has tracheal or bronchial involvement, is located in the cervical esophagus, or would require catheter placement through a stenosis that is not able to be bypassed.

Endoscopic Chemotherapy

Early studies indicated a possible utility in local injection of chemotherapies into tumors via endoscopy. Agents investigated with this approach include 5-fluorouracil and a cisplatin-epinephrine-injectable gel. Similar interventions have been applied in cases of gastric cancer with varying degrees of success.

An alternate approach is electrochemotherapy. In this technique, systemic chemotherapy is administered intravenously with subsequent endoscopic electrical pulses delivered to the tumor. This electrical stimulation destabilizes the tumor cells' membranes and results in increased uptake of the chemotherapeutic agent. A phase I study was performed for this approach that used systemic bleomycin and an endoscopic electrode to apply eight electrical pulses at an amplitude of 760 V per centimeter and a frequency of 5 kHz. Adverse effects included hoarseness, coughing up of sloughed-off necrotic tissue, pneumonia, and weight loss. No serious complications such as cardiac arrhythmias or perforations were reported. As this was a preliminary safety efficacy study, its future use is hypothetical, but it shows promise as an additional approach to palliative chemotherapy in EC.

Endoscopic Chemical Administration

Direct injection of 95–100% ethanol into esophageal tumors was an early palliation approach that resulted in ulceration, necrosis, and sloughing of the obstructive mass. Sequential aliquots of up to 10 cm^3 of ethanol are injected in multiple sessions. Complications reported include esophageal perforation, mediastinitis, and esophageal-airway fistulas. The use of ethanol injection is limited in modern palliative therapies. It may still be considered a low-cost alternative in some scenarios.

Nonendoscopic Palliation and Palliation of Nondysphagia Symptoms

Systemic Chemotherapy and Chemoradiation

The standard of care for treatment with palliative intent is chemoradiation. Chemotherapy with platinum-based agents with concurrent radiation therapy improves 5-year survival, regardless of endoscopic interventions. Additional studies with biological agents indicate potential utility in targeting HER2, EGRFR, and c-MET as all three are overexpressed in EC. Phase 3 trials are currently underway investigating multiple targeted chemotherapeutic agents.

A large meta-analysis of 41 randomized controlled trials with 11,853 patients suggested that even palliative chemotherapy on its own (without concurrent radiation) increased quality of life and length of survival. It did not significantly increase treatment-related deaths. The analysis reported that toxicity was more common when patients were on multiple chemotherapy agents or a targeted agent. The most com-

monly used agents are 5-fluorouracil and cisplatin. The only agent that improved progression-free survival as a monotherapy was ramucirumab (an antibody that targets VEGFR2 and blocks angiogenesis). Palliative chemotherapy alone achieves a median survival of 10 months in multiple studies. Trastuzumab is an antibody targeting HER2 and has been shown to extend survival by a few months in combination with other chemotherapies.

Management of Bleeding: Hemostatic Powder, Argon Plasma Coagulation, Angiography

Hemostatic powders have been shown to achieve hemostasis in bleeding esophageal tumors, particularly if bleeding is diffuse. Resolution is usually short term, but this technology may be useful as a temporizing measure until an alternate approach can be used. APC, as described above, may also be used for hemorrhage from tumor. Data suggest a success rate of up to 66% in achieving hemostasis from malignant etiologies. Cryotherapy may also reduce friability of tumors. Covered SEMS have been used to tamponade bleeding from esophageal tumors, particularly in patients who also have significant dysphagia. If endoscopic hemostasis is unable to be achieved, angiography is the second-line intervention.

Malnutrition

Malnutrition may occur secondary to poor oral intake due to dysphagia, anorexia, or side effects from therapy. Enteral nutrition may be required as a result to maintain caloric intake. This can be achieved via nasogastric tube, gastrostomy tubes, or jejunostomy tubes. Parenteral nutrition may also be considered; however, studies have found this to be less effective at improving the nutritional status in patients with cancer, at least in part due to metabolic changes associated with malignancy.

Perforation

Perforation most commonly occurs as a result of therapeutic interventions. Small, contained perforations that are immediately recognized may be successfully managed with endoscopic clips or SEMS. Patients who develop hemodynamic instability, delayed perforations, or large perforations may require surgical management. There are several techniques available for surgical repair, including primary closure, drainage, and esophagectomy. Optimal management consists of multidisciplinary consultation and assessment of the patient's clinical status.

Surgical Approaches

Palliative esophagectomy, either open via thoracotomy or via minimally invasive techniques, is considered a last resort and a salvage form of palliation due to high morbidity and mortality. Patients who underwent minimally invasive surgery reported slightly better quality of life compared to those who underwent open surgical intervention in the immediate postoperative period; however, in both open and minimally invasive approaches, patients reported a global decline in symptoms and quality of life after 6 months.

Esophageal bypass is another method of palliation. In 1920, the Kirschner technique was described, which uses a gastric conduit (a Roux-en-Y anastomosis) to bypass an esophageal stricture but is associated with high morbidity and mortality, 60% and 40%, respectively. In 1979, the Postlethwait method was reported, which uses a Y type gastric tube with external drainage. An additional approach is using an ileocolonic bypass in circumstances when the patient does not have a usable stomach (i.e., post gastrectomy). Drainage tubes that are left in place, as in the Postlethwait method, are associated with decreased quality of life and adverse events such as leakage or abscess formation. One group investigated a drainage tubeless bypass surgery (DRESS bypass) and found that it was a viable approach. It utilized esophagostomy in the right supraclavicular region to eliminate the need for an external drain.

Potential complications from surgical palliative approaches include pulmonary disease (particularly pneumonia), hemorrhage, anastomotic leak, thromboembolism, strictures, esophageal-pulmonary fistulas, chylothorax, and delayed gastric emptying. One study comparing surgical palliation with esophagectomy, SEMS placement, and use of enteral nutrition found that the esophagectomy group experienced a complication rate of 96.4% but had the highest median survival time compared to the other two groups. Younger patients may tolerate surgical palliation with greater success than older patients.

Conclusions

Despite advances in GI oncology, advanced esophageal cancer continues to be associated with a poor prognosis. Patients commonly develop dysphagia and subsequent malnutrition, which impacts their quality of life as well as their ability to tolerate treatment regimens. Bleeding and perforation occur less commonly but often result in significant morbidity. Multidisciplinary collaboration is essential with consideration of endoscopic, medical, and radiation therapies tailored to the patient's stage of disease, comorbidities, and goals of care.

Questions

1. A 93-year-old man with recently diagnosed stage IV esophageal adenocarcinoma presents to the ED with fatigue and lightheadedness. He endorses worsening dysphagia from the tumor as well. He was found to have symptomatic anemia to a hemoglobin of 6.8 and requires transfusion of one unit of PRBCs. Endoscopy shows slight oozing of the tumor. One week later, he is admitted again for the same symptoms and again found to have a hemoglobin under 7. Which endoscopic ablative technique should be considered for palliation of this patient's symptoms?
   A. Cryoablation
   B. Argon plasma coagulation
   C. Photodynamic ablation
   D. Endoscopic laser ablation

Answer: B. APC is indicated for palliation of dysphagia and also has high rates of success in hemostasis from bleeding tumors.

2. A 67-year-old woman with esophageal cancer presents to your office for follow-up esophageal dilation for relief of dysphagia 1 month ago. Symptoms initially improved, but have now worsened. You offer her esophageal stenting, but she states she is hesitant to have a device in her long term due to complications she read about online. What is the best stent choice for this patient?
   A. Self-expanding plastic stent
   B. Biodegradable stent
   C. Fully covered self-expanding metal stent
   D. Partially covered self-expanding metal stent

Answer: C. SEPS have high rates of complications and generally should not be used. While a biodegradable stent would not be in the patient long term due to material breakdown, it also does not offer long-term symptom relief. pcSEMS are more difficult to remove than fcSEMS due to tissue ingrowth at the ends, and so fcSEMS would be the ideal choice in this patient.

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Part IV

Esophageal Motility Disorders, Esophageal Injury, and Benign Disease of the Esophagus

Pathophysiology of Esophageal Motility Disorders

27

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Objectives

1. To identify the broad categories of esophageal dysmotility
2. To describe the pathophysiology of outflow-based motility disorders
3. To describe the pathophysiology of peristalsis-based motility disorders

Pathophysiology of Esophageal Motility Disorders

The Chicago Classification v4.0 (CCv4.0) of esophageal motility disorders categorizes esophageal motility disorders as either disorders of esophagogastric junction (EGJ) outflow or disorders of peristalsis [1]. There exist numerous causes of esophageal motility disorders. It is therefore helpful to understand the potential underlying pathophysiology of an esophageal motility disorder to guide the development of an individualized treatment plan.

Disorders of Esophagogastric Junction Outflow

A subset of esophageal motility disorders is based upon resistance located at the lower esophageal sphincter. Using CCv4.0, these disorders are categorized as disorders of esophagogastric junction (EGJ) outflow. Within this category, these disorders are further classified based upon the presence or absence of peristalsis. Broadly, there are three acknowledged types of achalasia and esophagogastric junction outflow obstruction (EGJOO) [1]. The etiologies of these disorders are wide-ranging and overlapping.

Achalasia

Achalasia is a rare esophageal motility disorder with an incidence of 1:100,000. Men and women equally are impacted by the disease occurring across all ages [2]. The three types of achalasia generally share a common finding of loss of the esophageal myenteric plexus, resulting in the classic definition of a hypertensive, nonrelaxing lower esophageal sphincter. While the evolution of achalasia across a patient population can have varying etiologies, it is felt that there is a chronic inflammatory process involving the esophageal myenteric process incurring damage from lymphocyte predominate infiltrative process involving CD3+ and CD8+ T cells [3–5]. There is a known loss of the interstitial cells of Cajal and in particular to the specific loss of inhibitory ganglion that comprise the myenteric plexus of the esophagus [2–5]. The myenteric plexus exists between the circular and longitudinal muscular layers of the esophagus. Vagal nerve fibers synapse with the myenteric plexus. The post-ganglionic neurons are comprised of both excitatory and inhibitory neurons that release acetylcholine and nitric oxide (NO) as well as cytokine vasoactive intestinal peptide (VIP), respectively. The lower motor neurons are sequentially activated, allowing for swallow-induced peristalsis. If the peripheral aspects of a decentralized vagus nerve are stimulated, contraction is elicited in all segments of the esophagus. Within the esophagus, there is a predominance of cholinergic excitatory innervation that is replaced distally by inhibitory innervation. If the more distal inhibitory nerves are stimulated, there is increased latency of contraction. In the proximal esophagus, there is reduced latency with the predominance of cholinergic nerves [6]. The coordination of these neurons leads to a milieu that is necessary for coordinated esophageal peristalsis. With loss of the inhibitory cells, there is a reduction in the release of NO and cytokine VIP with resultant

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non-relaxation of the lower esophageal sphincter and impaired esophageal peristalsis occurs [2–5]. Rat models have demonstrated induced agangliosis through use of benzyldimethyltetradecylammonium chloride. Furthermore, biopsies of patients undergoing surgery for achalasia have shown loss of inhibitory neurons additionally supporting this pathway for the development of achalasia [5]. Within each of the three subtypes of achalasia, there has been found to be variation in the degree of neuronal loss. Type I achalasia more consistently has absence of these neurons, whereas in type III achalasia, there exist more early changes of cell loss without complete loss. These findings have led to the belief that the variation between the subtypes of achalasia represents a spectrum of disease [2–5].

Without a clear inciting cause, an inflammatory pathway directed at myenteric cells of the esophagus is thought to be involved in the early stages of achalasia. T-cell-mediated inflammation is commonly identified as associated with this degenerative process [2–5]. An autoimmune-directed process is considered, for some patients, to be the precipitating cause. In these patients, there are antibodies to the neurons of the myenteric plexus with an HLA II antigen [2, 3]. Interestingly, these autoantibodies have been noted in patients with gastroesophageal reflux disease as well. Additional studies, however, isolated the serum from patients with achalasia and used it to induce phenotype and functional changes that replicated achalasia. This was not seen in the serum of patients with gastroesophageal reflux disease [3, 4]. Autoimmune diseases are more frequently found in patients with achalasia relative to the general population. Common autoimmune diseases found in patients with achalasia include scleroderma, systemic lupus erythematous, rheumatoid arthritis, type 1 diabetes, and Sjögren's syndrome. Limited case reports have shown patients with achalasia responding to immunosuppressive therapy [2].

Additional mechanisms leading to loss of the myenteric plexus are centered on infectious causes. Classically, Chagas disease, caused by infection with the protozoan *Trypanosoma cruzi*, induces findings consistent with achalasia [2, 3]. Beyond Chagas disease, there are several viral models created that have led to loss of ganglion cells. There have been case reports and studies linking polio, varicella, JC virus, and human papillomavirus to the onset of achalasia. There have been limited data indicating measles and herpes as potential inciting infections [2, 3]. Commonly, the potential pathogens are neurotrophic with chronic latent and active phases. The common aspect of viruses such as herpes simplex indicates a more complex pathway involving predisposition or additional environmental factors, leading to the development of achalasia [2, 3].

Genetic pathways leading to achalasia have been established and are thought to lead to susceptible individuals. Through mice models, it has been demonstrated that disruption of the NO synthase 1 gene leads to a hypertensive lower esophageal sphincter with impaired relaxation [2]. A small percentage of cases of achalasia are attributable to an autosomal-recessive disease, Allgrove syndrome, that is characterized by achalasia, alacrimia, autonomic disturbance, and adrenal insufficiency [2, 4, 5]. Further genetic syndromes associated with achalasia include multiple endocrine neoplasia type 2 B syndrome, which is associated with increased risk of cancer; Riley–Day syndrome leading to a familial dysautonomia; and Smith–Lemli–Optiz syndrome that leads to a reductase deficiency. Down's syndrome and congenital central hypoventilation syndrome additionally have associations with achalasia [2, 4].

Not as commonly discussed, but relevant, is the evolution of eosinophilic esophagitis (EoE) leading to achalasia as a result of muscular involvement. Broadly, eosinophilic derangements of the gastrointestinal tract can involve the mucosa, muscle, or serosa [5, 7]. Dysmotility is seen when there is eosinophilic involvement of the muscular layer, which can impact muscle contractility, nerve function, and result in fibrosis with subsequent strictures. Further supporting EoE as a potential underlying contributor is the finding of abnormal high-resolution esophageal manometry in patients with eosinophilic esophageal muscle involvement [5, 8].

It is important to remember the possibility of a paraneoplastic syndrome etiology when considering the diagnosis of achalasia. Either through direct injury to the neurons or as a result of an autoimmune-type process with tumor-produced neural antigens, malignancy can lead to achalasia [2]. Small cell lung cancer, neuroblastoma, and prostate cancer have been indicated as malignancies with the potential to induce achalasia through these mechanisms [2].

In some patients, achalasia evolves as a result of a constricting process at the level of the lower esophageal sphincter. With this type of inciting cause, pseudoachalasia should be considered. These processes can include strictures, hernias, prior surgeries (such as an antireflux surgery or bariatric surgery), tumors, and vascular malformations (such as thoracic aortic aneurysms) [2]. Pseudoachalasia has the potential for resolution or improvement when the underlying cause is addressed. It is therefore important to consider this possibility when the clinical diagnosis of achalasia is being pursued.

There are multiple pathways that can potentially lead to the evolution of achalasia. The inciting event varies amongst patients with the loss of the neuronal cells of the myenteric pathway serving as the final common pathway leading to achalasia.

Esophagogastric Junction Outflow Obstruction

With the evolution of high-resolution esophageal manometry and refined diagnostic categories, esophagogastric junction outflow obstruction (EGJOO) evolved as a diagnosis that identifies a hypertensive incompletely relaxing lower esophageal sphincter with preserved peristaltic function [1]. Due to the heterogeneity of causes and clinical presentations, EGJOO represents a broad category with unclear prevalence. Based on tertiary referral center patterns, 3–21% of patients have been found to meet manometric criteria for EGJOO. A review of a series shows a slightly female prevalence (51–88%), with an age range of 56–61, and a trend toward an elevated BMI (25–30) [7]. To better typify the cause and potential treatment, EGJOO is viewed to be a result of one of several etiological causes: mechanical, functional, medication-induced, and artifactual [5, 7, 9].

Commonly found mechanical obstructive causes include strictures, hiatal hernias, and prior antireflux surgery. Similar to pseudoachalasia, these obstructive processes lead to elevated resting pressure of the lower esophageal sphincter with impaired relaxation [7, 10]. Prior series have identified a range of prevalence for these mechanical processes: physical obstruction (8–66%), fundoplication (9–100%), hiatal hernia (25–71%), and stricture (8–36%). Less commonly encountered etiologies include tumors, vascular abnormalities (e.g., aneurysm of thoracic aorta, esophageal varices), and central obesity leading to increased intra-abdominal pressure [5, 7, 9].

Structural changes of the tissue at the level of the lower esophageal sphincter, such as eosinophilic esophagitis, can lead to fibrosis and stricture, as seen in achalasia [5, 9]. Similar findings can be seen with malignancy of the distal esophagus. It is thought that the infiltrative or inflammatory aspects of these disease processes lead to impairment of the coordinated neuromuscular function of the lower esophageal sphincter [5].

Focused attention should be made to the role of opioids in the etiology of EGJOO. Several studies have specifically evaluated the impact of opioids on esophageal function [9]. High-resolution esophageal manometry completed on patients who chronically use opioids has shown the presence of EGJOO at a higher rate compared to those who discontinued opioids at least 24 h in advance of the manometry [9]. Interestingly, in these studies, type III achalasia was more commonly diagnosed in patients taking opioids. Additionally, in patients with EGJOO, opioid use is more common relative to controls (30% versus 9%) [9]. This potential etiology is an important consideration as it represents a potential point of intervention.

In certain patients, there are manometric findings and a clinical picture supportive of EGJOO; however, there is no clear inciting cause and the outflow obstruction is described as functional, [9]. In these patients, there is consideration that EGJOO could represent an achalasia variant. For some, this finding represents a dynamic process that is in evolution to achalasia. For others, this is a static process without identifiable progression [5, 9].

Lastly, there is a subset of patients undergoing high-resolution esophageal manometry who are found to meet diagnostic criteria for EGJOO but do not have supportive symptoms [9]. This can represent a diagnostic dilemma for the clinician as the finding may not be in line with presenting symptoms or there can be overlap in symptoms in competing disease processes such as gastroesophageal reflux disease. From an etiologic standpoint, these findings are classified as artifactual and may not be of clinical significance. Additional adjunctive tools, such as timed barium esophagram, functional lumen imaging probe (FLIP), and upper endoscopy, may be used to further evaluate a potentially artifactual finding [5, 9].

EGJOO represents a diagnosis made primarily through high-resolution esophageal manometry. Presenting symptoms and clinical course are variable and thus seeking potential underlying etiologies through careful patient evaluation and judicious use of adjunctive diagnostic tools is imperative.

Disorders of Peristalsis

Disorders of peristalsis include absent contractility, distal esophageal spasm (DES), hypercontractile esophagus (HE), and ineffective esophageal motility (IEM) (Fig. 27.1). Furthermore, the CCv4.0 classifies disorders of peristalsis into two subcategories. First, disorders of peristalsis with reduced contractile vigor or integrity of peristalsis, which includes absent contractility and IEM. Second, disorders of peristalsis with esophageal spasticity or hypercontractility, which includes DES and hypercontractile esophagus, including jackhammer esophagus. Of note, according to the CCv4.0, DES and hypercontractile esophagus represent patterns of esophageal motility with unclear clinical relevance [1].

Esophageal peristalsis can be classified as either primary or secondary. Primary peristalsis is elicited by volitional swallowing that initiates coordinated contractions in the circular and longitudinal esophageal muscles. Secondary peristalsis is triggered by esophageal distention [11, 12].

The esophagus is composed of striated muscle in the proximal third or the cervical esophagus and smooth muscle in the thoracic or distal two-thirds of the esophagus (Fig. 27.2). Esophageal striated muscle is innervated by excitatory motor

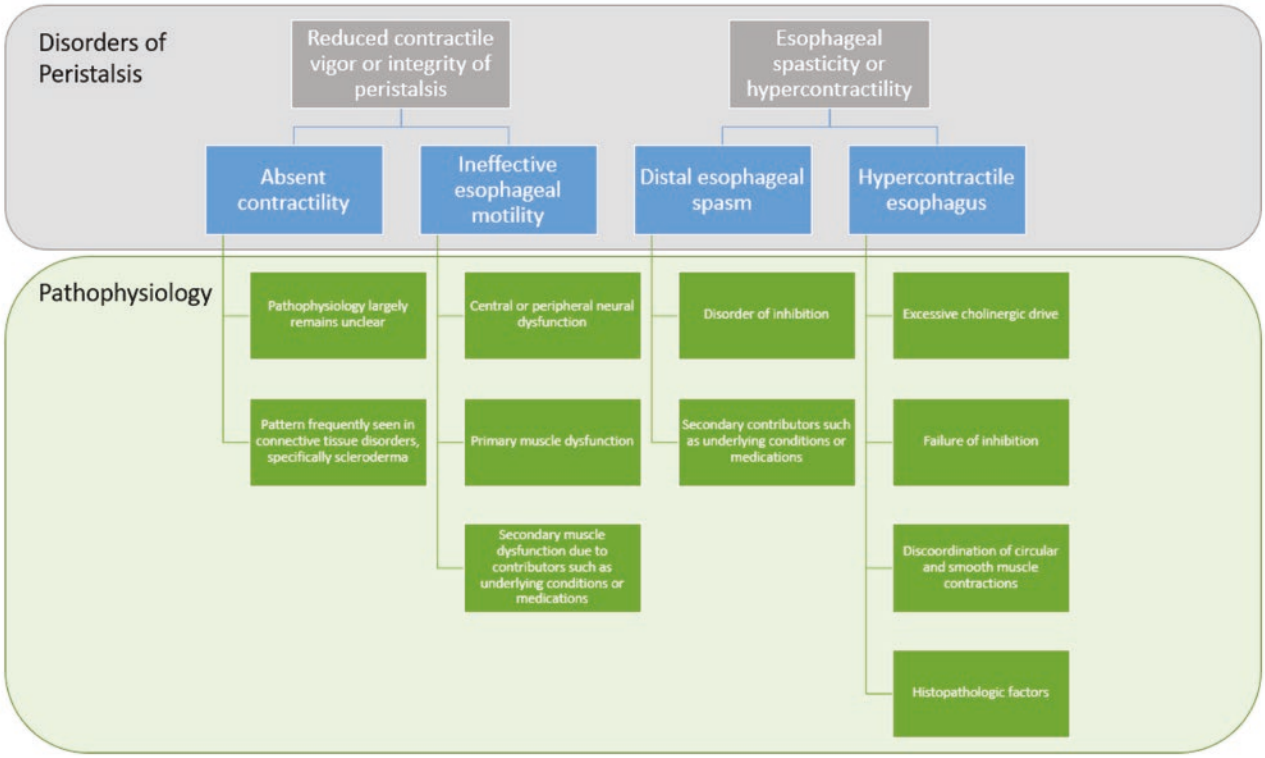

Fig. 27.1 Pathophysiology of Disorders of Peristalsis

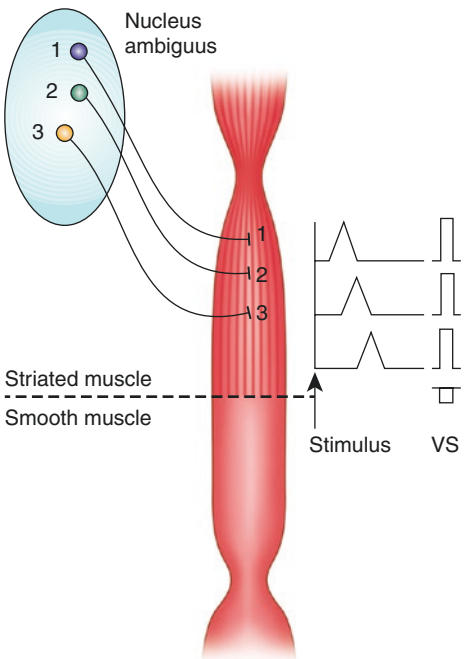

Fig. 27.2 Vagal stimulation (VS). The esophagus is composed of striated muscle in the proximal third or the cervical esophagus and smooth muscle in the thoracic or distal two-thirds of the esophagus. Esophageal striated muscle is innervated by excitatory motor neurons in the nucleus ambiguous of the brainstem. Esophageal smooth muscle is innervated by inhibitory and excitatory neurons receiving inputs from the dorsal motor nucleus of the vagus nerve [6]

neurons in the nucleus ambiguous of the brainstem. Esophageal smooth muscle is innervated by inhibitory and excitatory neurons receiving inputs from the dorsal motor nucleus of the vagus nerve. Excitatory or cholinergic neurons release acetylcholine whereas inhibitory neurons release NO [6, 13]. There are variations in cholinergic and nitrergic innervation throughout the esophagus with greater cholinergic innervation proximally and greater nitrergic innervation distally. Imbalances in excitatory and inhibitory neurotransmitters can result in esophageal dysmotility [12].

Absent Contractility

Absent contractility consists of normal lower esophageal sphincter (LES) relaxation and 100% failed peristaltic contractions on high-resolution esophageal manometry [1]. When this pattern is observed, achalasia should also be considered in the differential, particularly when high-resolution esophageal manometry reveals borderline lower esophageal integrated relaxation pressures with provocative maneuvers such as the rapid drink challenge and/or multiple rapid swallow [1]. Absent contractility is frequently recognized in connective tissue disorders, specifically scleroderma where neuropathy, myopathy, and esophageal fibrosis contribute to failed esophageal peristalsis. The pathophysiology of absent contractility otherwise largely remains unclear [14].

Ineffective Esophageal Motility (IEM)

Ineffective esophageal motility is a manometric diagnosis characterized by normal deglutitive relaxation of the lower esophageal sphincter (LES) with ≥70% ineffective (defined as a distal contractile integral or DCI of ≥100 mmHg-s-cm and <450 mmHg-s-cm) or ≥50% failed (DCI <100 mmHg-s-cm) peristalsis based on the CCv4.0 [1].

IEM results from neuronal or muscular dysfunction, or a combination of both. Central or peripheral neural dysfunction can diminish esophageal smooth muscle contractions and affect esophageal peristalsis. Ineffective or failed esophageal peristalsis can result from impairment of cholinergic excitatory innervation [6, 13]. Muscle dysfunction can be idiopathic or due to secondary factors. Secondary contributors to IEM can include medications with anticholinergic properties or underlying conditions that may affect esophageal smooth muscle function such as scleroderma or amyloidosis. Medications such as phosphodiesterase inhibitors and skeletal muscle relaxants can affect esophageal motility by reducing contractile vigor [13, 15].

Furthermore, IEM is a pattern frequently identified in high-resolution esophageal manometry in patients with gastroesophageal reflux disease (GERD) [16]. GERD has been described as both a potential cause and consequence of IEM [13, 15]. In animal models, inflammation due to esophagitis has been demonstrated to inhibit acetylcholine release and esophageal smooth muscle contraction [16]. Peristaltic dysfunction delays bolus clearance and prolongs reflux exposure time, which can lead to esophageal injury and inflammation. The severity of esophageal peristaltic impairment has been linked with the level of acid exposure and IEM has been found to be more prevalent in patients with more severe GERD [16, 17].

IEM is thought to be the most common pattern of esophageal dysmotility identified on esophageal manometry with an estimated prevalence of 20–30% [13, 16]. Other conditions associated with IEM include EoE, Barrett's esophagus, esophageal adenocarcinoma, acute ethanol ingestion, chronic alcoholism, and a history of endoscopic submucosal dissection [16]. It is noteworthy that IEM can also be present in asymptomatic healthy individuals and identification of this manometric diagnosis should warrant clinical correlation [13].

Distal Esophageal Spasm (DES)

Distal esophageal spasm is characterized by normal relaxation of the LES coupled with ≥20% of swallows with premature or spastic contractions with a distal latency (DL) less than 4.5 s and a DCI of 450 mmHg-s-cm or greater as defined by the CCv4.0 [1]. DES is uncommon with an estimated prevalence of between 3 and 9% in symptomatic patients [18].

DES is thought to be a disorder of inhibition with a deficiency of NO resulting in premature and simultaneous contractions in the distal esophagus [18, 19]. Increased thickness of the esophageal smooth muscle has also been observed in DES patients. It has been hypothesized that increased smooth muscle thickness could either be contributing to simultaneous contractions or the result of reduced inhibitory innervation [12, 19]. DES and achalasia both involve NO deficiency, and it has been speculated that these disorders may exist on a spectrum and that some cases of DES could progress to achalasia over time [19, 20]. DES has also been observed with GERD, opiate use, and EoE [8, 20].

Hypercontractile Esophagus

Hypercontractile esophagus (HE) is an esophageal motility disorder that is defined as a heterogeneous pattern observed on high-resolution esophageal manometry wherein the esophageal body exhibits vigorous contractions in the context of a normally relaxing LES [21]. A hypercontractile swallow is defined by a DCI of >8000 mmHg-s-cm. The manometric diagnosis of HE is made when at least 20% of supine swallows are hypercontractile in the absence of a mechanical obstruction [1].

Hypercontractile peristalsis is thought to result from either excessive cholinergic drive, failure of inhibition, or uncoordinated contractions of the circular and smooth muscles [11, 14, 21]. HE can also be observed in conjunction with esophagogastric outflow obstruction (EGJOO). HE associated with EGJOO is hypothesized to have two potential underlying mechanisms. First, downstream obstruction may be causing upstream pressurization. Second, abnormal nitrergic inhibition may contribute to both esophageal hypercontractility and incomplete EGJ relaxation with deglutition [11, 21]. Additionally, histopathological changes similar to those noted in achalasia have been observed in disorders of esophageal spasticity such as loss of inhibitory ganglion cells in myenteric plexus, loss of interstitial cells of Cajal, and lymphocytic infiltration [11].

HE is a pattern that has also been associated with opioid use. Opiates are thought to cause NO inhibition, resulting in high-amplitude esophageal contractions and impaired LES relaxation [11, 21]. Finally, HE has also been observed in EoE and the association is incompletely understood [21]. Eosinophils have secretory products that can affect esophageal smooth muscle contraction and a variety of esophageal motility disorders, including HE, have been described in patients with EoE [8, 21].

Summary

Esophageal motility disorders are classified by the CCv4.0 as either disorders of EGJ outflow or disorders of peristalsis [1]. Understanding the pathophysiology of the various types of esophageal motility disorders informs clinical decision-making and is a critical underpinning of treating patients with foregut disease. This understanding is beneficial when encountering patterns of esophageal dysmotility with potentially modifiable or reversible causes, such as opiate use or hernias. In other cases, the identification of certain underlying conditions associated with esophageal dysmotility such as an autoimmune disorder or malignancy can lead to additional or alternative points of intervention for the patient. Equally important is recognizing that not all patterns of esophageal dysmotility are clinically significant and that the decision to pursue intervention should be individualized and is dependent on presenting symptoms and the overall clinical picture.

Questions

1. In achalasia, there is a reduction in which molecule?
   A. Nitric oxide
   B. Cytokine VIP
   C. Acetylcholine
   D. A and B

Answer: D. Both nitric oxide (NO) and cytokine VIP are reduced in achalasia.

2. Which of the options below is not identified as a potential cause of hypercontractile esophagus?
   A. Obstruction
   B. Abnormal nitrergic inhibition
   C. Opiate use
   D. Chagas disease

Answer: D. Chagas disease is not commonly associated with hypercontractile esophagus. It is cited as a cause of achalasia.

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28

Diagnostic Testing for Esophageal Motility Disorders: Barium Radiography, High-Resolution Manometry, and the Functional Lumen Imaging Probe (FLIP)

Amit Patel, Felice Schnoll-Sussman, and C. Prakash Gyawali

Objectives

1. Recognize clinical settings where barium radiography may be helpful in the evaluation of esophageal symptoms or in the assessment of the outcome of achalasia therapy
2. Identify the indications for and contraindications to the performance of esophageal high-resolution manometry (HRM)
3. Explain the HRM study protocol with provocative maneuvers and recognize the data acquired from HRM evaluation
4. Describe the settings in which the functional lumen imaging probe (FLIP) may be utilized as a complementary test to HRM and barium radiography for evaluation of esophageal motor function and transit symptoms
5. Express how information acquired from FLIP, such as esophagogastric junction distensibility index (EGJ-DI) and esophageal body contractile patterns in response to volumetric distension, may contribute to diagnosis and management of patients with esophageal symptoms

Introduction

Esophageal symptoms, particularly dysphagia, regurgitation, and/or atypical chest pain, can originate from esophageal motility disorders. Evaluation starts with a careful history, which can be supplemented with patient self-report symptom questionnaires. An esophagoscopy with biopsies is typically performed to rule out mechanical or mucosal etiologies. Subsequently, esophageal diagnostic testing utilized for the evaluation of these symptoms and/or disorders may include barium radiography, esophageal high-resolution manometry (HRM), and/or the functional lumen imaging probe (FLIP) (Fig. 28.1).

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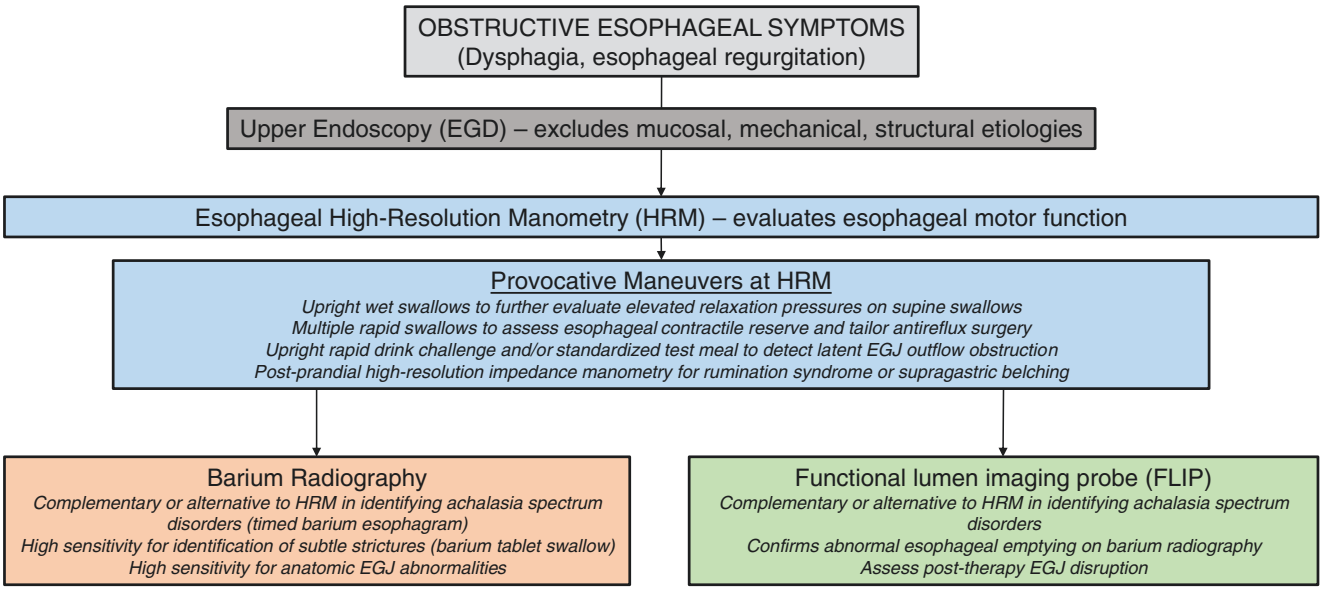

Fig. 28.1 Algorithm for evaluation of obstructive esophageal symptoms. Evaluation typically starts with an upper endoscopy; a barium esophagram is sometimes performed initially, but endoscopy is necessary for biopsies to rule out eosinophilic esophagitis or for endoscopic dilation. High-resolution manometry (HRM) is indicated when endoscopy is normal or suggests a motor disorder. Provocative maneuvers during HRM augment identification of obstructive findings. When HRM is equivocal, barium studies and functional lumen imaging probe (FLIP) can provide complementary evidence supporting or refuting an obstructive motor process

Barium Radiography

Introduction

Barium radiography has specific value when anatomic abnormalities are suspected, such as esophageal diverticula, paraesophageal hernia, or strictures. In addition to evaluating esophageal anatomy, barium radiography was previously the primary technique of choice in the assessment of esophageal motility and continues to have specific value in esophageal evaluation, particularly when esophageal manometry is not readily available. Barium radiography identifies oropharyngeal function and aspiration risk in addition to esophageal patency and bolus transit, which correlates with impedance manometry. Unfortunately, there is a dearth of information comparing these techniques when esophageal motor function is disordered. Older literature suggests that barium esophagram is less sensitive than esophageal manometry as a tool to diagnose esophageal motor disorders. Despite this, barium studies continue to have diagnostic utility in certain clinical settings (Fig. 28.2).

Indications and Patient Selection

Barium radiography of oropharyngeal function (videofluoroscopy or modified barium swallow, MBS) is utilized in identifying the location and severity of oropharyngeal neuromuscular dysfunction and determining the influence of bolus consistency and posture on bolus clearance or aspiration risk. Upper esophageal sphincter (UES) function and the presence of a Zenker's diverticulum can be identified.

Standard barium radiography can identify strictures and provide a road map prior to endoscopic dilation when complex and/or long strictures are suspected. Solid bolus barium radiography (i.e., barium pill swallow, marshmallow dipped in barium, barium cracker) can identify subtle strictures and narrowing. Barium studies are frequently utilized in assessing the anatomic relationship between the lower esophageal sphincter (LES) and the crural diaphragm (CD) at the esophagogastric junction (EGJ), especially prior to and following antireflux surgery.

The timed barium esophagram (TBE) is a valuable tool to determine the effectiveness of achalasia treatment. TBE is considered the diagnostic test of choice for the assessment of esophageal emptying after endoscopic or surgical treatment of achalasia, and it can identify incomplete emptying, a potential predictor of symptom relapse in as many as one-third of patients with achalasia with symptom remission after therapy.

Protocol and Technical Considerations

Videofluoroscopy or MBS provides lateral and anteroposterior views of the oral and pharyngeal phases of swallowing

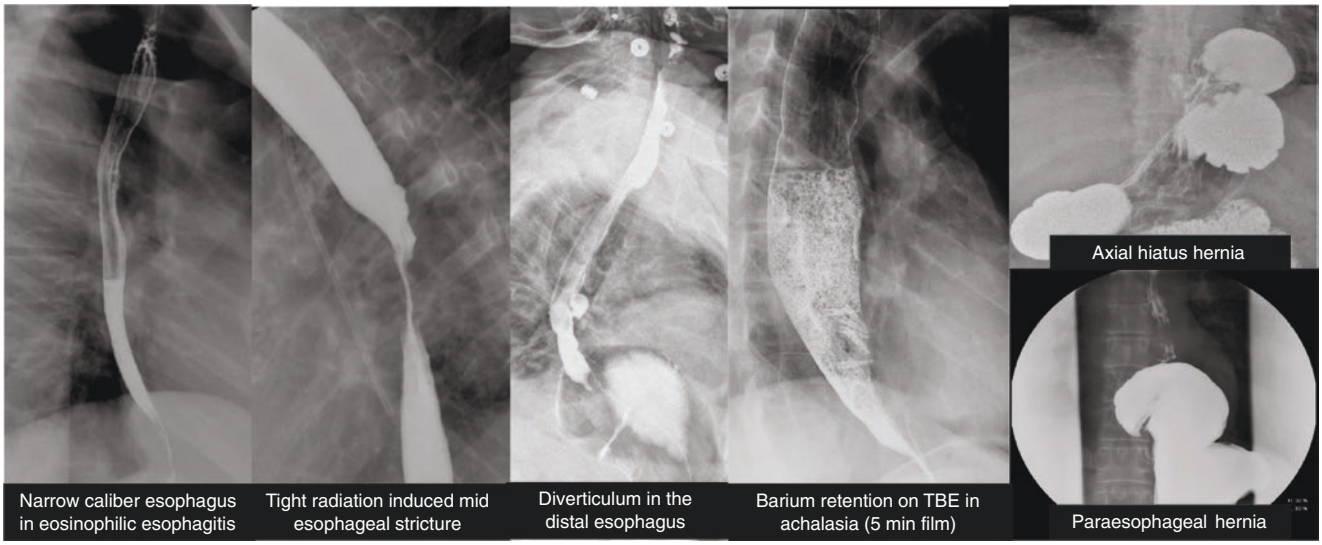

Fig. 28.2 Examples of abnormal barium radiographs. Barium studies have high value in identifying and defining strictures, diverticula, and other structural processes in the esophagus. A timed barium esophagram (TBE) can demonstrate abnormal esophageal emptying in achalasia and esophageal outflow obstruction, which can be used to follow achalasia outcome following definitive therapy. Barium studies have high value in documenting esophagogastric junction (EGJ) anatomy, including axial and paraesophageal hiatus hernias

using boluses of varying consistency (thin liquid, thick liquid, semisolid, solid). During the procedure, a speech pathologist typically instructs the patient on neck position and maneuvers that are most likely to be associated with adequate oropharyngeal clearance into the esophagus without aspiration. Alternatively, if significant aspiration is identified, enteral feeding may be recommended.

Barium pills, gelatin barium cubes, or marshmallows may be used to evaluate esophageal dysphagia when endoscopy is normal to simulate regular eating. Abnormal passage or retention of a 13 mm barium tablet can be indicative of an obstructive process at the EGJ. However, stasis can occur at the aortic arch even in healthy individuals, and stasis correlates poorly with abnormal motility. TBE requires the rapid administration of 200 mL of low-density barium sulphate in the upright position, followed by upright X-ray films of the esophagus at 1, 2, and 5 min.

Outcomes and Interpretation

Specific swallow therapies can be recommended based on videofluoroscopy findings, including enteral feeding when aspiration risk is determined to be high. Barium radiography of the tubular esophagus is utilized in identifying diverticula, strictures, webs, and tumors. Esophageal motor function is sometimes assessed with barium radiography; although a relationship exists between impaired passage of liquid barium and ineffective peristalsis, this relationship is weak and manometry is superior in assessing motor function. Stasis of contrast, a dilated lumen, and a bird's beak sign at the EGJ are classic features of achalasia on radiography, useful if manometry is not tolerated or unavailable, although type 3 achalasia may not demonstrate these findings. Rather than single or double-contrast barium radiography, TBE has particular value in evaluating achalasia, especially following achalasia therapy. Barium height at 1 min (abnormal when >5 cm) and 5 min (abnormal >2 cm) are useful in identifying abnormal esophageal emptying. There are no studies that directly compare TBE with non-timed barium esophagram.

Healthcare Costs

In the initial evaluation of dysphagia, barium radiography is less expensive compared to endoscopy. However, if a stricture were to be identified, follow-up endoscopy and dilation of the stricture following the initial barium radiography are more expensive than up-front endoscopy with stricture dilation. Further, the diagnosis of eosinophilic esophagitis, an important cause of dysphagia, requires endoscopic biopsies. For these reasons, barium radiography is now considered a complementary or second-line evaluation for esophageal dysphagia, although it remains the test of choice for oropharyngeal dysphagia.

Based on relevant Current Procedural Terminology (CPT) codes for 2021 from the Centers for Medicare and Medicaid Services (CMS), barium esophagram and modified barium swallow are associated with CPT codes 74220 (single-contrast study), 74221 (double-contrast study), and 74230 (modified barium swallow). CPT code 74220 is reported as 0.60 Global Physician Work Relative Value Units (RVUs)

with 2021 Medicare National Average Fee Schedule Amount of $103.28. CPT code 74221 is reported as 0.70 Global Physician Work Relative Value Units (RVUs) with 2021 Medicare National Average Fee Schedule Amount of $115.85. CPT code 74230 is reported as 0.53 Global Physician Work RVUs with 2021 Medicare National Average Fee Schedule Amount of $136.43.

Esophageal High-Resolution Manometry (HRM)

Introduction

HRM technology gathers esophageal intraluminal pressure data from closely spaced circumferential sensors on an esophageal catheter, which are displayed by dedicated software as smooth, color-contour topographic maps (widely known as *Clouse plots*, in honor of HRM pioneer Ray Clouse of Washington University). HRM represents a monumental advance over conventional manometry, since motor phenomena not previously appreciated can be detected, software tools can be utilized to interrogate pressure data, and interpretation is intuitive. The paradigm shift from conventional manometry to HRM allows real-time identification of esophageal anatomic landmarks during data acquisition, improved diagnostic accuracy with higher inter-rater agreement for the diagnosis of esophageal motor disorders, and categorization schema for achalasia spectrum disorders that has management implications (the Chicago Classification, which will be presented in the next chapter).

Indications and Patient Selection

HRM is indicated for the evaluation of esophageal symptoms (especially dysphagia and regurgitation but also chest pain and heartburn) not explained by endoscopy or barium radiography and/or not responsive to antisecretory therapy, as well as suspected abnormal esophageal emptying of motor etiology. HRM is also commonly utilized to localize the proximal border of the LES for the placement of catheter-based reflux monitoring probes. In patients with suspected gastroesophageal reflux disease (GERD) symptoms, HRM may assist in ruling out motor etiologies for symptoms (such as achalasia spectrum or spastic disorders), evaluating for behavioral disorders (such as rumination syndrome or supragastric belching), and assessing esophageal peristaltic performance prior to invasive antireflux procedures. HRM is also utilized to investigate transit symptoms following foregut surgery (particularly antireflux interventions) and/or bariatric procedures (particularly laparoscopic band placement).

Contraindications to performing HRM studies are infrequent. Absolute contraindications can include structural or infiltrative esophageal obstruction (i.e., malignancies), narrow or disfigured nasal passages or abnormal oropharyngeal anatomy precluding insertion or advancement of the HRM catheter, and frank aspiration with liquid swallows (although dry swallows can still be performed if HRM is absolutely needed for achalasia diagnosis). Relative contraindications consist of coagulopathies or anticoagulant use (increasing risk for epistaxis), the inability to follow instructions to withhold swallows or swallow on command, or the inability to tolerate catheter placement (placement during sedated endoscopy can be considered in select cases).

Equipment and Patient Preparation

Equipment preparation consists of different pressure calibration protocols for solid-state and water-perfused HRM catheters. Supplies used during the HRM study include viscous lidocaine, cotton-tipped swabs, lubrication jelly, water-filled syringes for test swallows, a cup with water and a straw, tape for securing the catheter to the nostril, an emesis basin, and towels.

Patient preparation includes medication review to consider withholding medications with the potential to impact esophageal motility, including opioids, prokinetics, calcium channel blockers, and anticholinergics, among others. Decisions regarding withholding medications should be based on the particular medication, HRM study indications, clinical setting, and the potential ramifications for patient management. Review of prior esophageal studies (upper endoscopy or barium radiography) helps identify anatomic abnormalities, such as hiatus hernia, prior foregut surgery, or dilated esophagus. Any allergies to topical analgesia (lidocaine) are reviewed. Patients are typically instructed to remain nil per os (NPO) for at least 4–6 h prior to the HRM study to minimize aspiration risk, though a liquid diet may be recommended for 1–2 days prior to the HRM study if there is suspicion of esophageal retention or abnormal emptying.

Protocol and Technical Considerations

The HRM catheter is typically inserted through the larger of the two nostrils with the patient sitting upright facing the operator while sipping water through a straw to relax the UES and LES. Distracting patients during catheter insertion (by asking them to squeeze soft balls, listen to music, open their mouths, watch the workstation screen, etc.) can maximize successful catheter insertion and minimize patient discomfort.

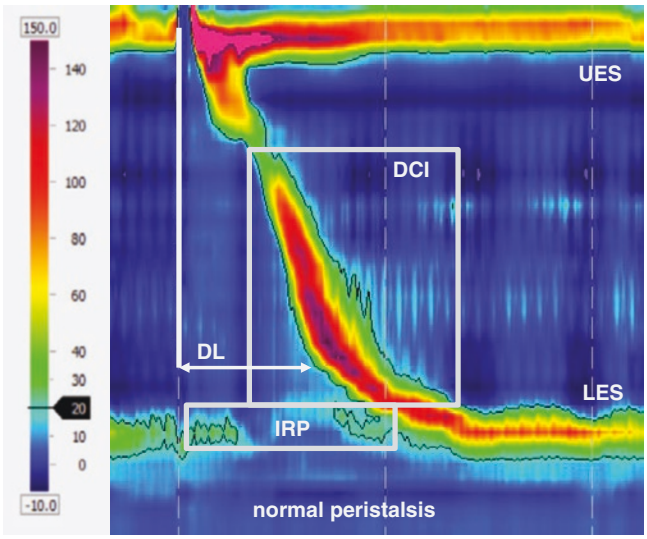

Fig. 28.3 High-resolution manometry (HRM) Clouse plot of a supine 5 mL water swallow. The Clouse plot is anchored by two bands of pressure, the upper esophageal sphincter (UES) and lower esophageal sphincter (LES), both of which relax to allow bolus transit during a test swallow. The peristaltic sequence is seen as a band of pressure progressing distally from the UES. HRM software tools are utilized to interrogate the HRM Clouse plot. Integrated relaxation pressure (IRP) is a measure of adequacy of LES relaxation with swallows and measures nadir LES pressure over 4 s, which can be continuous or discontinuous. Distal latency (DL) measures timing of peristalsis as the time duration between UES relaxation and arrival of the peristaltic sequence in the distal esophagus, where fast esophageal body peristalsis transitions into slower esophagogastric emptying at the contractile deceleration point (CDP). Distal contractile integral (DCI) measures vigor of esophageal smooth muscle contraction. These three cardinal metrics are utilized to characterize esophageal motor disorders by the hierarchical Chicago Classification of motor disorders

The HRM operator should be trained in recognizing anatomic landmarks, particularly the UES, LES, and CD (Fig. 28.3). An appropriately placed HRM catheter extends from the pharynx into the stomach, with at least 2–3 sensors in the stomach, and with clear visualization of bands of pressure representing the UES and LES. Although traversing the LES is essential for an adequate HRM study, traversing the CD is optimal but not critical to interpretation. Location of the CD is best appreciated during deep breaths, which enhance inspiratory CD contraction and trans-EGJ pressure inversion. Catheter coiling in the esophagus may produce a "butterfly" mirror image, which should be promptly identified. Re-positioning of the catheter across the EGJ can be facilitated by having the patient raise their arms above their head, stand up (to straighten the esophagus and potentially reduce a hiatus hernia), and/or gulp water (to facilitate LES relaxation); further, the operator can torque the catheter counterclockwise. If necessary, the catheter can be placed during sedated endoscopy. After appropriate placement of the catheter, the patient is moved to a supine position (with a slight head-of-bed elevation of 10°–15°) and a slight lean to the left, for the administration of standard test swallows.

The HRM test protocol typically begins with the landmark phase, a "quiet" baseline recording of at least 30 s without swallow or gagging artifacts, for acquisition of resting UES and LES metrics. This resting phase can be acquired later during the study if the patient has difficulty tolerating the catheter at the outset. The Chicago Classification of motility disorders is based on a foundation of 10 ambient temperature liquid 5 mL swallows (typically in the supine position) at least 20–30 s apart. Operators should recognize and reject artifacts (i.e., double swallows, transient LES relaxations, gagging, belching) and obtain 10 "clean" swallows whenever possible.

Provocative maneuvers during the HRM study protocol afford additional insight into esophageal motor function. Maneuvers with supportive data and clinical utility include multiple rapid swallows (MRS), rapid drink challenge (RDC), and upright test swallows (Fig. 28.4). MRS is performed by administering five 2 mL supine liquid swallows in intervals of <3 s. A physiologic (normal) MRS response features deglutitive inhibition of esophageal body peristalsis and LES relaxation during repetitive swallowing, followed by an augmented esophageal body contraction sequence after the final swallow. Contraction reserve indicates higher contraction vigor following MRS compared to single swallows, quantified using the distal contractile integral (DCI). The absence of MRS contraction reserve may be associated with post-fundoplication dysphagia and higher reflux burden compared to intact contraction reserve. Absence of contraction reserve in the context of ineffective esophageal motility (IEM) might impact surgical planning and perhaps avoidance of tight 360° fundoplication to minimize the risks of post-operative dysphagia. Since MRS is easy to perform and interpret, reproducible, and clinically useful, it is now recommended as part of the standard HRM protocol.

While MRS offers a physiologic challenge, RDC consists of a volume challenge, with the patient drinking 200 mL of water through a straw as quickly as tolerated while seated. Although deglutitive inhibition and profound LES relaxation may be seen similar to MRS, obstructive patterns including elevated integrated relaxation pressure (IRP) and pan-esophageal pressurization suggest latent EGJ outflow obstruction even when not apparent during single swallows.

Single upright swallows are particularly useful when supine swallows demonstrate elevated IRP but intact esophageal body peristalsis, previously designating EGJ outflow obstruction (EGJOO). This is a heterogeneous manometric pattern, sometimes artifactual and infrequently a precursor of achalasia. The clinical diagnosis of EGJOO now requires upright swallows to demonstrate persistent IRP elevation and additional evaluation beyond HRM (barium radiography

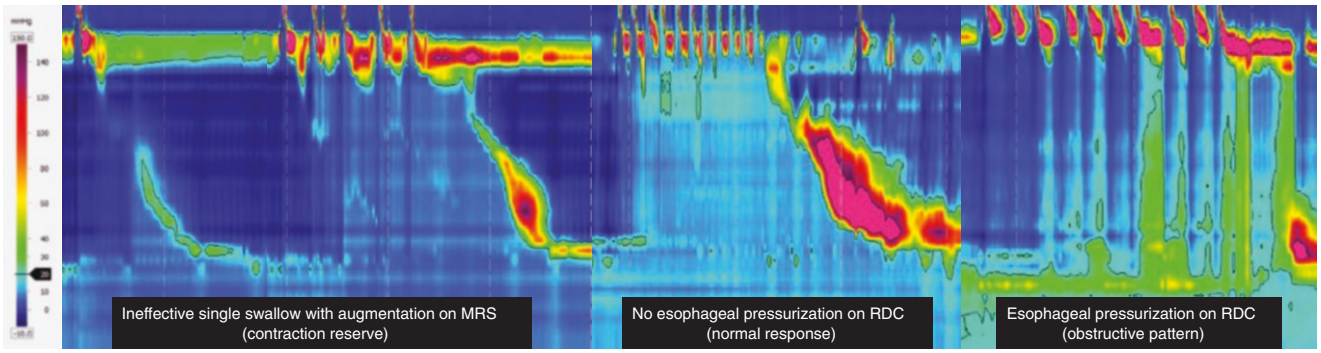

Fig. 28.4 Common provocative maneuvers utilized during high-resolution manometry (HRM). Multiple rapid swallows (MRS) consists of 5 swallows of 2 mL water administered in rapid succession while supine. During the swallows, there is inhibition of esophageal body peristalsis and relaxation of the lower esophageal sphincter (LES). After the final swallow, there is a robust contraction sequence with higher distal contractile integral (DCI) compared to mean DCI from single swallows—this is termed contraction reserve. When single swallows are consistently ineffective, the presence of contraction reserve indicates retention of adequate smooth muscle function, making standard fundoplication feasible. The absence of contraction reserve may indicate a higher propensity for post fundoplication dysphagia and higher esophageal reflux burden. Rapid drink challenge (RDC) consists of rapid ingestion of 200 mL of water through a straw in the sitting position. The normal esophagus is able to handle this volume challenge with esophageal smooth muscle inhibition and LES relaxation similar to that seen with RDC. When there is motor or structural obstruction at the esophagogastric junction (EGJ), there may be pressurization in the esophageal body with an increase in the trans-EGJ pressure gradient

and/or FLIP). Other provocative maneuvers such as viscous swallows, solid swallows, solid test meals, and pharmacologic provocation also have the potential to enhance the diagnostic yield of HRM, but normative values and clinical outcomes need additional study to merit routine inclusion of these maneuvers in the HRM study protocol.

Outcomes and Interpretation

HRM is a safe procedure; adverse events are typically minor and rare. Patients may experience nose or throat discomfort, gagging, or retching, but epistaxis or aspiration are far less common. Infection or perforation from an HRM procedure has not been formally reported in the literature.

Dedicated software tools have been developed for the interpretation of pressure data, displayed as three-dimensional Clouse plots, with time along the *x*-axis, esophageal length along the *y*-axis, and color contours representing pressure along the *z*-axis. Software tools calculate and quantify three cardinal metrics utilized in study interpretation (Fig. 28.3):

1. Integrated relaxation pressure, IRP: evaluates LES nadir pressure over four continuous or discontinuous seconds during swallow-induced LES relaxation. An abnormally high IRP (>15–20 mmHg depending on HRM system) identifies achalasia spectrum disorders.
2. Distal latency, DL: assesses sequencing and timing of peristalsis and measures the duration from UES relaxation to the contractile deceleration point, the inflection point which segregates smooth muscle esophageal body contraction from ampullary emptying; an abnormally short DL (<4.5 s) defines premature (spastic) swallows.
3. Distal contractile integral, DCI: quantifies the vigor of esophageal smooth muscle contraction, by incorporating contraction amplitude, length, and duration of contraction; the DCI segregates failed (<100 mmHg/cm/s), weak (100–450 mmHg/cm/s), normal (450–8000 mmHg/cm/s), and hypercontractile (>8000 mmHg/cm/s) swallows.

The three cardinal HRM metrics are utilized by the Chicago Classification to categorize motor patterns, as described in the next chapter. Overall, HRM studies have good reproducibility, and the image-based paradigm of Clouse plots are intuitive, assisting understanding of motor patterns by novice and expert interpreters alike. The Chicago Classification ensures standardized nomenclature and interpretation and utilizes a hierarchical algorithmic analysis of motor patterns. An HRM report should include patient information, study indications, anatomic details, motor parameters (LES, esophageal body, and UES), provocative maneuver data, impedance bolus transit information, and the Chicago Classification diagnosis, followed by clinical implications and recommendations.

Healthcare Costs

Based on relevant CPT codes for 2021 from the CMS published by the American Medical Association, high-

resolution impedance manometry (i.e., esophageal manometry with evaluation of bolus transit) is associated with CPT codes 91010 and 91037. CPT code 91010 (esophageal motility study with interpretation and report) is reported as 1.28 Global Physician Work RVUs with 2021 Medicare National Average Fee Schedule Amount of $227.50. CPT code 91037 (esophageal function test with nasal catheter intraluminal impedance electrode placement, recording, analysis, and interpretation) is reported as 0.97 Global Physician Work RVUs with 2021 Medicare National Average Fee Schedule Amount of $178.65.

Functional Lumen Imaging Probe (FLIP)

Introduction

The use of impedance planimetry in the esophagus via a catheter-mounted, fluid-filled balloon allows real-time measurement of esophageal and luminal cross-sectional areas (CSA) and intraluminal pressures using volumetric balloon distension. The ratio of CSA to intraluminal pressure assesses compliance, quantified by FLIP as distensibility index (DI). The transoral endoluminal FLIP (EndoFLIP) was initially approved by the US Food and Drug Administration (FDA) in 2010 with subsequent FDA approval of the EndoFLIP version 2.0 in 2017, which includes FLIP topography detailing esophageal body contractile patterns.

Indications and Patient Selection

Although there is widespread enthusiasm and ongoing investigation into potential uses for FLIP throughout the spectrum of esophageal diseases (including eosinophilic esophagitis and gastroesophageal reflux disease), the strongest data for its value exists for obstructive esophageal motor disorders, particularly achalasia spectrum disorders. For example, when symptoms and/or clinical data suggest an esophageal motor disorder but HRM is borderline, inconclusive, or not tolerated, FLIP may identify an achalasia spectrum or spastic esophageal disorder. FLIP can also arbitrate the commonly encountered manometric diagnosis of EGJ outflow obstruction (EGJOO), where the IRP is elevated but without esophageal body contractility abnormalities meeting criteria for a diagnosis of achalasia. FLIP may also be helpful in evaluating the adequacy of LES disruption after therapy in achalasia spectrum disorders.

Equipment

FLIP equipment features an 8 or 16 cm compliant balloon mounted at the distal end of a dedicated 24-cm long flexible catheter; the balloon-catheter combination is disposable and intended for single-use. The longer (16 cm) balloon allows the assessment of esophageal body secondary contractions in addition to the evaluation of EGJ compliance. The balloon includes 16 paired impedance planimetry sensors (1 cm apart on the longer balloon, 0.5 cm apart on the shorter balloon), which acquire CSA measurements during balloon distension during the FLIP study. Meanwhile, a single sensor located at the distal end of the balloon measures pressures. The proximal end of the catheter is attached to the FLIP device, with automated control of balloon volume from a pre-filled 80 mL syringe and dynamic display of motor function and EGJ compliance throughout the study.

Protocol and Technical Considerations

The FLIP protocol is typically performed immediately following sedated upper endoscopy while the patient remains sedated. After pressure calibration of the FLIP catheter, the catheter is inserted transorally, and the balloon is positioned across the EGJ, with the distal 2–4 sensors in the stomach. The endoscope may be reinserted to confirm appropriate placement through the EGJ but should be removed prior to balloon distension. The catheter is held in place by the operator near the mouth to maintain appropriate positioning during balloon distension and data acquisition.

As per accepted protocols, the balloon is sequentially distended to increasing volumes. Initial distension (20 mL for the shorter balloon, 30 mL for the longer balloon) with a waiting period of 30 s facilitates confirmation of landmarks and triggering of distension-associated secondary peristalsis. Subsequent filling of the balloon at 10-mL aliquots, with waiting periods of 30–60 s to appreciate contractile patterns and acquire EGJ diameter and distensibility measurements, is performed to target volumes of 40 mL for the shorter balloon and 60 mL for the longer balloon (these volumes have the most extensive normative data, and measurements at these volumes are considered the most reliable). If intra-bag pressures do not exceed 20 mmHg and/or EGJ outflow obstruction is suspected, additional distension of the longer balloon to 70 mL is appropriate in order to ensure adequate balloon distension to acquire accurate CSA (and thus, DI) values. If a hiatus hernia is present, measurements should typically be acquired at the level of the intrinsic LES. After completion of the FLIP protocol with acquisition of metrics, the balloon should be emptied into the pre-filled syringe, and the catheter removed and disposed of.

Outcomes and Interpretation

Throughout the FLIP protocol at increasing balloon volumes, the FLIP device displays balloon pressures and lumen CSA, as well as the calculated DI values, in real-time (Fig. 28.5). The DI at the EGJ (noted as a waist-like constriction at FLIP) represents the most studied and clinically useful metric acquired from FLIP and is considered consistently abnormal (reflective of EGJ outflow obstruction) if ≤2 mm^2/mmHg, borderline or indeterminate if 2–3 mm^2/mmHg, and normal if >3 mm^2/mmHg. When EGJ-DI values are indeterminate, EGJ diameter measurements <12 mm at intra-bag pressures of >20 mmHg may be supportive of EGJ outflow obstructive physiology.

Further, the FLIP 2.0 display also displays diameter changes over time in a topographic manner (similar to HRM), reflecting real-time, distension-induced secondary peristaltic patterns. FLIP allows classification of these contractile patterns, which can include repetitive anterograde contractions (RACs; runs of at least 3 consecutive anterograde contractions), repetitive retrograde contractions (RRCs), absent contractility, and contractile patterns not meeting criteria for the first three types. RACs represent expected secondary peristalsis among normal controls, but RRCs, which should not be seen in normal controls, may be supportive of impaired esophageal inhibition. The presence of RRCs in the setting of a normal EGJ-DI may suggest spastic esophageal motor disorders.

Combining EGJ-DI and distension-induced esophageal body contractile patterns can lead to a FLIP panometry diagnosis. Normal FLIP panometry (normal EGJ-DI >3 mm^2/mmHg with EGJ diameter >18 mm, RACs without RRCs) in the setting of normal esophagoscopy rules out a major esophageal motor disorder (Fig. 28.6). On the other hand, abnormal EGJ-DI provides complementary or alternative data to HRM in the identification of achalasia spectrum disorders. Specifically, FLIP may be particularly useful when HRM is borderline or inconclusive, especially when symptoms and/or clinical data raise suspicion for an achalasia spectrum disorder. FLIP can also provide information on the adequacy of management of achalasia spectrum disorders, during as well as after therapy [such as pneumatic dilation, Heller myotomy, or per-oral endoscopic myotomy (POEM)]. FLIP can clarify the clinical significance of manometric diagnoses of EGJOO and can identify the subset of these patients who are likely to respond well to achalasia-type EGJ-disruptive therapies.

Healthcare Costs

The equipment costs are about $25,000 and $65,000 for the FLIP 1.0 and 2.0 systems, respectively, with an approximate $350 cost for each catheter. Based on relevant CPT codes for 2021 from the CMS published by the American Medical Association, FLIP is associated with CPT code 91040 (esophageal balloon distension study, diagnostic, with provocation when performed), which is reported as 0.97 Global Physician Work RVUs with 2021 Medicare National Average Fee Schedule Amount of $562.13.

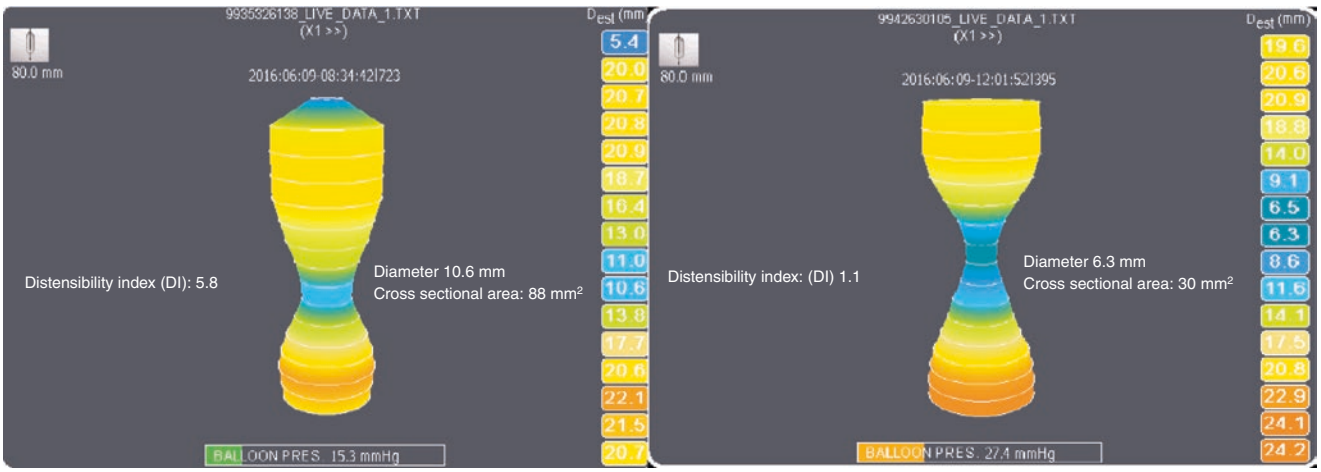

Fig. 28.5 Functional lumen imaging probe (FLIP) uses impedance planimetry to measure cross-sectional area at multiple levels in the distal esophagus during sedated endoscopy. The FLIP catheter has multiple pairs of impedance electrodes within a distensible balloon, which can be volumetrically distended with conductive fluid during the FLIP study. The relationship between cross-sectional area and intraballoon pressure defines distensibility index (DI, normal >3 mm^2/mmHg). DI is measured at the narrowest segment of the distal esophagus, representing the esophagogastric junction (EGJ). A low DI can be seen in achalasia spectrum disorders and can be used as a marker of adequacy of EGJ disruption in achalasia

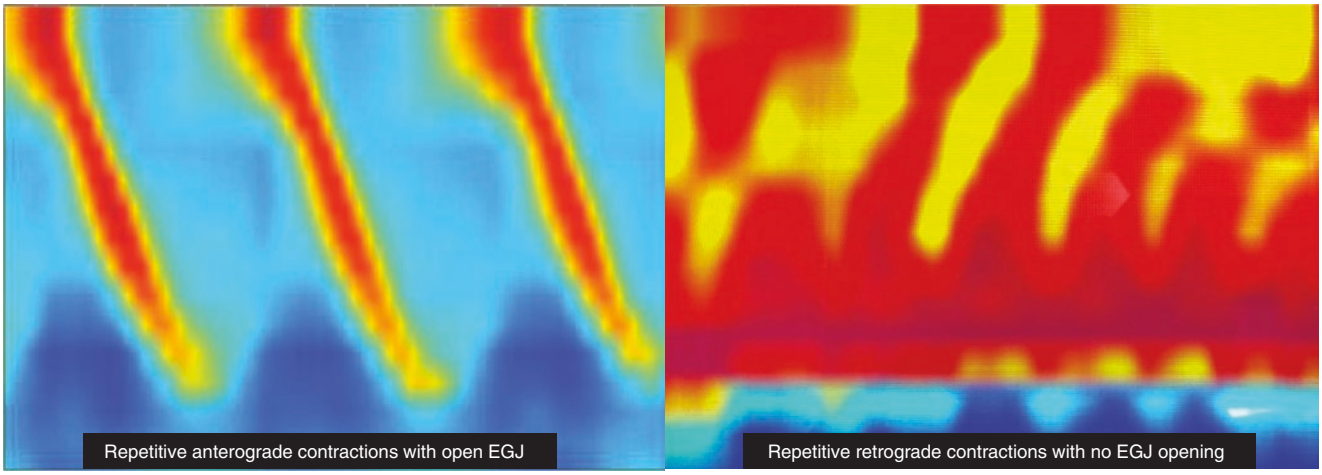

Fig. 28.6 Functional lumen imaging probe (FLIP) can also be used to assess secondary esophageal body peristalsis in addition to determination of esophagogastric junction (EGJ) opening during volumetric distension of a 16-cm balloon during sedated endoscopy. When lumen diameters measured across multiple pairs of impedance electrodes are plotted with time on the *x* axis, esophageal length along the *y* axis, and diameter as a function of topographical color (akin to high-resolution manometry) along the *z* axis, secondary peristalsis induced by volumetric distension can be visualized. Repetitive anterograde contractions are seen in health, associated with EGJ opening as volumetric distension progresses. Repetitive retrograde contractions with lack of EGJ opening may be seen in spastic motor disorders with EGJ obstruction

Conclusions

After initial esophagoscopy assessment, esophageal transit symptoms should prompt diagnostic evaluation for potential esophageal motor disorders; barium radiography, esophageal HRM, and/or FLIP should be considered, based on the clinical context (Fig. 28.1). Esophageal HRM is typically indicated for this evaluation of esophageal motor function and identification of esophageal motor diagnoses via the Chicago Classification version 4.0. Provocative maneuvers at HRM, which can include supine multiple rapid swallows, upright single swallows, and upright rapid drink challenge, provide additional insights into motor function beyond single test swallows, and in the latter case, may help detect latent EGJ outflow obstruction. Barium radiography, particularly with a timed upright protocol and/or barium tablet challenge, may provide complementary information, especially in the setting of suspected achalasia spectrum disorders or in evaluation after achalasia therapy. FLIP technology can provide complementary (or alternative) information to HRM and barium radiography, especially in the identification of achalasia spectrum disorders, in the evaluation of manometric diagnoses of EGJOO, and for assessment of EGJ disruption after therapy for achalasia.

Questions

1. Which of the following HRM metrics evaluates relaxation of the lower esophageal sphincter and helps identify achalasia spectrum disorders?
   A. Distal contractile integral
   B. Integrated relaxation pressure
   C. Distal latency
   D. Distal esophageal impedance
2. Which of the following combinations of FLIP panometry findings is observed in healthy subjects and rules out major esophageal motor disorders?
   A. Repetitive retrograde contractions and EGJ-DI $\leq$2 mm^2/mmHg
   B. Absent contractility and EGJ-DI 2–3 mm^2/mmHg
   C. Repetitive anterograde contractions and EGJ-DI >3 mm^2/mmHg
   D. Diminished contractile activity and EGJ-DI $\leq$2 mm^2/mmHg

Conflicts of Interest AP: none; FSS: Medtronic, Ironwood, Ethicon; CPG: Medtronic, Diversatek, Ironwood, Takeda, Quintiles, IsoThrive.

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The Chicago Classification of Esophageal Motor Disorders

29

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Abbreviations

CC v4.0	CC Version 4.0
CC	Chicago Classification
CD	Crural diaphragm
CDP	Contractile deceleration point
DCI	Distal contractile integral
DES	Distal esophageal spasm
DL	Distal latency
EGJ	Esophagogastric junction
EGJ-CI	EGJ contractile integral
EGJOO	EGJ outflow obstruction
FLIP	Functional lumen imaging probe
GRADE	Grading of Recommendations Assessment; Development; and Evaluation
HRM	High-resolution manometry
IEM	Ineffective esophageal motility
IRP	Integrated relaxation pressure
LES	Lower esophageal sphincter
MRS	Multiple rapid swallow
OIED	Opioid induced esophageal dysfunction
PEP	Panesophageal pressurization
POEM	Per-oral endoscopic myotomy
RDC	Rapid drink challenge
RIP	Respiratory inversion point
TBE	Timed barium esophagram

Objectives

1. To describe the history and evolution of the Chicago Classification
2. To present the current-day recommended standard esophageal high-resolution manometry protocol
3. To review the current day fourth version of the Chicago Classification of esophageal motor disorders
4. To describe the complementary relevance of additional data, including provocative manometric maneuvers, supportive diagnostic tests, and symptom presentation in determining clinical relevance and treatment plans

Introduction

The Chicago Classification (CC), now in its fourth iteration [CC Version 4.0 (CC v4.0)], represents the quintessential interpretation and classification scheme for the evaluation of motor function and the diagnosis of motility disorders with esophageal high-resolution manometry (HRM). The seminal contributions of Ray Clouse guided the conversion of esophageal motility data from line tracings and widely spaced catheter-based sensors into brightly colored pressure topographic maps (*Clouse plots*), commonly referred to as esophageal HRM. The indications, preparation, and technical considerations for the performance of esophageal HRM are discussed in the preceding chapter. The adoption and uptake of esophageal HRM in clinical settings led to the need to develop a collaborative, standardized approach for nomenclature and interpretation of HRM studies, prompting formation of the International HRM Working Group and the subsequent development of the first iteration of the CC (Fig. 29.1).

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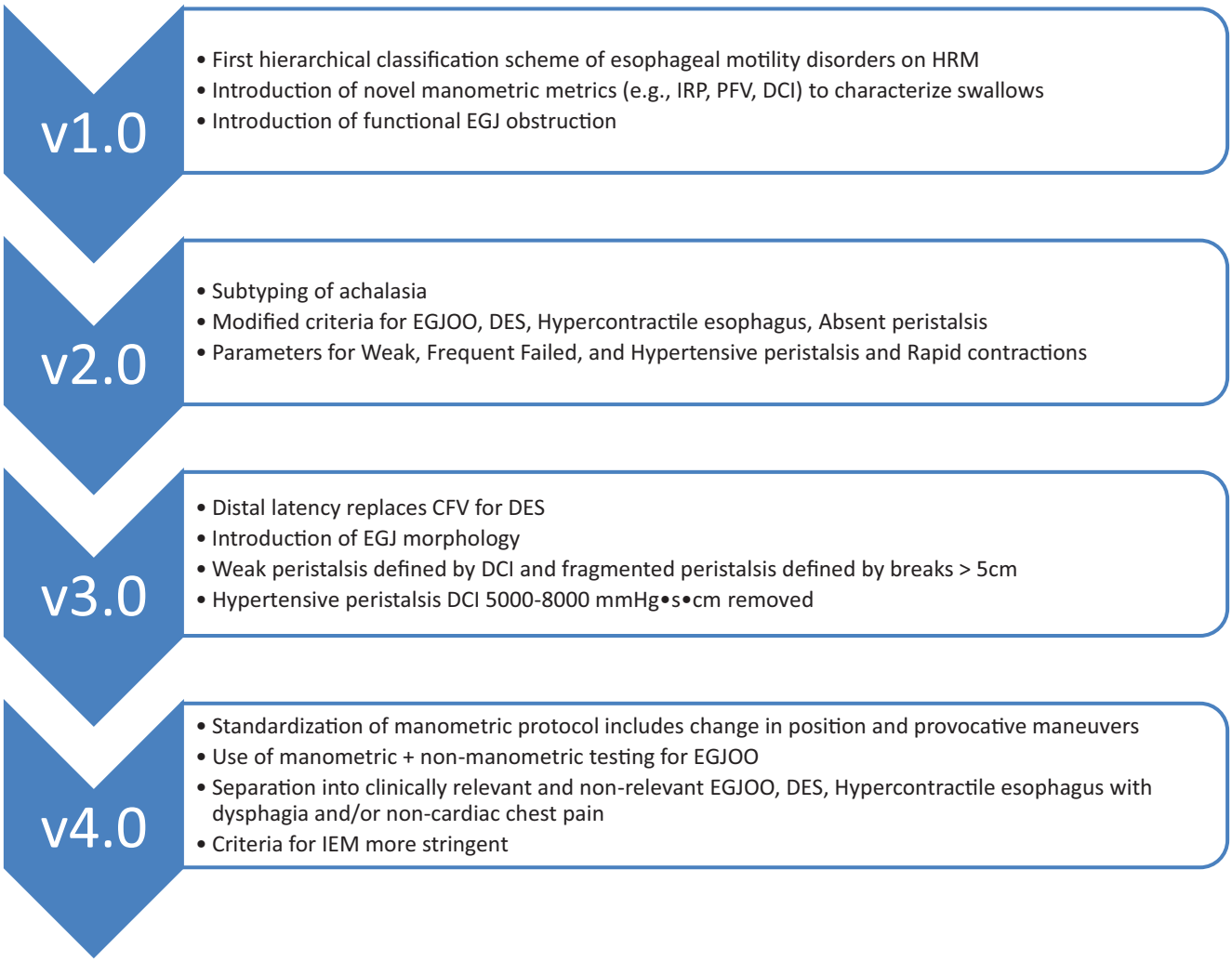


Fig. 29.1 The Chicago Classification is an iterative process that has evolved from v1.0 to v4.0

The First Chicago Classification—Version 1.0

The International HRM Working Group held their inaugural meeting in San Diego, and the first full version of the CC soon followed, with publication and dissemination in 2009. This first version of the CC introduced an algorithm largely guided by data from a comprehensive analysis of esophageal HRM studies from 75 normal subjects and 400 patients performed by Pandolfino and colleagues. Most notable in CC Version 1.0 was its inclusion of the integrated relaxation pressure (IRP), a then-novel metric whose central place in the understanding and quantification of esophagogastric junction (EGJ) relaxation has endured. In fact, the IRP has remained the cornerstone metric of each successive iteration of the CC, from a hierarchical perspective. The IRP was defined as the average pressure during the 4 s with the most complete relaxation (contiguous or non-contiguous) within the 10 s relaxation window after a swallow. Characterization of esophageal peristalsis as either normal, failed, hypotensive, or rapidly conducted was determined by the pressurization front velocity, the slope between the distal temporal margin of the transition zone and superior margin of the EGJ. Finally, contractile vigor was determined by the distal contractile integral (DCI), a measure of pressure across time and space. Applying these parameters, Version 1.0 of the CC described three types of achalasia; those with impaired EGJ relaxation and either (1) absent contractility, (2) panesophageal pressurization (PEP), or (3) spastic contractions. Functional EGJ outflow obstruction was defined by impaired EGJ relaxation with some preserved peristalsis. Disorders with intact EGJ relaxation included absent peristalsis, failed or hypotensive peristalsis, hypertensive peristalsis, and rapidly propagated pressurization. Thus, the CC Version 1.0 pioneered the standardization and dissemination of a blueprint for the classification of esophageal motor disorders based on HRM.

Updates in the Chicago Classification—Versions 2.0 and 3.0

Two major revisions to the CC were published in 2012 (Version 2.0) and 2015 (Version 3.0). A prominent primary update with Version 2.0 was the sub-typing of achalasia into achalasia type I (akin to classic achalasia), II (characterized by PEP), and III (spastic achalasia), with the inclusion of EGJ outflow obstruction (EGJOO) as a possible achalasia-spectrum variant. Importantly, this subtyping of achalasia had both prognostic and therapeutic implications. A second development was the emergence of distal latency (DL) as a metric for defining spastic (premature) contractions, replacing pressurization velocity as the defining criterion. This advancement stemmed from a study conducted by Pandolfino and colleagues of 1070 patients, recognizing that patients with high contractile front velocity or rapid contractions varied widely in terms of symptoms and motor diagnosis, with the majority having weak peristalsis or being normal. In contrast, they reported that patients with short DL values, signifying premature contraction, had dysphagia symptoms and were labeled as spastic achalasia or distal esophageal spasm. This development also came with the introduction of the contractile deceleration point (CDP), described by Pandolfino and colleagues after the publication of CC Version 1.0, as an important landmark in determining the DL and distinguishing normal from abnormal peristalsis, particularly when evaluating for spasm and altered bolus transit across the EGJ. A further major update with the CC Version 2.0 was the characterization of jackhammer esophagus, at the time synonymous with hypercontractile esophagus and identifiable by the presence of repetitive vigorous contractions, distinct from hypertensive or nutcracker peristalsis, patterns that could be observed in asymptomatic healthy populations. Another refinement involved expounding on the distinction between frequent failed peristalsis and weak peristalsis.

Version 3.0 of the CC further contributed detailed descriptions of EGJ morphology and focused on streamlining the criteria for peristaltic disorders to ease the application of the CC in clinical practice. Cutoffs for DCI were utilized to define failed peristalsis (<100 mmHg•s•cm), weak peristalsis (100–450 mmHg•s•cm), and hypercontractile peristalsis (>8000 mmHg•s•cm). The practice of using the term hypertensive peristalsis to describe swallows with DCI values between 5000–8000 mmHg•s•cm was discontinued, given the unclear clinical significance of this entity. Finally, fragmented peristalsis represented a new classification term, used to describe swallows with large peristaltic breaks in the 20 mmHg isobaric contour.

The Current Chicago Classification—Version 4.0 (Fig. 29.2)

With significant expansions in the clinical and research applications of HRM along with the emergence and development of novel therapies for achalasia, the core International HRM Working Group agreed in 2019 to proceed with a major update to the CC. In order to optimally foster the development of a rigorous and inclusive classification scheme generalizable across regions, practice types, and socioeconomic structures, representatives from six societies within the Federation of Neurogastroenterology and Motility from around the world were elected. This resulted in a diverse 52-member working group, representing 20 countries across five continents. Polling among the working group members revealed the following seven priority areas for update in the CC: standardization of the HRM study protocol, refinement of criteria for EGJOO, ineffective esophageal motility (IEM), distal esophageal spasm (DES), hypercontractile esophagus, and achalasia, as well as guidance on the assessment of EGJ barrier function.

The development of the CC v4.0 incorporated several additional significant and notable elements. Since normative thresholds for HRM parameters vary across manometry systems and with patient position (e.g., supine vs upright), CC v4.0 clarified the diagnostic thresholds for the IRP accordingly (Table 29.1). Further, recognizing that patterns on HRM do not always correspond with actionable pathology and that manometric patterns do not always provide conclusive diagnoses, a key priority of Version 4.0 was to add context on the importance of relevant symptoms and supportive data beyond standard HRM information (e.g., provocative maneuvers and/or adjunctive diagnostic tests) for certain scenarios in order to increase diagnostic confidence and guide clinical decision making. In addition, all recommendations articulated in CCv4.0 were formulated utilizing the formal RAND Appropriateness Method and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process to assess the quality of supportive evidence, when appropriate.

Standardized HRM Protocol (Fig. 29.3)

For the first time, a standardized HRM protocol was presented in CC v4.0 by which to apply and interpret HRM. Standardization of the study protocol in this fashion allows motility labs to utilize the same nomenclature (i.e., "speak the same language") and minimize misclassifications.

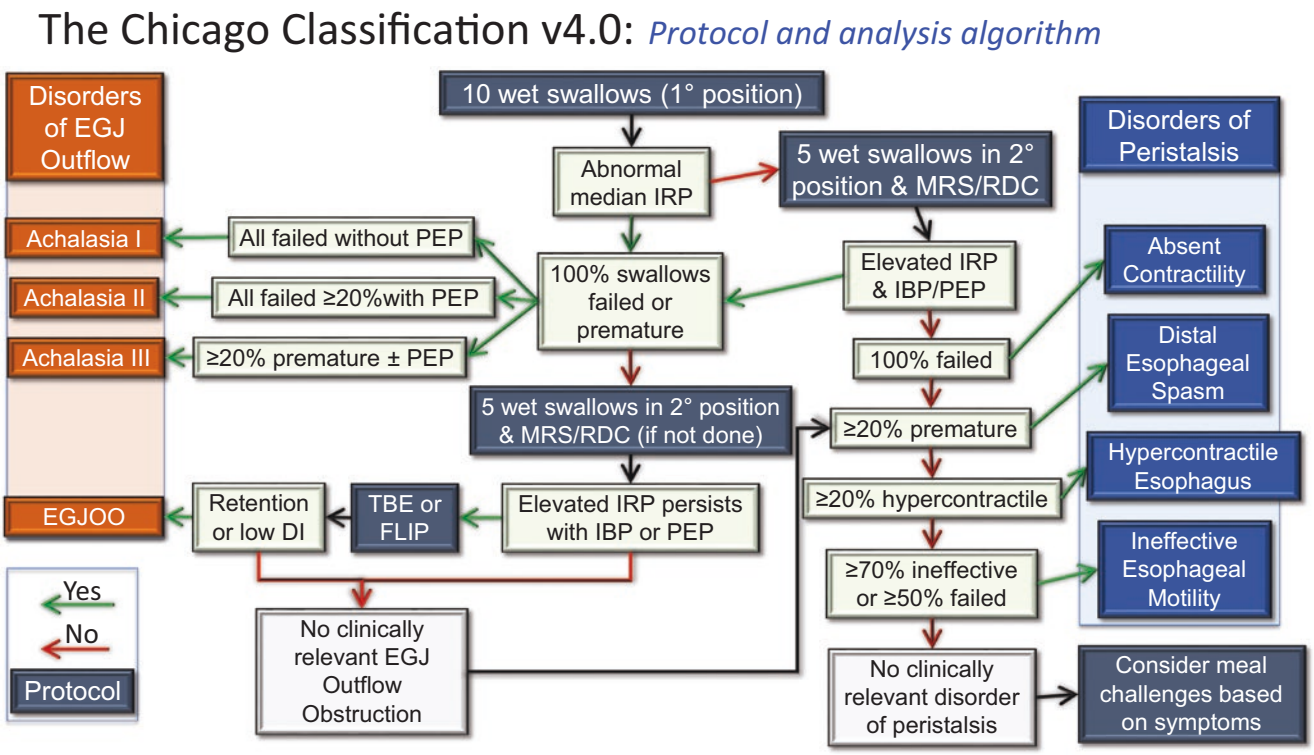


Fig. 29.2 According to the Chicago Classification version 4.0, the protocol can begin with either 10 wet swallows in the supine or upright position. In the case of an abnormal median IRP a diagnosis of achalasia type 1, 2, or 3 can be considered, and if not meeting criteria for achalasia requires an elevated IRP with position change with intrabolus pressurization in the supine position with confirmation of outflow obstructive physiology on time barium esophagram and/or FLIP as well as presence of obstructive symptoms to meet criteria for EGJ outflow obstruction. If the median IRP is normal in the primary position then disorders of peristalsis are considered, including absent contractility (as long as the median IRP remains normal with position change), distal esophageal spasm (if obstructive symptoms are present), hypercontractile esophagus (if obstructive symptoms are present), or ineffective esophageal motility

Table 29.1 Cardinal high-resolution manometry (HRM) metrics

HRM metric	Description	Thresholds
Integrated relaxation pressure (IRP)	Maximal relaxation of the esophagogastric junction with deglutition, referenced to gastric pressure, in mmHg	Abnormal if median IRP: *Medtronic*: ≥15 supine; ≥12 upright *Diversatek/Laborie*: ≥22 supine; ≥15 upright
Distal contractile integral (DCI)	Vigor of distal esophageal peristalsis from transition zone to the proximal lower esophageal sphincter, as a function of amplitude, duration, and length of contraction, in mmHg•s•cm	Failed: <100 mmHg•s•cm Weak: 100–450 mmHg•s•cm Normal: 450– 8000 mmHg•s•cm Hypercontractile: >8000 mmHg•s•cm
Distal latency (DL)	Latency of deglutitive inhibition measured from upper esophageal sphincter relaxation to the contractile deceleration point, in seconds	Premature (spastic): <4.5 when DCI ≥450 mmHg•s•cm

The Internal HRM Working Group agreed that the basic protocol of 10 supine wet swallows is often insufficient to establish a definitive motility diagnosis to explain esophageal symptoms and guide management, prompting recommendation for the routine inclusion of provocative maneuvers as a part of the HRM protocol. Specifically, the optimal HRM study protocol recommended by the CC v4.0 includes wet swallows in both the supine and upright positions, as well as at least one supine multiple rapid swallow (MRS) sequence, and an upright rapid drink challenge (RDC). In certain scenarios, it is deemed reasonable to limit the testing protocol to 10 supine or 10 upright wet swallows, such as in cases of clear-cut achalasia, particularly if there are aspiration risks present. The CC v4.0 also highlights the utility of ancillary maneuvers, such as the RDC, solid food swallows, or pharmacologic provocation, to elicit evidence of obstruction and potentially identify motor etiologies for symptoms. If clinically suspected, postprandial HRM studies with impedance sensors may also be helpful to identify rumination.

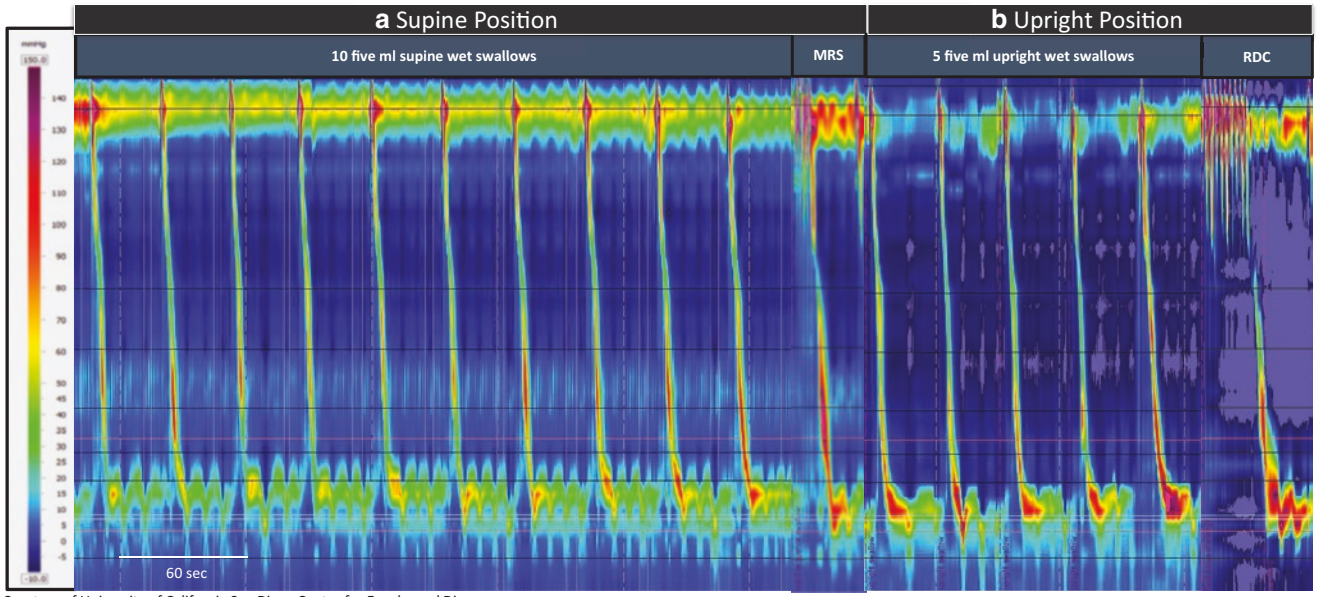


Fig. 29.3 Example of the CCv4.0 standard protocol. In this example, the protocol begins in the supine position. (**a**) Following a 60-s adaptation phase, 3 deep breaths, and 30-s baseline phase the swallows are initiated (as pictured) with ten 5 mL supine wet swallows and a multiple rapid swallow (MRS) sequence. (**b**) Then the patient is transitioned to an upright position. Following a 60-s adaptation phase, 3 deep breaths, and 30-s baseline phase, the swallows are initiated (as pictured) with five 5 mL supine wet swallows and a rapid drink challenge

Chicago Classification Version 4.0 of Esophageal Motility Disorders

CC v4.0 broadly classifies esophageal motility disorders on HRM as either (1) disorders of EGJ outflow or (2) disorders of esophageal peristalsis. With regard to updates from prior CC iterations, diagnoses of achalasia and absent contractility have largely stood the test of time and remain mostly unchanged. EGJOO, IEM, and fragmented peristalsis underwent considerable re-definitions with Version 4.0. The manometric criteria for diagnoses of DES and hypercontractile esophagus are largely unchanged given the absence of data to prompt major modifications, but both diagnoses now require concomitant symptoms of dysphagia and/or non-cardiac chest pain in order to meet criteria for esophageal motor patterns of clinical relevance.

Disorders of EGJ Outflow (Table 29.2)

The median IRP of 10 wet swallows (supine or upright) represents the first branching point of the CC Version 4.0 algorithm. An elevated median IRP (acknowledging differences in thresholds based on HRM system and patient position, Table 29.1) warrants consideration for disorders of EGJ outflow (i.e., achalasia or EGJOO).

Table 29.2 Disorders of esophagogastric junction (EGJ) outflow

Diagnosis	CC v4.0 criteria of elevated supine and/or upright median IRP *AND*	Additional considerations
Type I achalasia	100% failed peristalsis (DCI <100 mmHg•s•cm)	Distinction between types I and II achalasia may be somewhat arbitrary
Type II achalasia	100% failed peristalsis with ≥20% of swallows with panesophageal pressurization (PEP) at isobaric contour of ≥30 mmHg	PEP values ≥70 mmHg may have embedded spasm
Type III achalasia	100% absent peristalsis (either failed or spasm) with ≥20% of swallows with spasm (distal latency <4.5 s)	Per-oral endoscopic myotomy (POEM) considered first-line therapy for appropriate candidates
EGJ outflow obstruction (EGJOO)	Not meeting criteria for types I–II–III achalasia above, requires elevated IRP in *both* supine and upright positions	Conclusive and clinically relevant diagnosis of EGJOO requires elevated supine intrabolus pressure, at least one supportive non-HRM confirmatory diagnostic modality (i.e., functional lumen imaging probe or timed barium esophagram), and dysphagia and/or non-cardiac chest pain symptoms

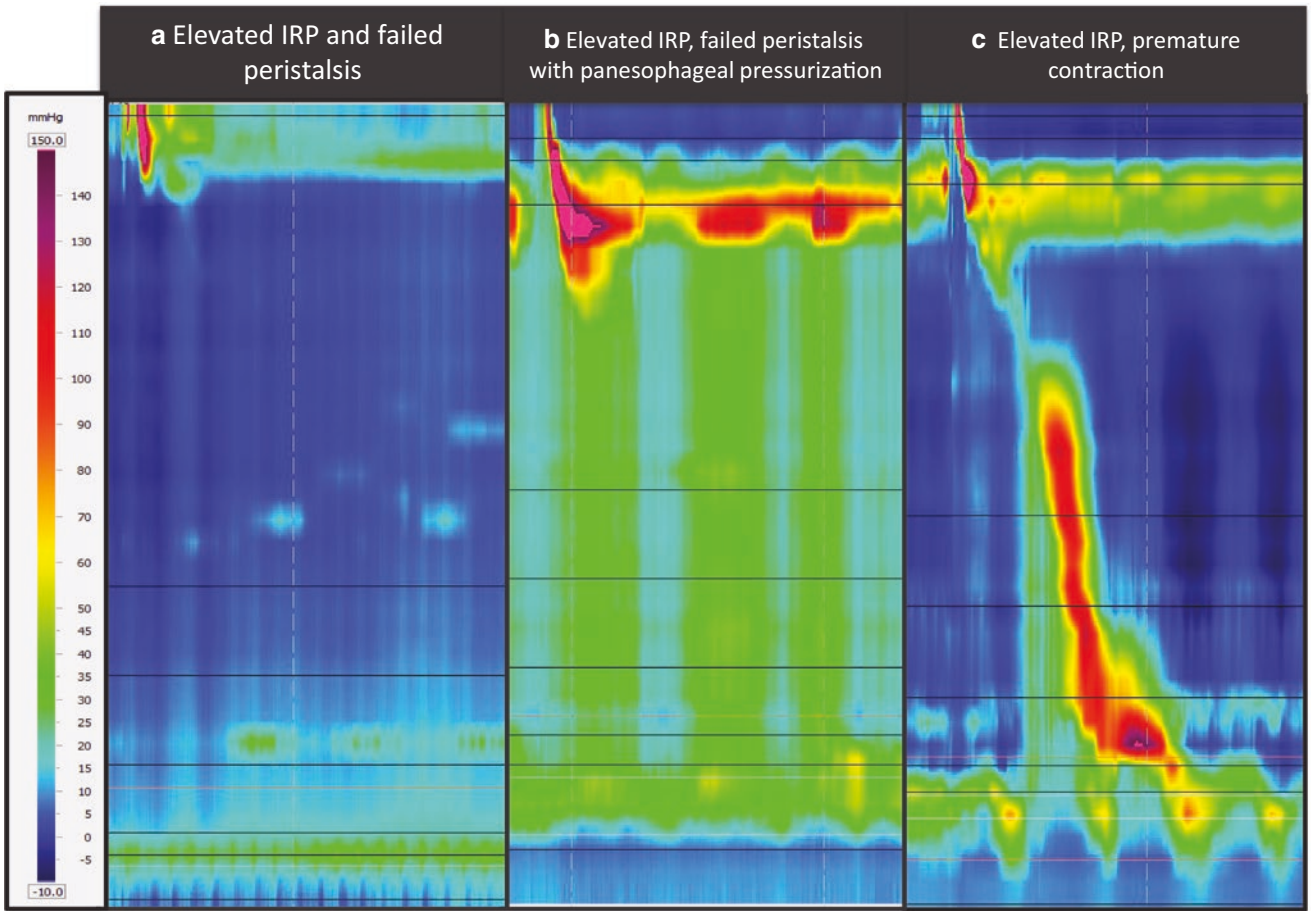


Fig. 29.4 Examples of swallows seen in achalasia type 1, 2, or 3. (**a**) The IRP is abnormal with failed peristalsis (DCI <100 mmHg•s•cm), as can be seen in all achalasia subtypes. (**b**) The IRP is abnormal with failed peristalsis and panesophageal pressurization, as is seen with ≥20% of swallows in type 2 achalasia. (**c**) The IRP is abnormal with a premature contraction (distal latency <4.5 s in the setting of a normal DCI). If this is present in 20% or more of swallows with failed peristalsis in the remaining swallows, this is consistent with type 3 achalasia

Achalasia (Fig. 29.4)

The conclusive manometric criteria for achalasia types I and II are consistent with prior CC iterations requiring an elevated median IRP (either in the supine and/or upright position) and 100% failed peristalsis. PEP remains a defining feature of type II achalasia, although CC v4.0 notes that the distinction between type I and II can be somewhat arbitrary and not necessarily predictive of distinct treatment outcome aside from extreme cases with minimal esophageal pressurization, severe esophageal dilatation, or sink-trap deformity. On the other hand, very high levels of pressurization within PEP may represent embedded esophageal spasm, potentially masking type III achalasia. Version 4.0 notes that several scenarios may shift interpretation of HRM towards an inconclusive diagnosis of types I or II achalasia, warranting supportive testing to guide clinical decisions, such as with a timed barium esophagram (TBE) and/or functional lumen imaging probe (FLIP). Specifically, (1) 100% absent contractility with IRP values near the upper limits of normal in both the supine and upright positions or (2) evidence of peristalsis with changing patient position in a pattern otherwise consistent with types I or II achalasia may be considered inconclusive for achalasia.

Type III achalasia requires an elevated median IRP (either in the supine and/or upright positions) with spasm (premature contraction, defined as DL <4.5 s with DCI >450 mmHg•s•cm) in at least 20% of wet swallows. Although prior iterations of the CC were ambiguous as to whether a diagnosis of type III achalasia required 100% failed peristalsis, Version 4.0 clearly requires 100% absent peristalsis (defined as either failed peristalsis or spasm). Therefore, per CC v4.0, patients who have an elevated IRP, elevated intrabolus pressurization, and swallows with a mixture of spasm and otherwise "normal" peristalsis meet criteria for EGJOO with spastic features rather than a conclusive diagnosis of type III achalasia. Greater proportions of test swallows with spasm increases confidence in managing it as type III achalasia. Per-oral endoscopic myotomy (POEM) with extension of the myotomy proximally, tailored to the length of the spastic segment, is the generally accepted first-

line treatment for type III achalasia, given superior outcome compared to therapies focused only on LES disruption. Version 4.0 acknowledges that opioid-induced esophageal dysfunction (OIED) can mimic type III achalasia and that HRM studies should be done withholding opioids if possible, based on medication half-life. Given their potential reversibility, cases of OIED should be directed toward opioid cessation and conservative therapeutic approaches, if possible.

EGJ Outflow Obstruction

CC v4.0 brings major updates in the diagnosis and characterization of EGJOO, a heterogeneous diagnosis commonly encountered with CC v3.0. As with prior iterations of the CC, a diagnosis of EGJOO should be considered when the median IRP is elevated but esophageal body peristalsis is sufficiently intact to exclude achalasia. However, while some cases of EGJOO represent variant or evolving achalasia and should be managed accordingly, a substantial proportion is unrelated to LES dysfunction, instead representing effects of artifact, sliding hiatal hernia, mechanical obstruction, OIED, etc. Consequently, interventions to disrupt the LES are not appropriate for most cases of EGJOO; irreversible interventions such as myotomy should be reserved for a carefully selected, well-characterized subgroup.

Given the problem of over-diagnosis encountered with CC v3.0, a major focus of CC v4.0 was to refine the identification of actionable EGJOO. New criteria for EGJOO stipulate an elevated IRP in *both* supine and upright positions as well as at least 20% of wet supine swallows with intrabolus pressurization (without meeting criteria for achalasia). Isolated elevations in supine IRP (with normal upright IRP) or upright IRP (with normal supine IRP) should be considered inconclusive for actionable EGJOO. Further, a manometric diagnosis of EGJOO should always be considered clinically inconclusive, requiring that there also be relevant symptoms of dysphagia and/or non-cardiac chest pain and supportive evidence of obstructive physiology from a non-HRM test such as a TBE or FLIP study. Responses to provocative maneuvers, such as MRS, RDC, solid swallows, or pharmacologic provocation, may also strengthen confidence in a manometric EGJOO diagnosis. For example, outflow obstructions and esophageal pressurization with RDC, outflow obstruction with a solid test meal, and/or abnormal EGJ function with pharmacologic provocation constitute supportive evidence for a manometric diagnosis of EGJOO.

CC v4.0 also encourages the description of EGJOO in the context of the associated esophageal body peristaltic pattern. Specifically, EGJOO may be described with spastic features, with hypercontractile features, with ineffective motility, or without evidence for disordered peristalsis. However, the distinction between type III achalasia and EGJOO with spastic features can be challenging and depends on the presence of some "normal" peristalsis. Likewise, EGJOO with hypercontractile features may represent reactive hypercontractility to mechanical EGJ obstruction or the hypercontractility may represent a primary motility disorder involving the LES. In contrast, diagnoses of EGJOO with ineffective motility or EGJOO without evidence of disordered peristalsis are more likely to represent a manifestation of reflux physiology or a normal variant, especially if there is minimal evidence of intrabolus pressurization or PEP. In brief, supportive testing is always warranted for further characterization of these inconclusive EGJOO diagnoses to guide clinical management.

Disorders of Peristalsis (Table 29.3)

Following the algorithmic classification of CC v4.0, a disorder of peristalsis should be considered if the median IRP is normal or if the median IRP is elevated but criteria for a con-

Table 29.3 Disorders of esophageal peristalsis

Diagnosis	CC v4.0 criteria of normal median IRP *AND*	Additional considerations
Absent contractility	100% failed peristalsis	Borderline median IRP values should prompt consideration of type I achalasia, especially if prominent dysphagia
Distal esophageal spasm (DES)	≥20% of swallows with premature contraction (distal latency <4.5 s) in setting of dysphagia and/or non-cardiac chest pain symptoms	≥20% of swallows with premature contraction but DCI <450 mmHg•s•cm is inconclusive for manometric diagnosis of DES
Hypercontractile esophagus	≥20% of swallows with hypercontractility (DCI >8000 mmHg•s•cm) in setting of dysphagia and/or non-cardiac chest pain symptoms	Must rule out distal esophageal/EGJ mechanical obstruction; three sub-types (single-peaked hypercontractile swallows, jackhammer with repetitive prolonged contractions, hypercontractile swallows with vigorous LES after-contraction)
Ineffective esophageal motility (IEM)	>70% of swallows ineffective (DCI <450 mmHg•s•cm) and/or fragmented (peristaltic break >5 cm in 20 mmHg isobaric contour with normal DCI), *or* ≥50% swallows failed (DCI <100 mmHg•s•cm)	50–70% of swallows ineffective is inconclusive for diagnosis of IEM and should prompt supportive data (poor bolus transit on impedance or barium esophagram, lack of contraction reserve on multiple rapid swallow sequences)

clusive manometric diagnosis of EGJOO are not met. Consistent with CC v3.0, disorders of peristalsis may include absent contractility, DES, hypercontractile esophagus, and IEM. Fragmented peristalsis was, however, eliminated and merged with IEM. CC v4.0 also recommends a hierarchical classification among disorders of peristalsis, with DES, then hypercontractile esophagus, and finally IEM, acknowledging potentially overlapping features.

Absent Contractility (Fig. 29.5a)

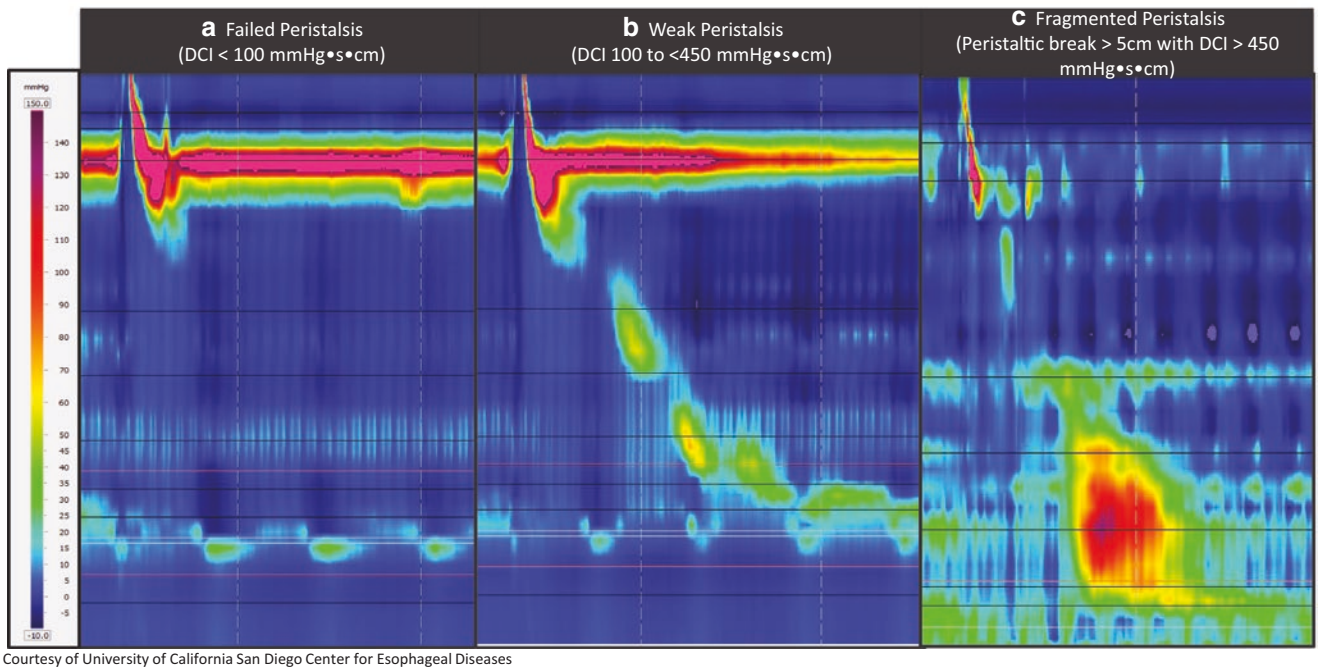
The criteria for absent contractility remain unchanged for CC v4.0, with a conclusive diagnosis requiring normal median IRP in the supine and upright positions and 100% failed peristalsis (DCI <100 mmHg•s•cm). Version 4.0 points out that for cases meeting criteria for absent contractility with a median IRP near the upper limit of normal (i.e., supine IRP of 10–15 mmHg on the Medtronic system), particularly in patients with prominent dysphagia, it is imperative to consider type I achalasia as an alternative diagnosis. Manometric provocative maneuvers (such as RDC, solid test meal) and/or adjunctive modalities (such as TBE, FLIP) help to make this important distinction.

Distal Esophageal Spasm (Fig. 29.6a)

As in CC v3.0, CC v4.0 maintains the requirement of ≥20% of swallows with premature contractions (DL <4.5 s) for a diagnosis of DES. However, the manometric finding by itself is inconclusive and the diagnosis also mandates the presence of dysphagia and/or non-cardiac chest pain to meet criteria for clinically relevant DES. The ≥20% of swallows with premature contractions must also exhibit a DCI >450 mmHg•s•cm to be classified as indicative of spasm. In terms of clinical relevance, DES is an exceedingly rare finding and, when encountered, often falls within the spectrum of type III achalasia. Similar to the distinction between EGJOO with spastic features and type III achalasia, greater proportions of swallows with evidence of spasm and prominent dysphagia and/or chest pain increase the confidence in the diagnosis of a primary spastic disorder. Alternatively, a significant proportion of DES patterns may represent a secondary response to gastroesophageal reflux. Further data are warranted to better distinguish among phenotypes of manometric DES and guide management approaches.

Hypercontractile Esophagus (Fig. 29.6b–d)

A subtle modification made in CC v4.0 was to shift jackhammer esophagus to a subtype of hypercontractility rather than considering the two synonymous. The importance of ruling out mechanical obstruction at the distal esophagus or EGJ, which can induce a reactive hypercontractile response, is also highlighted. Furthermore, consistent with the hierarchical organization of disorders of peristalsis, the criteria for



Courtesy of University of California San Diego Center for Esophageal Diseases

Fig. 29.5 Examples of ineffective swallows. An ineffective swallow can be (**a**) failed, with the DCI <100 mmHg•s•cm, (**b**) weak, with the DCI 100 or greater yet less than 450 mmHg•s•cm, or (**c**) fragmented, where the DCI is normal and there is a large break in peristaltic integrity. A conclusive diagnosis of ineffective esophageal motility requires ≥50% failed peristalsis or ≥70% ineffective swallows. In absent contractility, 100% of swallows are failed

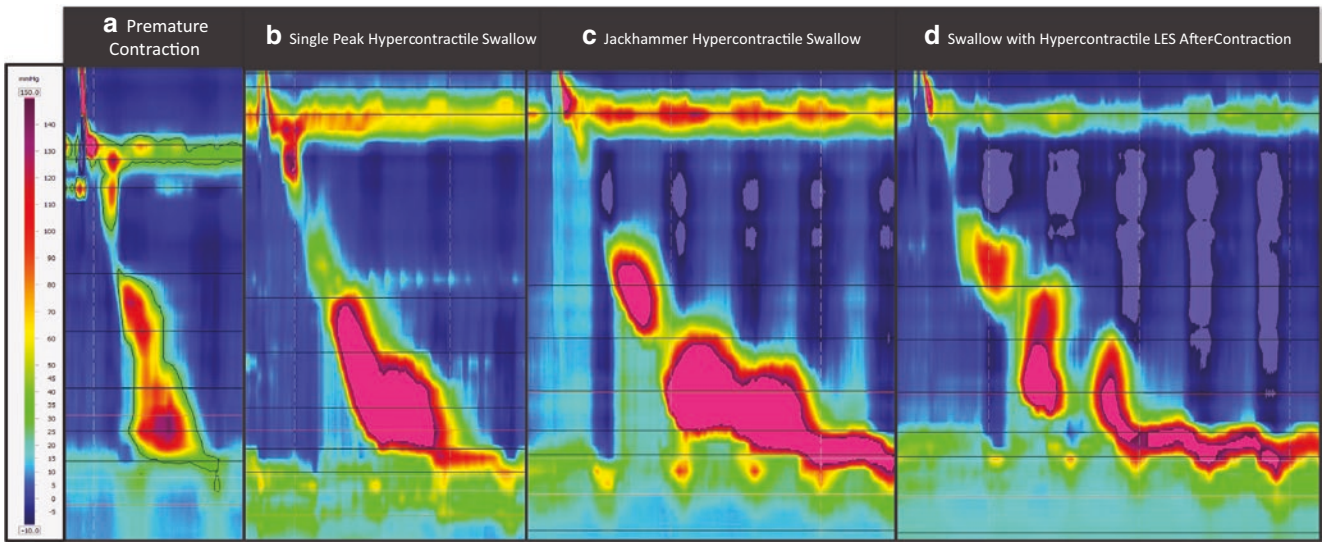


Fig. 29.6 Examples of premature or hypercontractile swallows. (**a**) Normal IRP with a premature contraction (distal latency <4.5 s in the setting of a normal DCI). If present in 20% or more of swallows, this is consistent with manometric distal esophageal spasm. In (**b**–**d**) the IRP is normal and DCI is >8000 mmHg•s•cm with distinct phenotypes of hypercontractile swallows including, (**b**) single-peak hypercontractile, (**c**) repetitive prolonged contractions (Jackhammer), or (**d**) hypercontractile LES after contraction

type III achalasia or DES cannot be present. Consequently, CC v4.0 requires ≥20% hypercontractile swallows (DCI >8000 mmHg•s•cm) in the supine position and symptoms of dysphagia and/or non-cardiac chest pain to make a clinically relevant and conclusive diagnosis of hypercontractile esophagus.

New in CC v4.0, hypercontractile esophagus is considered a heterogeneous condition, comprised of three subtypes: (1) jackhammer with repetitive prolonged contractions (especially in the post-peak phase) generally associated with greater DCI values and more profound symptoms, (2) single-peaked hypercontractile swallows that are often a reaction to mechanical outflow obstruction, and (3) hypercontractile swallows with a vigorous LES after-contraction. CC v4.0 suggests a more cautious management strategy for hypercontractile esophagus, particularly without jackhammer features. As with EGJOO, conservative medical therapy should be exhausted prior to consideration of myotomy.

Ineffective Esophageal Motility (Fig. 29.5)

In combination with the "upgrading" of IEM and fragmented peristalsis from minor motility disorders as in prior iterations of the CC (CC v4.0 does not differentiate between major or minor motility disorders), CC v4.0 combines these entities and applies more stringent criteria for an IEM diagnosis. Specifically, a conclusive diagnosis of IEM requires " >70%" of swallows to be ineffective (DCI <450 mmHg•s•cm) or fragmented (>5 cm break in the 20 mmHg isobaric contour of for swallows with DCI >450 mmHg•s•cm). Alternatively, ≥50% failed swallows (DCI <100 mmHg•s•cm) also constitutes IEM. If 50 to 70% of swallows are ineffective, the study may be considered inconclusive for a diagnosis of IEM. In such cases, poor bolus transit on impedance at HRM, absence of contractile reserve on MRS sequences, and/or poor transit on barium esophagram may be considered supportive evidence for IEM.

EGJ Barrier Metrics

In addition to defining and classifying motility disorders with greater reliability, ease, and yield, a major advantage of HRM lies in evaluating EGJ barrier function as it pertains to both dysphagia and reflux disease. Impaired EGJ barrier function leads to excessive distal esophageal acid exposure or, in severe cases, esophagitis. Hence, proposed HRM metrics assessing EGJ integrity are clinically important and were a focus for inclusion in CC v4.0. However, the EGJ is a complex sphincter comprised of both a crural diaphragm (CD) and lower LES component, each of which is subject to independent physiological control mechanisms and pathophysiology. No single metric can capture all attributes of EGJ barrier function. The working group considered several potential metrics of EGJ integrity, including LES–CD separation, the EGJ contractile integral (EGJ–CI), the respiratory inversion point (RIP), and intragastric pressure. Strong recommendations were made regarding LES–CD separation as indicative of hiatus hernia, although the numerical threshold for defining hiatal hernia was not agreed upon. There was also no agreement on the significance of the RIP, only that it

could localize either above the LES or between the LES and CD in cases of hiatus hernia. There was agreement on how to measure the EGJ–CI and that it should be referenced to gastric pressure in units of mmHg cm, but the numerical threshold indicative of a hypotensive EGJ varied widely among reports and was not agreed upon. Intragastric pressure was endorsed as an important metric worthy of further study, but there was no agreement on a numerical threshold indicative of abdominal obesity. In brief, while there was support for their quantification, there was no agreement on the threshold values defining abnormality for any of these metrics.

Conclusion

Esophageal HRM studies should be interpreted and reported with the CC v4.0 algorithm. This state-of-the-art current iteration was developed by a diverse international group of esophageal motility experts representing several international motility societies and with increased rigor, incorporating GRADE and RAND. Relative to prior CC versions, several major, clinically significant modifications have been made, largely aimed at minimizing over-diagnosis of manometrically inconclusive conditions. Specifically, CC v4.0 stipulates an ideal standardized study protocol for consistency among centers, emphasizes the need for and utility of additional supporting data in instances of inconclusive diagnoses (both manometric, with provocative maneuvers, and non-manometric, with TBE and/or FLIP), the importance of clinically relevant symptoms with inconclusive diagnoses, the elimination of a distinction between major and minor motility disorders, and more stringent criteria for diagnoses of EGJOO, DES, hypercontractile esophagus, and IEM. Future iterations of the CC will be inspired by fresh data and investigations focusing on therapeutic outcomes to build upon these refinements.

Questions

1. Which of the following Chicago Classification v4.0 diagnosis is met by an elevated median IRP, ≥20% of swallows with short latency (<4.5 s), and no normal peristalsis in the setting of dysphagia, no opiate use, and a normal upper endoscopy?
   A. Achalasia, type III
   B. Distal esophageal spasm
   C. Esophagogastric junction outflow obstruction
   D. Hypercontractile esophagus
2. In Chicago Classification v4.0 a conclusive diagnosis of EGJ outflow obstruction requires all of the following except:
   A. Symptoms of dysphagia and/or chest pain
   B. An elevated median IRP
   C. A timed barium esophagram showing impaired bolus transit or a functional luminal imaging probe study with a low distensibility index
   D. >50% of swallows with DCI >450 mmHg•s•cm

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Cricopharyngeal Disorders, Endoscopic, Stapled, and Open Cricomyotomy and Adjuncts for Zenker's Diverticulum

30

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Objectives

1. To describe the pathophysiology of cricopharyngeal disorders ranging from achalasia to Zenker's diverticulum
2. To explore clinical presentation and relevant workup for cricopharyngeal disorders
3. To describe the surgical management of cricopharyngeal disorders, including endoscopic and open surgical approaches

Introduction

Background

Zenker's diverticulum (ZD) is a pulsion diverticulum, an acquired herniation of mucosal and sub-mucosal layers through the posterior wall of the pharyngoesophageal junction [1]. This false diverticulum occurs through Killian's triangle, a weak point between the horizontal fibers of the cricopharyngeus and the oblique fibers of the inferior constrictors [2]. It is believed that cricopharyngeal achalasia is an early manifestation on the spectrum of upper esophageal dysmotility and when left untreated may lead to ZD. First described in 1769, it was not until a century later that the German pathologist Dr. Albert von Zenker further described the pathophysiology of the eponymous disorder. It is the most common upper gastrointestinal diverticulum with a reported prevalence of 0.01–0.11% with an annual incidence of 2 per 100,000 and is found almost exclusively in patients in the seventh and eighth decades of life. This condition has a higher preponderance for males than females with a 1.5:1.0 ratio [3, 4]. Geographically, this diverticulum is more common in those patients of northern European descent.

Relevant Anatomy

The anatomy of the upper esophageal sphincter (UES) is complex, but a deeper understanding can lead to improved surgical outcomes. The inferior pharyngeal constrictor (IPC) is the thickest, most developed of the three pharyngeal constrictors. Its most caudal portion is referred to as the cricopharyngeus (CP) muscle. This muscle comprises the majority of the UES which is a 2–4 cm high-pressure zone that includes the IPC, CP, and upper esophagus. The CP is primarily composed of striated muscle fibers. It receives motor innervation from the vagus nerve via the pharyngeal plexus and the recurrent laryngeal nerves. The CP is tonically contracted at rest, allowing it to behave like a sphincter in the UES. During swallowing, vagal tone is inhibited and sphincter pressure decreases prior to its opening. Failure of the UES to open leads to dysphagia symptoms and risk of aspiration [5, 6]. Reduced CP relaxation and achalasia may result from many neuromuscular diseases such as amyotrophic lateral sclerosis, polymyositis, myasthenia gravis, multiple sclerosis, Parkinson's disease, and cerebrovascular accidents. These conditions lead to pharyngeal weakness, reduced pharyngeal contraction, and hyolaryngeal elevation, which compound the reduced UES opening. Cricopharyngeal achalasia may also be idiopathic or result from gastroesophageal reflux disease among other etiologies and commonly presents as dysphagia, weight loss, regurgitation, dysphonia, globus, cough, choking, and aspiration [5].

Pathophysiology

The pathophysiology of Zenker's diverticulum is complex and multifactorial, with contributions from multiple processes [5]. Several hypotheses have been proposed to

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explain pathophysiology and include chronic gastroesophageal reflux, the natural aging process and loss of tissue elasticity, or anatomical predisposition. Several studies suggest a possible relationship between gastroesophageal reflux disease (GERD) and Zenker's diverticulum, but no direct causal relationship has been established [7–10]. Proposed explanations for GERD involvement include persistently elevated CP tone or spasms secondary to reflux, or that acid-induced esophageal shortening results in a gap between the constrictors and the CP, allowing for herniation caudal to the pharyngeal constrictors [11]. Cook et al. suggest CP dysfunction occurs due to muscle fiber degeneration and replacement with fibroadipose tissue. Histological analysis of CP muscle biopsies from patients with Zenker's diverticulum obtained at the time of diverticulectomy reveals abundant fibrosis within the CP muscle of Zenker's diverticulum compared to autopsy controls [12]. Additionally, Venturi et al. noted an increased collagen to elastin ratio in the CP muscle in Zenker's diverticulum patients. It is suspected that these changes are responsible for the decreased upper esophageal sphincter opening during deglutition in Zenker's diverticulum patients [13]. Inadequate relaxation of the cricopharyngeus from hypertrophy and fibrotic changes leads to increased proximal intraluminal pressure during swallowing. Over time, the increased pressure during swallowing against an incompletely relaxing upper esophageal sphincter results in a left-sided protrusion of proximal mucosal and submucosal layers proximally through a defect in Killian's triangle [14].

Clinical Presentation

Development of a diverticular pouch often results in retention of food particles, causing patient complaints of regurgitation of partially digested food, halitosis, aspiration, globus, and weight loss. Over 98% of patients will list progressive dysphagia as their primary complaint [15]. Rarely, a left-sided cervical bulge or gurgling can be palpated on physical exam, known as the Boyce sign [16]. Untreated advanced ZD can result in complications such as aspiration pneumonia, malnutrition, or even perforation. Some studies have reported an incidence of associated malignancy in 0.5% of cases. Progressive dysphagia with regurgitation of partially digested food should prompt an evaluation for ZD [17].

Evaluation

The diagnostic workup for cricopharyngeal achalasia and Zenker's diverticulum is essentially the same. The clinical assessment begins with a history and physical exam. Patients with cricopharyngeal achalasia will often complain of solid food dysphagia and may localize this to the base of the neck rather than the chest. To adequately evaluate dysphagia, a combination of clinical and radiographic tools must be used. Dysfunction of the UES is suggested by hypopharyngeal and post-cricoid pooling of secretions with intact pharyngeal strength. The modified barium swallow study (MBSS) is a video-fluoroscopic procedure designed to evaluate the passage of food/liquid through the mouth and pharynx into the esophagus. The MBSS allows for the simultaneous assessment of UES opening, hyolaryngeal elevation, and pharyngeal and tongue base contraction. The hallmark of UES dysfunction on MBSS is the posterior indentation at the pharyngoesophageal junction, usually between the C4 and C6 vertebrae (Fig. 30.1). This is identified as the cricopharyngeal bar. The presence of this thickening is not in itself diagnostic. This must be accompanied by evidence of bolus obstruction proximal to the UES. This study is also useful for identifying the pouch that is characteristic of a Zenker's diverticulum. The barium esophagram is the workhorse diagnostic tool for the evaluation of anatomic and physiologic esophageal abnormalities and is usually the first test to identify a narrowing or diverticulum at the level of the UES. Flexible upper endoscopy is essential to assist in preoperative planning and to rule out malignancy and to delineate anatomy. Esophagopharyngeal reflux, or regurgitation of swallowed food, may be seen on flexible endoscopic evaluation of swallowing almost immediately after the swallowed bolus disappears below the hypopharynx. This is a pathognomonic sign for Zenker's diverticulum [5]. High-resolution manometry can be used as an adjunct to confirm diagnosis of cricopharyngeal achalasia though is often not the first line. A recent study found significantly higher crico-

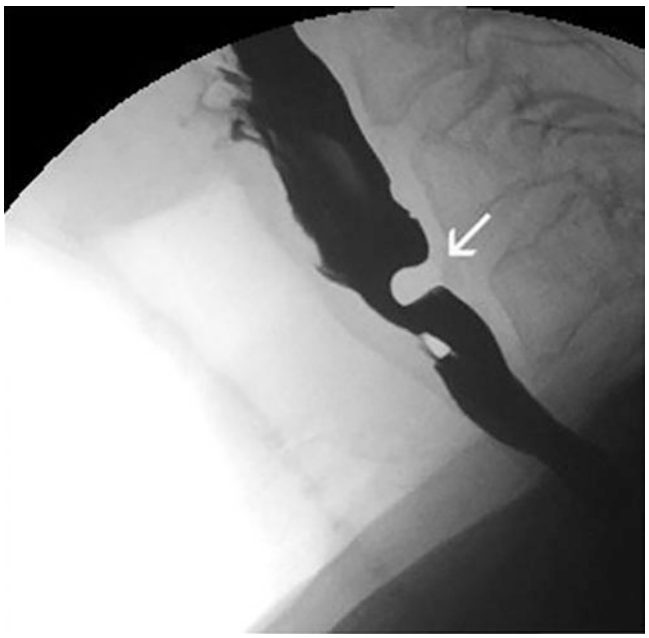

Fig. 30.1 Cricopharyngeal bar. Modified barium swallow image demonstrating prominent cricopharyngeal bar

pharyngeal residual pressures in patients with known ZD, but no differences in resting or maximum pressures were identified [18]. Several different classifications exist to describe ZD, but these are subjective and infrequently used.

Treatment Considerations

Treatment options for cricopharyngeal achalasia depend on the underlying cause of UES dysfunction, but all aim to reduce sphincter tone, mechanically enhance UES opening through myotomy or dilation, or improve swallowing function and UES opening with swallowing therapy and exercises [19]. Curative treatment of Zenker's diverticulum, on the other hand, is always surgical and is indicated for symptomatic patients. The most common interventions include open or endoscopic, either rigid or flexible. There is no consensus as to which procedure is superior, but rigid endoscopy has become the most common approach because it is associated with decreased hospital stay, decreased anesthesia time, and fewer complications when compared to the open approach [17, 20]. Flexible endoscopy is less common but may offer advantages over the other two treatments. All carry a success rate of 80–100% and individual patient factors must be considered when choosing the correct surgical approach. Regardless of procedure, the goals of therapy remain the same. Surgical myotomy rather than diverticulectomy is the desired outcome in order to decrease the high-pressure zone. This is achieved by dividing the cricopharyngeal muscle fibers and thereby disrupting the muscular ring which results in improved swallowing function and decreased intraluminal pressure Table 30.1.

Table 30.1 Overview of treatment modalities for cricopharyngeal disorders

	Advantages	Drawbacks
Cricopharyngeal achalasia		
Endoscopic botox injections	Effective	Temporary
	Minimally invasive	May affect surrounding tissues
Dilation	Minimally invasive	Low morbidity
Zenker's diverticulum		
Open approach	Able to address giant diverticula	Increased morbidity
	Less recurrence	Longer length of stay
Rigid endoscopy	Shorter length of stay	Higher recurrence rate
	Minimally invasive	Incomplete myotomy
Flexible endoscopy	No neck extension limitations	More technically challenging
	Overcomes limitations of stapler	Higher complication rate
		Higher recurrence rate

Treatment Modalities and Technical Considerations

Botulinum Toxin

Botulinum toxin provides a temporary chemodenervation leading to muscle paralysis by inhibiting the presynaptic release of acetylcholine [21]. There is a wide variation in the dose and technique used [22]. A range of 5–100 units has been reported. Botulinum toxin can be administered in the outpatient setting via transcutaneous transcervical electromyographic guided technique or in the operating room via direct suspension laryngoscopy and rigid esophagoscopy. The overall complication rate is minimal [22]. The impact of Botulinum toxin is noted within 1–2 weeks and may last up to 5–6 months. There is genuine concern for diffusion of Botulinum toxin to surrounding tissue causing worsening of dysphagia symptoms and so small volumes and high concentrations with injection into the posterior midline CP muscle should be used.

Dilation

Esophageal dilation dates back to the seventeenth century when it was performed with a whale bone. More recently, in the past few decades, UES dilation with a bougie dilator has been performed. Modern fixed-diameter wire-guided dilators, such as the Savary dilator, have been used with excellent efficacy and are safer due to the wire guidance of the bougie. Currently, most dilations are performed using controlled radial expansion (CRE) balloon dilators. UES dilation can be performed in the clinic setting using transnasal esophagoscopy (TNE) and transnasal insertion of the balloon catheter. However, it is useful to perform the initial dilation in the operating room so that the UES region can be examined, CP muscle palpated, and the largest balloon possible used for dilation. The UES is exposed using a Dedo laryngoscope placed in the postcricoid space just above the CP. This places the CP under slight tension. A thin caliber rigid suction is then used to palpate the CP to get an impression of how hypertrophic and/or spastic it might be. A complete flexible esophagoscopy is then performed using the TNE scope through the Dedo laryngoscope for assessment of the entire esophagus. Balloon dilation is then typically performed with a CRE esophageal balloon dilator to 20 mm for 30–60 s. The balloon is deflated and repeat esophagoscopy is performed to assess for any mucosal trauma or significant esophageal laceration and to confirm easier passage through the UES [5].

Myotomy

Upper esophageal dysfunction resulting from increased cricopharyngeal pressure is implicated in the development of Zenker's diverticulum. Therefore, CP myotomy is necessary in both cricopharyngeal achalasia and Zenker's diver-

ticulum management to normalize the opening size of the UES, reduce resting UES pressure, and decrease intrabolus pressure.

Open Approach

The first CP myotomy was performed by Samuel Kaplan in 1949 using an open transcervical approach under local anesthesia in a 28-year-old post-poliomyelitis patient with multiple unilateral cranial neuropathies [23]. Today, surgical CP myotomy is the gold-standard treatment for UES dysfunction. It may be performed via the traditional open transcervical approach or via endoscopy.

Open CP myotomy is performed under general anesthesia. It should always begin with a direct laryngoscopy and esophagoscopy to evaluate the cricopharyngeus muscle and to rule out the presence of early diverticulum. Under direct visualization, an endotracheal tube, Maloney dilator, or bougie may be placed within the lumen of the esophagus to provide moderate distension of the pharyngoesophageal segment. This aids in identification of the upper esophageal sphincter, the division of its fibers, and the evaluation of the appropriate myotomy depth. The esophagus is approached through a left cervical incision at the level of the cricoid cartilage with a neck crease from the sternocleidomastoid (SCM) muscle edge. Subplatysmal flaps are elated from the level of the thyroid notch to 2–3 cm below the cricoid cartilage. The medial border of the SCM is skeletonized to open the carotid triangle. As the omohyoid comes into view, this is retracted inferiorly or divided. The larynx is rotated to the right using a single hook anchored on the lateral border of the thyroid cartilage. The inferior cornu of the thyroid cartilage is used as a landmark for the level of the CP muscle. A CP myotomy is then performed using a No. 15 blade in the posterior midline from distal to proximal for a length of 2.5 cm to up to 6 cm. The incision should be carried slightly into the inferior constrictor proximally at the level of the mid-thyroid cartilage and into the muscle fibers of the cervical esophagus distally. Upon completion of the myotomy, the mucosa should be clearly seen without any overlying muscle fibers. One must inspect for and repair any luminal injuries immediately. These are typically repaired with interrupted 3–0 absorbable mattress sutures followed by a sternothyroid or omohyoid onlay muscle flap. The wound is then irrigated copiously, hemostasis is obtained, and the placement of a 10 French flat Jackson-Pratt drain is recommended. Multilayer closure is then performed [5].

The management of the diverticular sac during open surgery remains controversial. There are several options for management of the diverticulum, including resection, pexy, or inversion. Resecting the sac requires identification, dissection, and resection of the diverticulum with repair of the esophageal wall via linear stapler or suture [24]. Diverticulopexy, or suspension, involves mobilizing the sac and then suspending it superiorly to the prevertebral fascia or pharyngeal musculature. In its new position, the opening of the diverticulum is facing away from the hypopharynx, thereby preventing the accumulation of food contents in the pouch. Inversion involves placing a purse-string suture around the neck of the diverticulum and inverting the diverticulum through the suture followed by ligation [20]. The primary advantage of diverticulopexy and inversion over diverticulectomy is that the mucosal wall is not divided, thereby reducing the risk of fistula formation and mediastinitis. Of these techniques, however, the stapled diverticulectomy remains the most performed.

Rigid Endoscopy

The rigid endoscopic approach is performed with the patient supine and the head and neck placed in a "sniffing" position under general anesthesia. A bivalved diverticuloscope (Weerda Scope, Karl Storz, Tuttlingen, Germany) is inserted through the mouth and advanced to the hypopharynx and slowly passed into the esophageal inlet. The common party wall (the CP bar) is visualized and the diverticulum is exposed with the anterior tine of the scope into the esophagus and the posterior tine into the diverticulum pouch (Fig. 30.2). A rigid zero-degree Hopkins rod telescope may be used to further visualize the anatomy and contents of the pouch and esophageal inlet. Either the CO_2 laser or the endoscopic stapler can be then used to divide the party wall (Fig. 30.3). In dividing the common wall, a cricopharyngeal myotomy is performed and the diverticu-

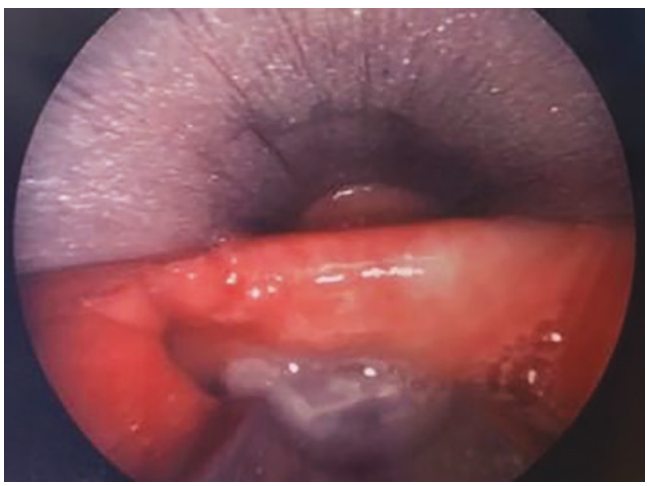

Fig. 30.2 Rigid endoscopic view of cricopharyngeal bar

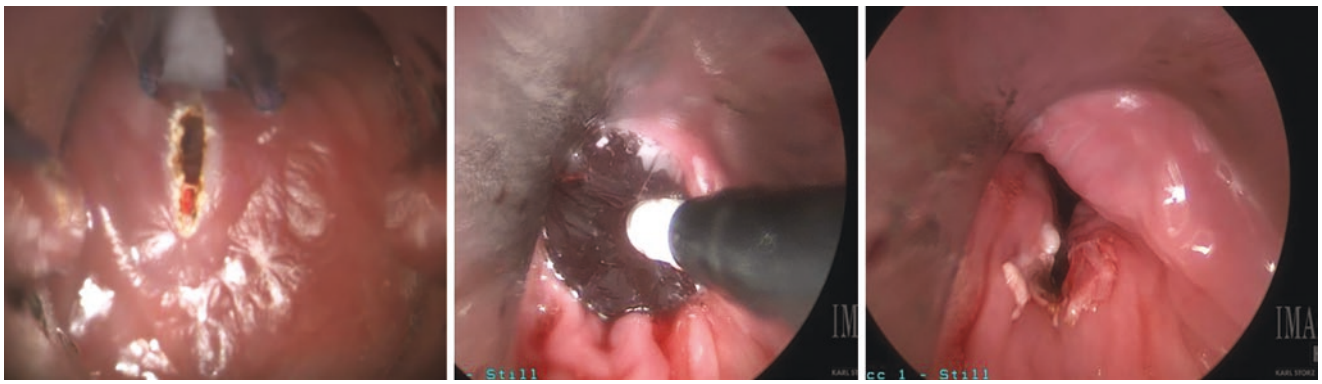

Fig. 30.3 Rigid endoscopic myotomy. Rigid endoscopic view shows the party wall with mucosotomy started with the rigid endoscopic CO_2 laser, followed by division of cricopharyngeus muscle fibers and completed myotomy

lum contents can drain more easily into the esophageal lumen during swallowing. With the stapler, a small remnant of the party wall is left behind. In addition, in patients with diverticula less than 2 cm in depth, CP myotomy with the stapler is not possible due to the inability of the stapler to pass deep enough to perform a complete myotomy. In such cases, CO_2 laser should be used [20]. With the laser, an incision is made starting at the midline of the party wall and extended to the bottom of the pouch, but the underlying buccopharyngeal fascia is not exposed. One way to avoid excessive surgery is to limit laser incision to division of the muscle fibers only [5].

In some cases, an endoscopic approach to diverticulotomy can be particularly challenging, usually due to difficulty attaining exposure. The most common reason for difficult exposure is a small or triangular mandible. Other major anatomic constraints for exposure include a large tongue and full dentition. In other cases, the diverticuloscope can be advanced to the diverticulum but the esophagus cannot be cannulated with the anterior tine of the scope due to excessive CP spasm or poor angle of the esophageal inlet. In these cases, the diverticuloscope should be advanced to the post-cricoid space in the closed position and advanced to the CP bar if possible. If the diverticuloscope tip is entirely within the diverticulum, it should be withdrawn slowly until the party wall is visualized. If it is too proximal without visualizing the party wall, the tines should be opened and the diverticuloscope placed into suspension. A 0° rigid telescope may then be advanced for a close-up view to identify the party wall. Alternatively, an ultraslim flexible esophagoscope can be used to confirm the esophageal entry point and the scope itself or a guidewire can be used to guide the diverticuloscope. In cases with significant pharyngeal narrowing due to cervical spine osteophytes, the narrower Dohlman diverticuloscope or a Benjamin Hollinger scope may be passed more easily [5].

Flexible Endoscopy

Flexible endoscopy is a novel approach for the treatment of ZD and has not yet attained the popularity of the rigid approach. Nevertheless, it may offer advantages over the other techniques. Because when a flexible rather than a rigid endoscope is used, patients with cervical mobility issues who would not be candidates for a rigid approach can be treated endoscopically without positional issues, accounting for up to 20% of patients. Another drawback to the rigid stapled technique is a concern for incomplete myotomy associated with linear stapler design inadequacies. Flexible endoscopy mitigates this limitation by dividing the cricopharyngeus under direct visualization using electrocautery or other cutting devices. Flexible endoscopy can be technically challenging and requires advanced training in flexible endoscopy.

The procedure is performed in the operating room under general anesthesia with endotracheal intubation. The patient is placed in a supine position and a flexible endoscope is used to intubate the esophagus and identify the appropriate anatomy. Carbon dioxide insufflation is used to minimize subcutaneous emphysema. A transparent cap can be placed on the tip of the endoscope to facilitate dissection, while others have described the use of a soft diverticuloscope to act as an overtube. The party wall is viewed in the vertical orientation in the middle of the screen, and the diverticulum is seen on the left of the screen while the true esophageal lumen is seen to the right (Fig. 30.4). Needle- or triangle-tip electrocautery on 'cut' is used to perform a mucosotomy, exposing the underlying cricopharyngeus muscle and limiting thermal spread to surrounding mucosa. This can be achieved either by direct incision over the wall or by submucosal tunnel similar to the per-oral endoscopic myotomy technique (Z-POEM) used for achalasia. The muscle is divided and continued distally until the septum is completely transected. Because the

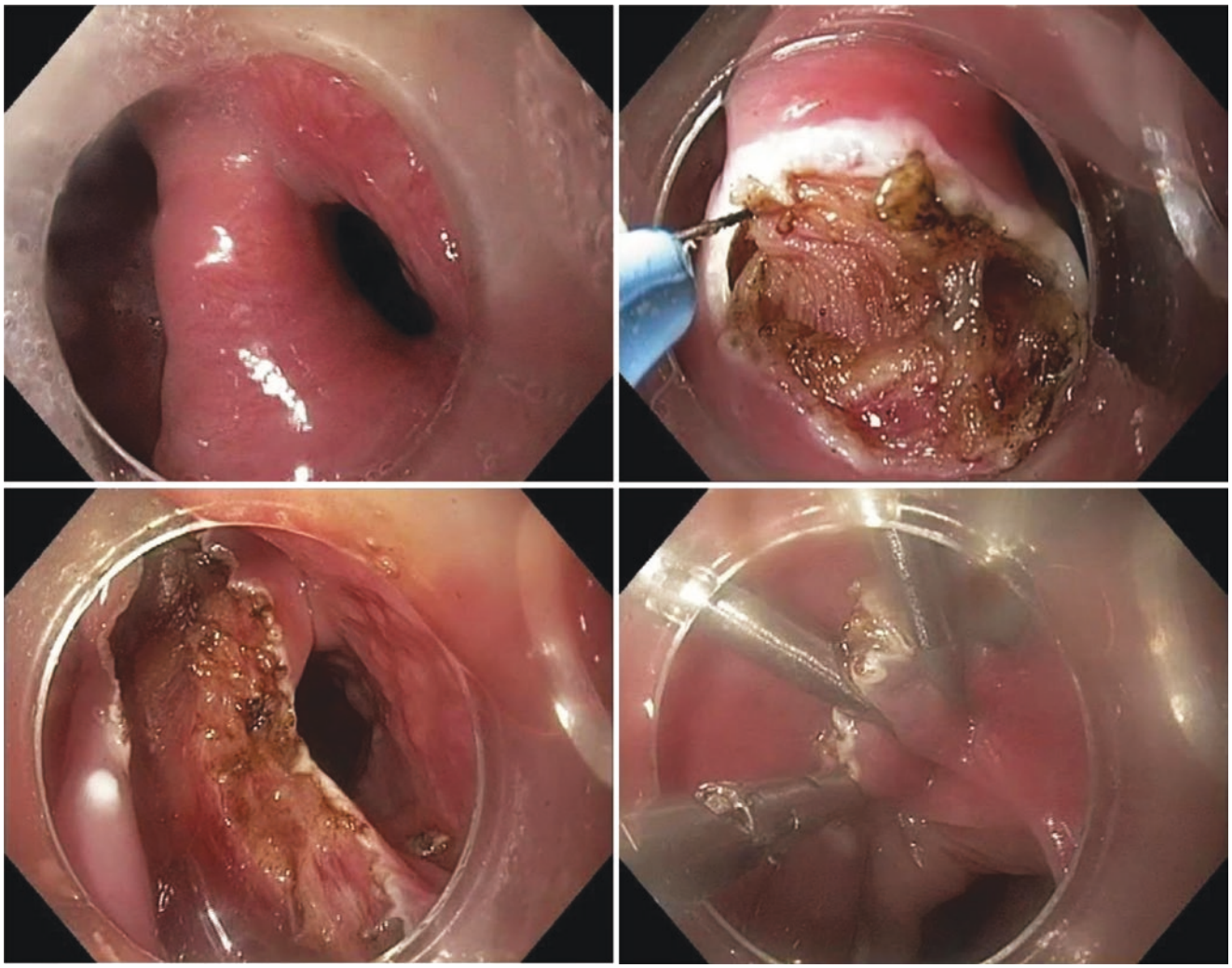

Fig. 30.4 Flexible endoscopic Z-POEM. The first pane shows the vertically oriented party wall with esophageal lumen to the right and diverticulum to the left. Mucosotomy is performed followed by division of muscle fibers. Pane 3 shows completed myotomy and submucosal tunnel followed by closure of the mucosotomy via endo-clips in the final image

dissection often includes the entirety of the party wall, caution must be taken not to enter the deep underlying cervical fascia, which can result in perforation, infection, or abscess. If a tunneled approach is used, care must be exercised to avoid the surrounding intact mucosa, which can be damaged by electrocautery. Hemorrhage may be controlled via compression or electrocautery. Once the myotomy is complete, the mucosotomy may be left open, but closure of the defect with endoscopic clips may be associated with decreased leak rates, especially if micro-perforations in the underlying fascia are present or in the case of Z-POEM.

An upper gastrointestinal series is performed postoperatively to exclude leak and evaluate the pouch (Fig. 30.5). Patients are started on a clear liquid diet and advanced to a full liquid diet and then a soft mechanical diet over a period of 1–2 weeks. Patients are advised to crush all pills, avoid straws and carbonated beverages, and keep the head of the bed greater than 30° to minimize aspiration risk.

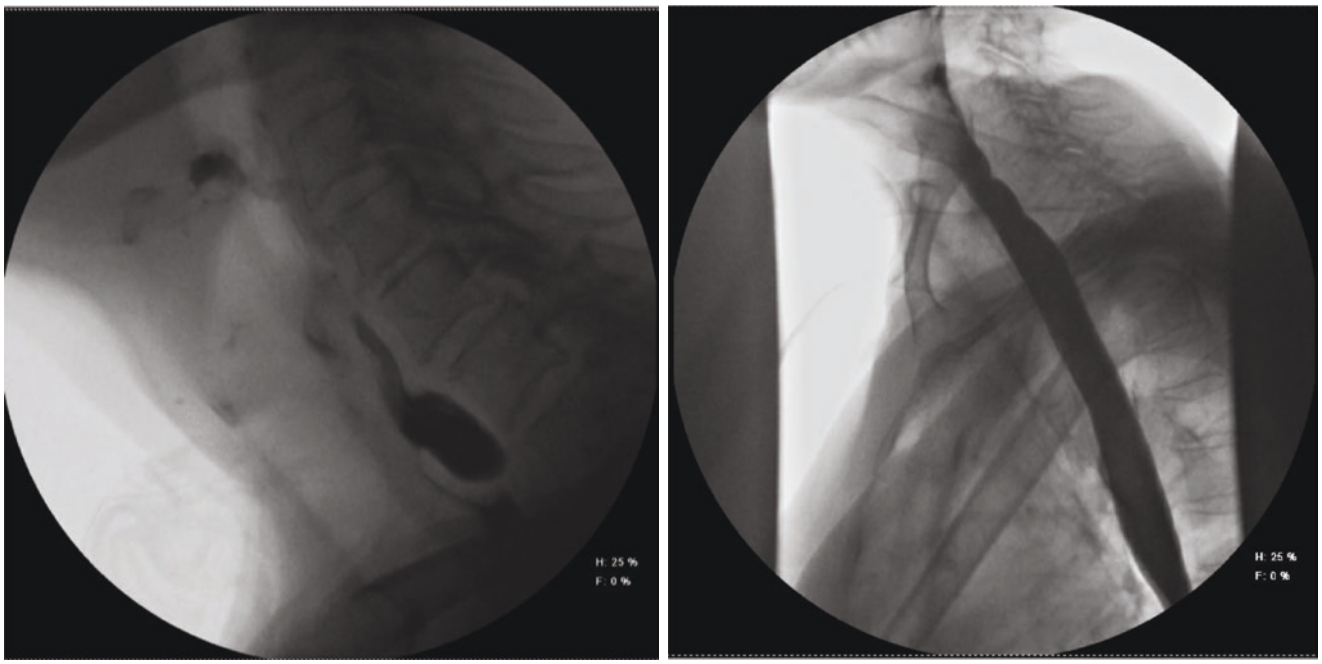

Fig. 30.5 Video esophagram before and after flexible endoscopic myotomy. The first pane depicts large pre-operative ZD followed by post-myotomy resolution of diverticulum after Z-POEM

Outcomes

Cricopharyngeal Achalasia

There is little consensus regarding the efficacy and safety of treatment options for cricopharyngeal achalasia. A recent review of 351 peer-reviewed studies reveals that the most commonly employed treatments were botulinum toxin injection (40%), endoscopic CP myotomy (30%), dilation with either balloon or bougie (25%), or open CP myotomy (15%) [25]. Though Botulinum toxin response rates vary from 40 to 100%, a systematic review concludes there is insufficient evidence for the use of Botulinum toxin at the UES to inform clinical practice [26]. Dilation shows similar results with success rates ranging from 65 to 100% and recurrence of 0 to 50% of patients [27]. In general, CP dilations are typically temporary procedures for the nonfibrotic UES and have a higher incidence of recurrence of symptoms.

Open Surgery

There is conflicting data in regard to optimal open surgical technique. While some larger studies have not demonstrated any advantage to adding a myotomy to diverticulectomy, others recommend the addition of a CP myotomy to prevent fistula and pouch recurrence [28–30]. Myotomy as sole treatment has been shown to result in good clinical outcome and, based on current data, myotomy should be performed when possible [31–33]. The most common complications in open surgery are leak and recurrent laryngeal nerve injury, at around 3% each.

Open vs. Endoscopic Surgery

The overall data identified in a review of 93 studies by Yuan et al. comparing open surgery and endoscopic procedures showed that endoscopic surgery resolved symptoms in 63–100% of patients, with a morbidity of 8.7% and a mortality of 0.2%. The most common complications in endoscopic surgery were cervical or mediastinal emphysema (2.2%), perforation (1.4%), dental injury (1.1%), and bleeding (0.9%). Mediastinitis, leak, respiratory infection, stenosis, recurrent nerve injury, and neck abscess all occurred at a rate of <1% [28]. Verdonch and Morton's systematic review showed an overall higher complication rate in open surgery than in endoscopic surgery (11% vs. 7%). Surgery-related deaths were infrequent in both groups (0.9% for the open surgery vs. 0.4% for endoscopic techniques). The average reported postoperative stay is shorter in endoscopic surgery than in open (3.9 days vs. 8.4 days). Recurrence after endoscopic treatment (especially stapling endoscopy) was higher for endoscopic surgery than for open (18.4% vs. 4.2%); however, many believe that re-operative via the endoscopic approach is usually successful and straightforward, with low

complication and morbidity rate [34]. Overall, open surgeries appear to have higher success than endoscopic approaches, but they also have more complications (7.9% vs. 4.3%). Deaths were infrequent in the two groups but potentially more frequent in open surgery (0.9% vs. 0.4%) [34]. Huntley et al. compared the outcomes of 38 open versus 41 endoscopic CP myotomy cases and found lesser surgical time and improved symptomatic outcomes in the endoscopic group [35]. A meta-analysis revealed no differences in nil per os duration, length of hospitalization, dental complications, major complications, or revision surgery. However, there was a significantly greater incidence of subcutaneous emphysema without mediastinitis or bleeding noted in the CO_2 laser group [36].

Comparison of Endoscopic Techniques

There are few studies directly comparing endoscopic techniques, and these are further limited by the variation in rigid and flexible endoscopic techniques. Swallowing outcomes after endoscopic repair are generally excellent, with greater improvement in dysphagia and regurgitation scores and a lower rate of symptomatic recurrence with CO_2 laser treatment compared to stapler [37, 38]. A recent meta-analysis evaluated 115 studies comparing rigid and flexible endoscopic approaches. Mortality, infection, and perforation were equal in both groups, but bleeding and recurrence were more likely after flexible endoscopic techniques (20% vs. <10% and 4% vs. 0%, respectively) [39]. Both techniques offer successful outcomes with low morbidity though slightly higher re-operation rate with flexible endoscopy. When evaluating flexible endoscopic outcomes, the type of flexible endoscopic approach must be considered in order to better understand the data. Clinical success and outcomes were shown to be improved in Z-POEM over traditional flexible septum division in a recent systematic review [40].

Conclusions

Cricopharyngeal achalasia and Zenker's diverticulum represent a spectrum of rare but treatable diseases resulting from cricopharyngeal dysfunction. Zenker's diverticulum is a false pulsion diverticulum that results from a high-pressure cricopharyngeal bar. Cricopharyngeal achalasia may be managed with endoscopic treatments such as Botulinum injections or dilations. Symptomatic patients with the presence of diverticulum should be managed with cricopharyngeal myotomy. There is no consensus as to the most effective treatment but regardless of technique, outcomes are excellent for open, rigid endoscopic, and flexible endoscopic approaches.

Questions

1. What is currently the most common method of surgical treatment for Zenker's diverticulum?
   A. Endoscopic stapling
   B. Endoscopy CO_2 laser cricopharyngeal myotomy
   C. Open diverticulotomy
   D. Open diverticulopexy

Answer: B. Endoscopic CO_2 laser cricopharyngeal myotomy

2. What is the most common presenting symptom of Zenker's diverticulum?
   A. Coughing
   B. Oropharyngeal dysphagia
   C. Odynophagia
   D. Difficulty breathing

Answer: B. Oropharyngeal dysphagia

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Minimally Invasive Management of Epiphrenic Diverticulum

31

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Objectives

1. To understand the diagnostic workup of patients with epiphrenic diverticula
2. To appreciate the role that esophageal motility disorders play in the formation of epiphrenic diverticula
3. To learn crucial preoperative and postoperative strategies to improve surgical outcomes in patients with an epiphrenic diverticulum
4. To review the key operative steps in the minimally invasive trans-hiatal repair of epiphrenic diverticula
5. To introduce burgeoning minimally invasive strategies for the repair of epiphrenic diverticula

Introduction

Esophageal diverticula are classified by both their anatomic location and by their mechanism of formation. Anatomically, esophageal diverticula are usually present at three locations: the pharyngoesophageal junction, the mid-esophagus, and the epiphrenic region. Another way of classifying esophageal diverticula is by their pathophysiologic origin: pulsion or traction. Pulsion diverticula occur secondary to an increase in intraluminal pressure and traction diverticula are caused by forces pulling from outside the esophagus. Pulsion diverticula are usually "false" and involve only the mucosal and submucosal layers. Conversely, true diverticula (traction) involve all layers of the esophagus (mucosa, submucosa, and muscularis) and are most commonly located in the mid-thoracic region where chronic inflammation from mediastinal disease (e.g., tuberculosis, histoplasmosis, or malignancy) can exert external traction on the esophageal wall. Pharyngoesophageal diverticula, also known as Zenker's, are more common than epiphrenic and mid-body esophageal diverticula [1–4]. While a variety of management strategies are available to treat each of these separate conditions, this review will focus on the comprehensive diagnostic assessment, perioperative management, and postoperative care of epiphrenic diverticula (ED). By the end of this chapter, the reader will have a thorough understanding of current management strategies for ED and key tips for the perioperative management of patients following their repair.

Epidemiology/Pathophysiology

Epiphrenic diverticula are pulsion or "false" diverticula and are among the least common type of esophageal diverticula. The estimated prevalence in North America is around 0.015% and most are located in the distal part of the esophagus [<10 cm from lower esophageal sphincter (LES)] [5]. They are more common on the right side of the esophagus and are typically present in middle-aged and elderly patients [3, 4]. Formation of ED is thought to be secondary to esophageal motility disorders (EMD), with most patients having an associated EMD as the time of the diagnosis (e.g., achalasia, diffuse esophageal spasm, nonspecific esophageal motility disorders, and nutcracker esophagus). Additionally, upwards of 50% of patients with an ED have a concomitant hiatal hernia and/or tortuous esophagus at the time of presentation [6]. In a retrospective analysis of patients with ED from 1990 to 2016, Sudarshan et al. found that achalasia was confirmed in 39% of patients, followed by diffuse esophageal spasm and hypertensive lower esophageal sphincter in 12% and 10%, respectively [5]. It is postulated that the lack of coordination between the distal esophagus and the LES in patients with EMD cause increased intraluminal pressure and progressive esophageal outpouching over time [2]. Understanding the association between EMD and ED is par-

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amount. Not addressing the underlying motility disorder will lead to poor outcomes, high rates of diverticulum recurrence, and disastrous postsurgical complications, such as esophageal staple line leaks.

Clinical Presentation

Up to 40% of patients are asymptomatic at the time of presentation and are found to have an ED incidentally on imaging. Patients who do have symptoms often complain of dysphagia, regurgitation, chest pain, heartburn, aspiration (nocturnal or pneumonia), and weight loss [3, 4]. Dysphagia has been reported as a leading symptom in over 90% of symptomatic cases [5]. Notably, the etiology of symptoms is usually due to the underlying motility disorder itself rather than the diverticulum and is thought to explain why there is poor correlation between diverticular size and symptom severity [3, 4]. However, if the diverticulum becomes large enough, extrinsic compression of the distal esophagus by the diverticulum can lead to dysphagia and weight loss. Similarly, regurgitation of undigested food, nocturnal aspiration, and aspiration pneumonia may be suggestive of a large and/or symptomatic diverticulum [3, 4].

Fortunately, malignant transformation of ED is exceedingly rare (<1% of cases). If patients do present with malignancy, it is most often squamous cell carcinoma and is thought to arise secondarily to food stasis and fermentation within the diverticulum. When discovered, malignancy is unfortunately often found at an advanced stage as these patients can be asymptomatic for many years prior to diagnosis. Although no screening programs for patients with unresected diverticula have been published, patients who develop cancer are often older, have large ED, and have had a lengthy history of symptoms [3, 4].

Diagnostic Evaluation

Contrast esophagram, upper endoscopy (EGD), and high-resolution esophageal manometry constitute the major components of the diagnostic workup for patients with ED. Endoscopic functional lumen imaging probe (EndoFLIP; Medtronic, Inc.), pH monitoring, and computed tomography (CT) may be helpful adjuncts when other studies are indeterminate. When symptoms of bloating, early satiety, epigastric pain or nausea are also present, gastric emptying studies may help to uncover underlying associated gastric motility conditions such as gastroparesis.

The first diagnostic test performed is often the barium esophagram (Fig. 31.1). This test provides the location of the ED (laterality and distance from the hiatus), the size of the diverticulum (pouch diameter and length and width of the neck), and the number of diverticula—all of which are crucial for preoperative surgical planning. Esophagography also provides important information about the diaphragmatic hiatus and gastroesophageal junction (GEJ), such as the presence of hiatal hernias or lesions suspicious for malignancy [3]. While not the best test for evaluating esophageal motility, it may provide clues of an EMD and can be used as an adjunct with subsequent manometry studies. Specifically, esophagography may show disordered contractions of the distal esophagus, corkscrew esophagus secondary to esophageal spasms, or the characteristic "bird's beak" appearance of a patient with achalasia [3].

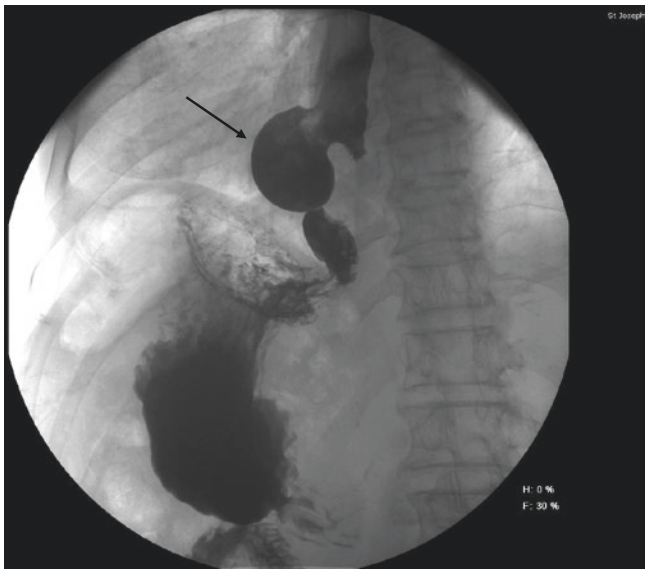

Fig. 31.1 Preoperative barium esophagogram showing a large epiphrenic diverticulum (arrow) above the gastroesophageal junction

EGD helps to categorize the size, location, and appearance of the diverticulum, specifically delineating the start and end of the diverticulum's neck (Fig. 31.2). It evaluates for the presence of impacted food within the diverticulum and can assist in preoperatively clearing undigested food and liquid. Additionally, an EGD assesses for mucosal lesions within the diverticulum and any other associated gastroesophageal pathology, including ulcers, Barrett's esophagus, and esophagitis [4]. Masses or suspicious lesions should be documented (biopsied) and addressed prior to planned surgical intervention. Often, it is helpful to identify the diverticulum on esophagram prior to EGD to help the provider avoid intubating and possibly perforating the diverticulum [4].

High-resolution manometry can be helpful to confirm the presence of an underlying EMD and guide therapy such as the extent of an esophagogastric myotomy [3, 4]. However, the absence of an EMD on manometry should not preclude surgical management. Due to the episodic nature of some EMD, patients may have normal manometry results despite having a true underlying motility disorder [2, 3, 7, 8]. Currently, it is

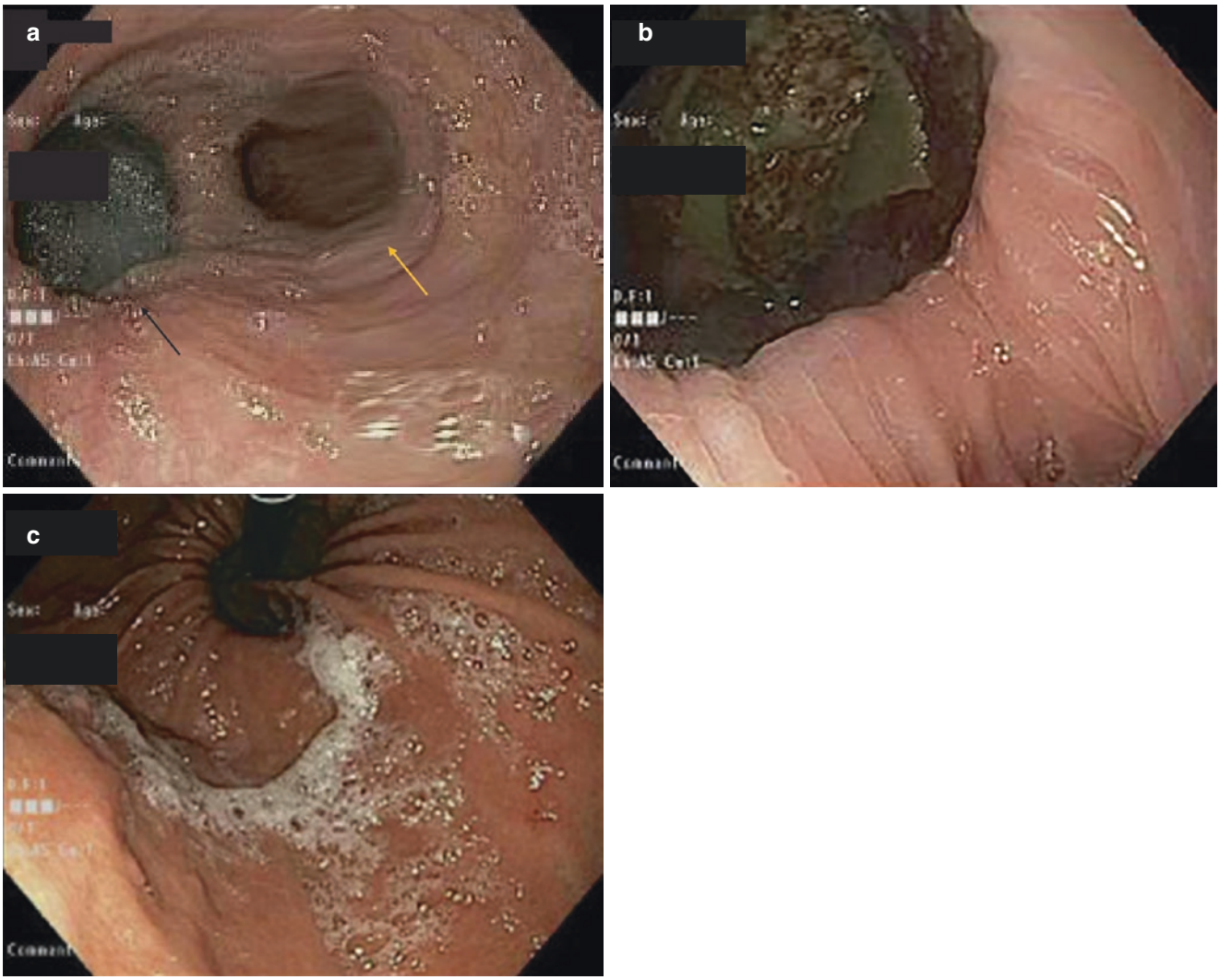

Fig. 31.2 Preoperative upper endoscopy (EGD) showing the (**a**) true lumen (yellow arrow) next to a large-mouthed epiphrenic diverticulum (black arrow) with (**b**) significant retained food debris. (**c**) This patient also had a concomitant hiatal hernia with a Hill Grade IV LES valve, shown on the retroflexed view

the authors' standard practice to obtain high-resolution manometry prior to surgical evaluation. The manometry probe is frequently placed at the time of EGD to confirm its placement at the LES and not inside the diverticulum. For a large diverticulum, the manometry probe may need to be guided endoscopically past the LES into the stomach.

Ambulatory pH monitoring can be helpful for patients presenting with heartburn as a dominant symptom to rule out underlying gastroesophageal reflux disease (GERD). However, if the diagnosis with prior imaging studies has confirmed EMD and ED as the underlying cause of symptoms, additional pH monitoring is not required. If an adequate esophagram is obtained demonstrating an ED, CT scans or other cross-sectional imaging are not mandatory for the workup of ED. If a mid-body or true diverticulum is suspected, CT scans may be helpful to identify other pathology that could be exerting extrinsic forces on the diverticulum. Alternatively, axial imaging with PO contrast may serve as an adjunct if patients are not able to tolerate an esophagram. Lastly, CT scans might be helpful to differentiate the diverticulum from other mediastinal diseases, such as abscesses, tumors, or hiatal hernia. On CT scans, ED appears as a thin-walled, air-filled structure in communication with the esophagus [9]. Endo-FLIP is an emerging procedure that uses impedance planimetry via volumetric distention to measure esophageal distensibility and diameter to provide information about LES function. While Endo-FLIP has been shown to be helpful in both the diagnosis and treatment monitoring of patients with achalasia, its role in the diagnosis and management of ED is unknown [10]. Lastly, if gastroparesis is suspected to be contributing to a patient's symptoms, gastric emptying studies may be warranted.

Management Strategies

Treatment of ED is reserved for patients who are symptomatic with complaints of dysphagia, regurgitation, or aspiration events and who are also good surgical candidates. Size alone in an asymptomatic patient is not an indication for surgery. Patient selection and shared decision making are paramount as complications from the repair of ED carry significant morbidity. The best care for patients with ED must involve a thorough diagnostic workup and evaluation by a multidisciplinary team with expertise in diseases of the foregut.

Non-Operative Management

Although the true clinical history of these diverticula has not been well-established, conservative measures with lifestyle and behavior modifications may be attempted in minimally symptomatic or high-risk patients. Although rare, spontaneous rupture of large diverticula have been reported [11, 12]. Nonetheless, small and asymptomatic diverticula are likely safe to closely monitor and treat conservatively. In one of the few studies to compare non-operative management to operative management, Zaninotto et al. showed that while no patient in the non-operative management group died from complications related to their diverticulum, those undergoing operative management had improved symptom resolution [11]. However, surgical intervention was not benign: the overall postoperative morbidity rate in their cohort was 23% [11].

Endoscopic Therapy

Endoscopic adjuncts may be helpful in treating symptomatic patients who are poor surgical candidates. Several case reports suggest botulinum toxin injections into the LES can be helpful for symptom control, especially in patients with underlying achalasia [13]. Similarly, patients with strictures of the LES may benefit from pneumatic dilation. However, both botulinum toxin injections and pneumatic dilation only provide temporary relief and do not address the ED itself; symptoms usually recur and patients remain at risk for aspiration [13].

Surgical Therapy

The surgical management of ED traditionally follows three key principles: (1) resection of the diverticulum, (2) addressing the underlying motility disorder, and (3) preventing postoperative GERD [3]. Some authors have suggested that a myotomy is not necessary in all cases and that a more selective approach should be followed [2, 7, 8]. However, prior studies have reported high rates of staple line leak in patients without a myotomy at the time of the index operation. Systematic review and meta-analysis by Chan et al. showed that staple line leaks were more common in patients without myotomy [14]. As most ED are associated with underlying EMDs, not treating the underlying cause leads to high intraluminal pressure postoperatively and a higher risk of postoperative staple line leaks. It is therefore our standard practice to perform both a myotomy and diverticulectomy in all patients presenting with symptomatic ED, regardless of their preoperative manometry. Our rationale is that preoperative manometry may not always show a motility disorder, even if one truly exists. This is secondary to the often-intermittent nature of some EMDs and some large diverticula may accommodate a fair amount of volume to offset the manometric pressure readings. As a result, manometry may be inaccurate at measuring high LES pressures [7]. In these patients, Endo-FLIP may be helpful to provide a better understanding of LES function.

Thoracotomy

Historically, the operative repair of ED had been achieved via a thoracotomy. In this approach, the right lung was deflated (to access the more common right-sided diverticula), the diverticulectomy and myotomy were performed, and a Belsey Mark IV fundoplication was used to mitigate GERD. A few surgeons still feel that the thoracic approach is especially useful to access diverticula extending higher than 5 cm from the GEJ [3] due to visualization and access to the distal esophagus. This technique, however, is associated with a significant recovery period and added morbidity.

Minimally Invasive Approaches

Since the advent of laparoscopy in the late 1980s, minimally invasive approaches to ED, either laparoscopic or robotic, are now considered the standard of care. Although comparing the outcomes between the major approaches is beyond the scope of this chapter, a few key points are worth noting. Numerous case series and retrospective reports have shown the effectiveness of minimally invasive approaches for treating ED [3, 5]. With the enhanced ability to perform a high mediastinal dissection utilizing surgical robotic instrumentation, even higher epiphrenic and mid-thoracic diverticula can be approached via the abdomen, sparing patients from a thoracotomy [16].

In this chapter, we focus on the technical description of our preferred method for surgical treatment of ED—the trans-hiatal minimally invasive approach. Preoperative, operative, and postoperative details are provided, as well as pearls and avoidance of pitfalls.

Trans-Hiatal Minimally Invasive Approach

Preoperative Considerations

Patients are instructed to maintain a clear liquid diet for 72 h prior to surgery to minimize the amount of solid debris in the diverticulum and esophagus. If a preoperative EGD was done as part of the work-up and showed a large diverticulum with significant food debris, a repeat EGD within 2–3 days of surgery prior to initiation of a clear liquid diet can be extremely helpful to decrease a patient's aspiration risk on induction and to reduce the amount of retained food in the diverticulum. It is important to always communicate closely with the anesthesia providers upon induction: establishing an airway with the head up and possibly with rapid sequence induction can decrease the risk of aspiration, especially in patients with achalasia as their underlying EMD.

Minimally Invasive Trans-Hiatal Operative Technique

Patients are placed in the supine position on the operating room table. Spreader bars may be used to facilitate a more ergonomic position between the legs from which the surgeon and/or assistant may operate. For robotic procedures, we also recommend padding and tucking the arms to minimize collision with the robot. The patient is placed in steep reverse Trendelenburg position. Intraoperative endoscopy is first performed to characterize the diverticulum, degree of esophagitis, the Hill grade of the LES, and to note any anatomic variations. The flexible endoscope is then withdrawn 20 cm from the incisors for later use during the procedure. After instillation of local anesthetic, five trocars are placed: left upper quadrant, left flank, epigastrium, right upper quadrant, and periumbilical. At least one of these ports should be 12 mm in diameter to accommodate a surgical stapler. The liver is retracted in a cephalad fashion. The gastrohepatic ligament is *divided* using a bipolar energy device, with care being taken to note the presence of an accessory or replaced hepatic artery. If there is a concomitant hiatal hernia, circumferential dissection of the hernia sac is performed, and the esophagus is mobilized within the mediastinum to allow for 2–3 cm of intra-abdominal esophageal length. Care is taken to identify and to preserve the anterior and posterior vagus nerves. The diverticulum is then identified and carefully dissected to isolate its neck from surrounding esophageal muscle fibers (Fig. 31.3). Once the diverticulum is isolated, it is

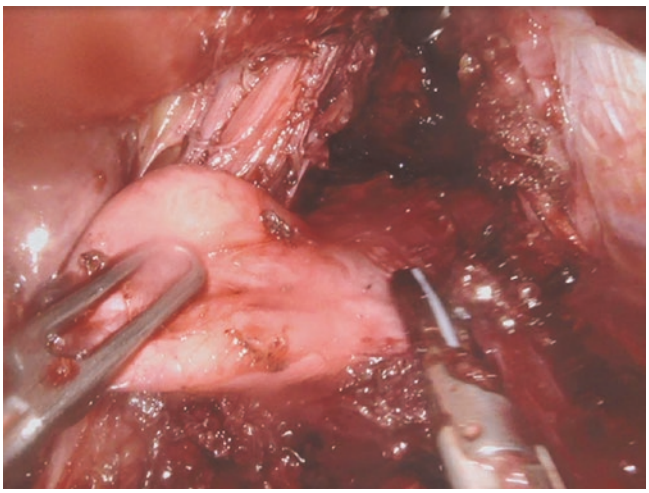

Fig. 31.3 Intraoperative image of a large epiphrenic diverticulum

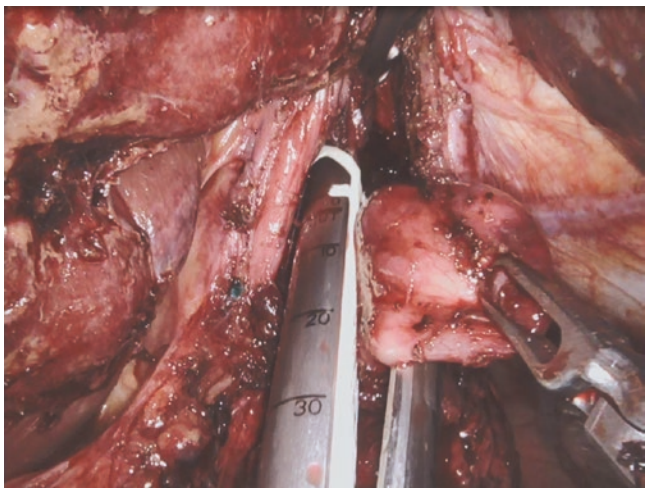

Fig. 31.4 Intraoperative image of an epiphrenic diverticulum about to be resected with a surgical stapler with vascular load

stapled across its base using either a vascular staple load for a thin-walled diverticulum or a bowel load for a thicker wall. Flexible endoscopic guidance or a bougie/Savary dilator (typically a 54 or 60 French) should be used prior to stapling to ensure patency of the true lumen of the esophagus (Fig. 31.4). Following stapling, repeat esophagoscopy is performed to ensure complete resection of the diverticulum, the absence of an esophageal or gastric leak, and to confirm esophageal lumen patency without narrowing (Fig. 31.5). We perform the leak test with endoscopic CO_2 insufflation while the staple line is being carefully covered with saline using the laparoscopic suction-irrigator.

After resection of the diverticulum resection, attention is turned to performance of the esophagogastric myotomy. Starting on the contralateral side of the diverticulum, the circular and longitudinal muscle fibers are divided, beginning 2 cm

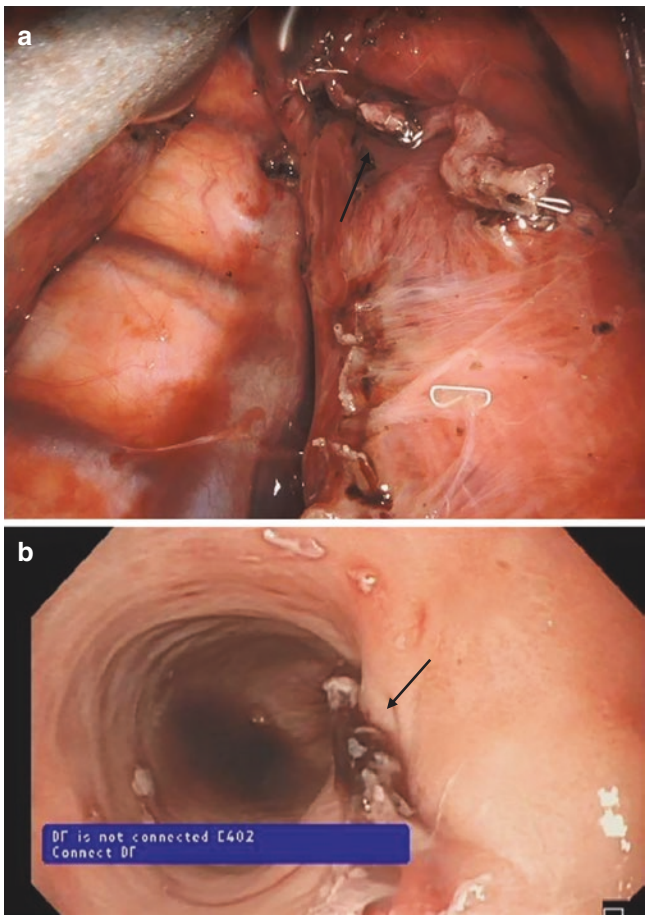

Fig. 31.5 Intraoperative image showing the (**a**) extraluminal and (**b**) intraluminal esophageal staple line (arrow) after diverticulum resection. Simultaneous endoscopy ensures no luminal narrowing and allows for a leak test to be performed with insufflation from the endoscope and saline on the staple line

proximal to the GE junction. This can be performed bluntly or with monopolar, bipolar, or ultrasonic energy devices. Care must be taken to avoid mechanical or thermal injury to the mucosa (Fig. 31.6). Occasionally, performing a contralateral myotomy is difficult given the diverticulum's original location. If this is the case, a myotomy that is easily accessible but still remote from staple line (i.e., near contralateral) is a reasonable alternative. The myotomy is extended retrograde to 6 cm above the GEJ or 2 cm above the proximal-most extent of the diverticulum, whichever is higher. The myotomy is then extended antegrade 2–3 cm onto the anterior wall of the stomach in order to fully disrupt the disordered muscle fibers of the LES. If the path of the anterior vagus nerve crosses the myotomy, a tunnel beneath the vagus is first created to salvage the nerve. This is done bluntly or sharply, with care being taken to not directly grasp or use electrosurgical energy on the nerve. Repeat endoscopy is again performed to confirm adequate myotomy length and that there is no mucosal injury.

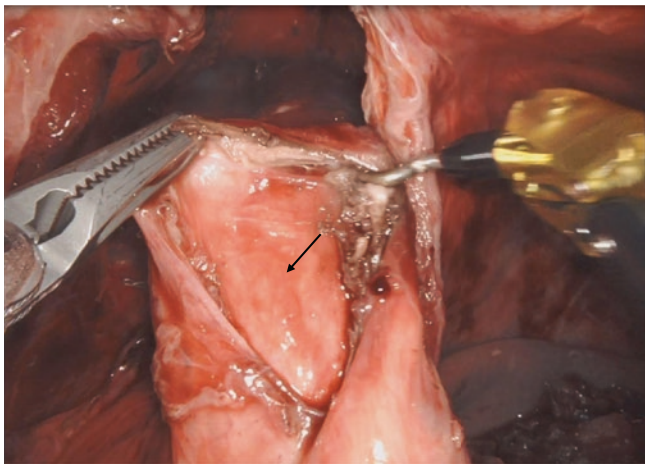

Fig. 31.6 A near contralateral myotomy through the circular and longitudinal muscle fibers to either 6 cm above the GEJ or beyond the diverticulum's proximal extent, and 2 cm onto the stomach is required. Mucosal exposure (arrow) with no overlying muscle fibers ensures complete myotomy

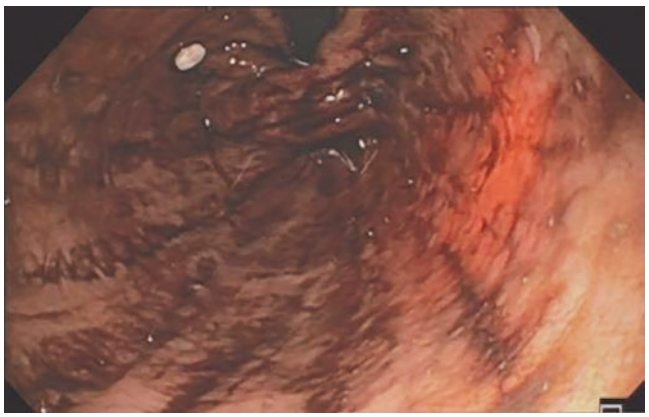

Fig. 31.7 A final endoscopic evaluation ensures complete resolution of the hiatal hernia (if present), a Hill Grade I valve, no esophageal or gastric injury, and complete resection of the diverticulum

Attention is then turned to performing an anti-reflux procedure. The posterior crura are re-approximated using non-absorbable sutures in a figure-of-eight fashion or in an interrupted fashion with pledgets. The fundus is then mobilized by dividing the short gastric vessels. A partial 270° wrap (Toupet) or anterior 180° wrap (Dor) is performed. A full 360° wrap (Nissen) is never performed given the patient's underlying EMD.

Final endoscopic evaluation ensures complete resolution of the hiatal hernia (if present), the presence of a Hill grade 1 LES valve, no evidence of esophageal or gastric injury, and complete resection of the diverticulum (Fig. 31.7). We will occasionally place a surgical drain for repairs with concomitant large paraesophageal hernias, difficult dissections, pleurotomies, or concern for intraoperative mucosal injury. In

those cases, a 15-French drain is placed through the right upper quadrant port site, traversing the anterior hiatus with the tip terminating in the mediastinum.

Surgical Pearls/Pitfalls

- Diverticulum dissection: Appropriate dissection around the neck of the diverticulum is crucial to performing an adequate resection. Often, with chronic inflammation from associated hiatal hernias or other mediastinal processes, the diverticulum may be adhered to the stomach wall. Freeing the diverticulum circumferentially ensures complete resection without inadvertent injury to the normal esophagus. Typically, there is no indication for reinforcement of the staple line. However, if concern arises or intraoperative endoscopy reveals a positive leak, the surgeon can consider oversewing the staple line, covering with an omental or pleural patch, or applying a fibrin sealant.
- Avoid narrowing the esophagus: It is essential that stapling off the diverticulum is completed with either direct endoscopic visualization or with the assistance of a bougie. If endoscopic guidance is not available, a 54–60 French Savary dilator is used to ensure that the esophageal lumen does not narrow after resection. When passing the Savary dilator, a wire is first passed into the stomach to serve as a guide for the dilator. This helps to guide the dilator into the true lumen of the esophagus and minimize the risk of perforation of the diverticulum.
- Myotomy: A myotomy through both the longitudinal and circular layers of the esophageal muscle is performed. Careful inspection is performed to make sure all muscle fibers are divided to minimize the chance of an incomplete myotomy. The myotomy extends to 6 cm above the GEJ or 2 cm above the proximal-most extent of the diverticulum, and 2–3 cm onto the stomach. Typically, the myotomy is performed contralateral or near contralateral to the location of the diverticulum. The myotomy is critical to addressing the underlying EMD.
- Intraoperative endoscopy: The use of intraoperative endoscopy is highly recommended. It allows the surgeon to visualize the patency of the esophagus, to assess for mucosal injury or leak, and to evaluate the wrap at the conclusion of the case. Carbon dioxide is always used for insufflation.
- Pleurotomy: With concomitant large hiatal hernias or with significant inflammation, making a tear in the pleura is not uncommon during mediastinal dissection. The most feared complication following a pleurotomy is a tension capnothorax which can lead to hemodynamic instability. If a tear is recognized, the surgeon should always alert the anesthesia team. Often, extending the tear will help to equalize pressure between the abdomen and chest to prevent tension physiology. If concerns persist, a chest tube may be placed either intraoperatively or postoperatively. Some centers choose to perform routine post-operative chest X-rays. Often, small capnothoraces can be seen. If the patient is clinically stable, these are often inconsequential and will resolve spontaneously. However, if the patient is symptomatic, the capnothorax is followed with serial CXR until symptoms resolve. A thoracostomy tube is placed only for large capnothoraces with hemodynamic compromise.

Postoperative Care

Highlights of our standard postoperative patient care pathway are outlined below

- Postoperative esophagogram: On the morning of postoperative day (POD) 1, an aqueous esophagogram is performed to evaluate for a postoperative leak. If no obvious leak is seen but clinical concern remains high a follow-up thin barium esophagogram may be performed. Large capnothoraces may also be incidentally found during this study.
- Diet: Postoperatively, patients are kept nil per os (NPO) until the POD 1 esophagram is performed. If it shows no leak, patients are then started on a clear liquid diet and advanced to a pureed diet. They are discharged on a pureed diet and advanced to an esophageal/mechanical soft diet in 2 weeks. All patients meet with a registered dietician while in the hospital. Patients are specifically instructed to avoid cold foods or liquid (e.g., Italian ice, ice cream, ice cubes) as these may induce esophageal spasms; warm foods alternatively can help to relax the esophagus. Patients are discouraged from using straws and drinking carbonated beverages as these may lead to gas bloat and gas pains.
- Medications: All medications are crushed for 2 weeks postoperatively. Oral pain medications are given as an elixir and all non-critical per-oral medications are limited (e.g., vitamins, supplements). Medications are reviewed and all extended-release versions of medications that cannot be crushed are converted to short-acting versions.
- Anti-emetics: Aggressive prevention of postoperative nausea and emesis is crucial to maintaining integrity of the hiatal reconstruction and fundoplication. We routinely use ondansetron in hospitals and discharge patients with either prochlorperazine or promethazine suppositories with liberal refills.
- Acid-suppression: As an adequate fundoplication should prevent gastric acid from reaching the diverticular staple line, we do not typically prescribe acid-suppression medications postoperatively. If the gastric mucosal integrity was violated during the procedure from an inadvertent

gastric mucosal injury or resection of gastric tissue (e.g., concomitant gastrointestinal stroma tumor removal), then we prescribe 1 month of an H2-blocker or proton pump inhibitor.

- Reduction of intra-abdominal pressure: Increased intra-abdominal pressure can lead to an acute recurrence of a hiatal hernia, wrap slippage, or even staple line leaks. As such, all patients are discharged with an aggressive bowel regimen to reduce constipation, straining, and intra-abdominal pressure. Patients are instructed to avoid heavy lifting for 2–4 weeks after surgery.

Per-Oral Endoscopic Myotomy (POEM)

Given that ED may present in elderly frail patients who are poor surgical candidates, alternative approaches have been explored that are less invasive. The POEM procedure has quickly gained worldwide acceptance and popularity for the treatment of achalasia due to its ability to perform an esophagogastric myotomy without any abdominal incisions [15]. In a similar fashion, endoscopic myotomy has been employed for treating esophageal diverticular disease with a technique coined as the D-POEM. The procedure consists of four main steps [15]. First, a submucosal saline injection is used to create a bleb approximately 2 cm proximal to the diverticulum, and a 1 cm mucosotomy is performed over the bleb. Second, submucosal tunneling is carried out on either side of the diverticulum until the bottom of the septum is reached. Given the association of EMD with ED, the submucosal tunnel is extended 2–3 cm past the GEJ to disrupt the gastric fibers of the LES. Third, the septum of the diverticulum is divided. Lastly, the mucosotomy is closed using endoscopic clips that slough off after a few weeks [15].

Given the rarity of ED and relative novelty of D-POEM, few studies evaluating the long-term success of this approach exist. However, the few case series that have been published show D-POEM to be both safe and effective for the treatment of ED [17–19]. Large-scale trials and reviews are needed to confirm the long-term efficacy of this approach and to compare its outcomes to the other readily available approaches. As no fundoplication is performed, this approach may not be appropriate for patients with reflux as a significant component of their symptoms or patients with a large concomitant hiatal hernia. Additionally, this is a technically challenging procedure and should only be performed by those with significant endoscopic training and expertise.

Surgical Outcomes and Complications

Short-term and long-term clinical success following minimally invasive ED repair is possible [20]. Additionally, these procedures have a relatively low mortality rate of less than 5% and a morbidity rate of 7–40% [3, 5, 11]. The most feared complication following ED surgery is a leak from the staple line. This occurs in around 3% of cases following the MIS approach and more frequently in patients not undergoing a concurrent myotomy [2]. Treatment of a postoperative leak can be challenging and should be addressed on a case-by-case basis that follows the key surgical principles of adequate surgical drainage with control of enteric contents, supportive nutrition, antibiotics, and aggressive acid suppression. Often, if a leak is found immediately after surgery and appears to be clinically significant, urgent re-exploration is needed. Patients without overt sepsis and/or small leak found on imaging may be observed or treated conservatively with esophageal stents, thoracic or abdominal drains, antibiotics, and supplemental nutrition. In all cases, a multidisciplinary team approach with general surgery, thoracic surgery, and interventional gastroenterology is needed to care for these patients.

Conclusions

While a rare entity, ED can be challenging to treat and disabling for patients. Almost always due to an underlying EMD, ED are false diverticulum that form due to high intraluminal pressures and a relative esophageal outflow obstruction. In this chapter, we outline the essential diagnostic steps and management strategies for treating ED. Key operative principles include both resecting the diverticulum and performing an associated contralateral myotomy. Although minimally invasive trans-hiatal approaches are currently the standard of care, new techniques such as the D-POEM are emerging that offer less invasive and, hopefully, less morbid options for high-risk patients. Foregut surgeons, thoracic surgeons, and gastroenterologists should be familiar with each of these options to be able to provide their patients with customized therapy. Ultimately, further work with well-designed studies is needed to continue to evaluate the effectiveness of each of these therapies and determine which patients may benefit most from each specific procedure.

Multiple Choice Questions

1. All of the following are part of the postoperative pathway of patients who underwent surgical treatment for their epiphrenic diverticulum *except*:

A. Crush all medications
B. Encourage cold drinks and ice cubes
C. Maintain a pureed diet for 2 weeks
D. Strict anti-emetic and bowel regimen

Answer: B. Cold can irritate the esophagus postoperatively and lead to esophageal spasms. All other answer choices are appropriate strategies for patients post-foregut surgery.

2. Which of the following is the motility disorder most commonly associated with an epiphrenic diverticulum?

A. Hypertensive lower esophageal sphincter
B. Nutcracker esophagus
C. Diffuse esophageal spasms
D. Achalasia

Answer: D. While all of the following motility disorders increase the risk of the formation of an epiphrenic diverticulum, the most common esophageal motility disorder associated with epiphrenic diverticula is achalasia.

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Disorders of Esophagogastric Junction Outflow and Peristalsis

32

Monika Lammi and Jessica Koller Gorham

Objectives

1. To review epidemiology, pathophysiology, and clinical presentation of esophageal motility disorders as defined by the Chicago Classification.
2. To examine results of diagnostic evaluation of various esophageal motility disorders.

Disorders of Esophagogastric Junction Outflow

Achalasia

EGJ Outflow Obstruction

Achalasia is a rare esophageal motility disorder characterized by incomplete lower esophageal sphincter (LES) relaxation and abnormal esophageal peristalsis.

Epidemiology

Achalasia has an estimated global incidence ranging from 0.03 to 1.63 per 100,000 persons per year and prevalence ranging from 1.8 to 12.6 per 100,000 persons per year. It can occur at any age, with a peak incidence between 30 and 60 years of age. The prevalence does not differ based on sex or race [1]. Patients with achalasia are more likely to suffer from autoimmune conditions. Achalasia increases the risk of development of esophageal squamous cell carcinoma and adenocarcinoma. The risk of squamous cell carcinoma is approximately 72 times higher and the risk of esophageal adenocarcinoma is 6 times higher in patients with achalasia compared to the general population [2].

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Pathophysiology

It is believed that achalasia results from selective loss of inhibition in the myenteric plexus of the distal esophagus and LES, resulting in an imbalance of inhibitory (vasoactive intestinal peptide [VIP] and nitric oxide [NO]) and excitatory (acetylcholine) activities. Failure of LES relaxation and abnormal peristalsis is caused by a localized decrease of VIP and NO resulting in unopposed excitatory activity. Inflammation in the myenteric plexus, most likely caused by an autoimmune response to viral or other environmental antigens in genetically susceptible individuals, leads to degeneration of myenteric ganglion neurons responsible for regulation of esophageal motility. Achalasia can also occur as a result of Chagas disease, a tropical illness characterized by degeneration of myenteric plexus after *Trypanosoma cruzi* infection [1, 3].

Clinical Features

The clinical presentation of achalasia is variable. Progressive dysphagia to solids and liquids is the most common symptom, occurring in over 90% of patients. Regurgitation is present in about 75% of patients and may cause respiratory symptoms related to aspiration. Pyrosis, related to stasis and fermentation of undigested food, is common in patients with achalasia. Because heartburn is a frequent symptom, it often leads to a delay in diagnosis due to misdiagnosis as GERD. Chest pain is present in 40% of patients. Many patients lose weight and can develop malnutrition.

The Eckardt Symptom Score is the most frequently used tool to evaluate symptoms and treatment response. The four symptoms of dysphagia, regurgitation, chest pain, and weight loss are assigned points (0–3 points) reflective of the severity of each symptom with total score ranging from 0–12. A higher score correlates with more severe symptoms. Symptoms can overlap with other disorders and severity does not correlate with objective testing. Comprehensive evaluation, therefore, is needed to confirm the diagnosis and determine the best therapeutic approach [1].

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Diagnosis

A diagnosis of achalasia is suspected in patients who present with the above classic symptoms and is confirmed with endoscopy, esophagram, and high-resolution esophageal manometry (HRM). Functional Lumen Imaging Probe (FLIP) can be used to help differentiate achalasia from esophagogastric junction outflow obstruction (EGJOO). Since heartburn may be present in up to 42% of patients, leading to a delay in diagnosis, patients who are initially suspected of having GERD but have negative pH testing should be evaluated for achalasia.

Manometric Testing

HRM is the current gold standard test used to make the diagnosis and differentiate the three clinically relevant subtypes (Types I, II, and III). All three subtypes have impaired GEJ relaxation and impaired peristalsis. Achalasia Type I is the second most common form, representing 20–40% of cases, and is characterized by aperistalsis (100% failed peristalsis) and absence of panesophageal pressurization. Achalasia Type II is the most common form, representing 50–70% of cases, and is characterized by panesophageal pressurization of more than 30 mmHg in at least 20% of swallows. Achalasia Type III is the least common form, representing 5% of cases, and is characterized by spastic contractions. The classification of achalasia into subtypes appears to be helpful in predicting prognosis and guiding treatment [1, 4] (Fig. 32.1).

Imaging

Barium esophagram may demonstrate a dilated esophagus with fluid retention and bird's beak tapering at the LES. In more advanced cases, severe dilatation and a sigmoid-like appearance may be seen (Fig. 32.2). Timed barium esophagram with a 13 mm tablet was developed to help make the diagnosis and guide therapy, as it allows to assess retention of barium, tablet, and rate of esophageal emptying [1] (Fig. 32.3).

Endoscopy

Endoscopy may show atrophic mucosa related to chronic stasis, dilated presbyesophagus with retained fluid or food. Resistance, puckering, and characteristic pop sensation upon entry into the stomach may be appreciated at the gastroesophageal junction (GEJ). Diagnosis based on endoscopy is low and classic findings may not be apparent early in the course of the disease. Endoscopy must be performed in all patients with dysphagia and suspected achalasia to rule out pseudoachalasia and other mechanical obstructions that may present with similar symptoms. Pseudoachalasia related to malignancy should be suspected in patients older than 60 years of age with rapidly progressive dysphagia and/or excessive weight loss. In such cases, cross-sectional imaging and/or endoscopic ultrasound may be beneficial if EGD does not demonstrate a malignant lesion [1].

FLIP

FLIP is an impedance planimetry system that uses a balloon catheter to display real-time pressure (i.e., distensibility) and dimension measurements in the esophagus and lower esophageal sphincter. FLIP has been shown to be helpful in diagnosing achalasia, especially in equivocal cases or when HRM placement is not feasible. Further studies assessing the role of FLIP in achalasia evaluation are needed [1].

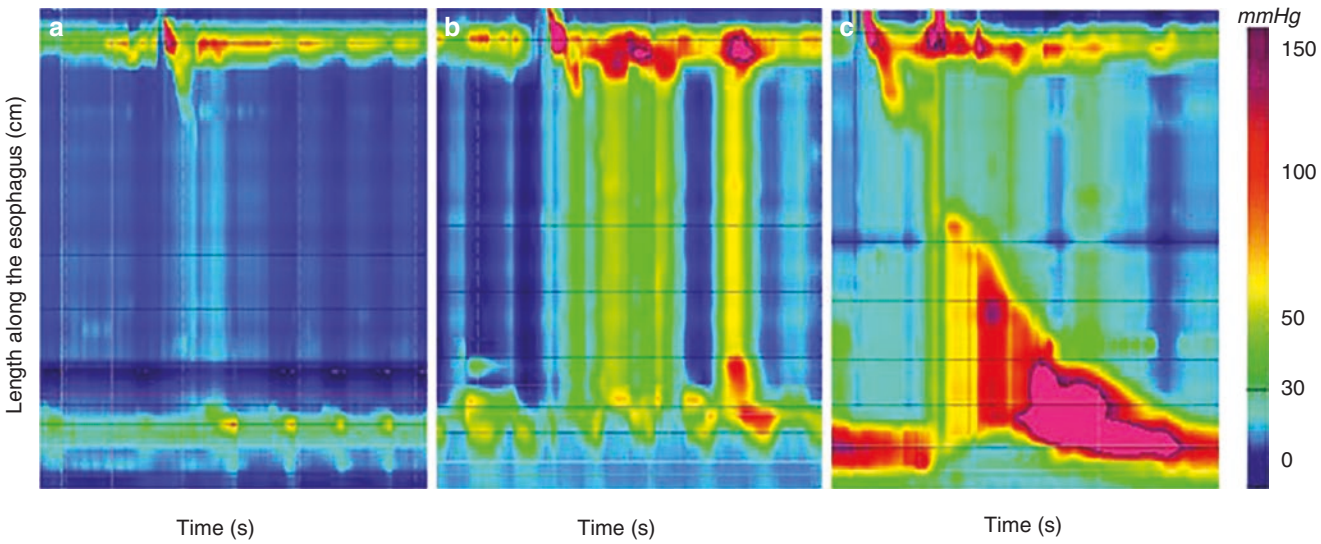

Fig. 32.1 High-resolution manometry of achalasia subtypes. All subtypes have impaired esophagogastric junction relaxation (**a**) Type I with failed peristalsis, (**b**) Type II with pan-esophageal pressurization, (**c**) Type III with esophageal spasm

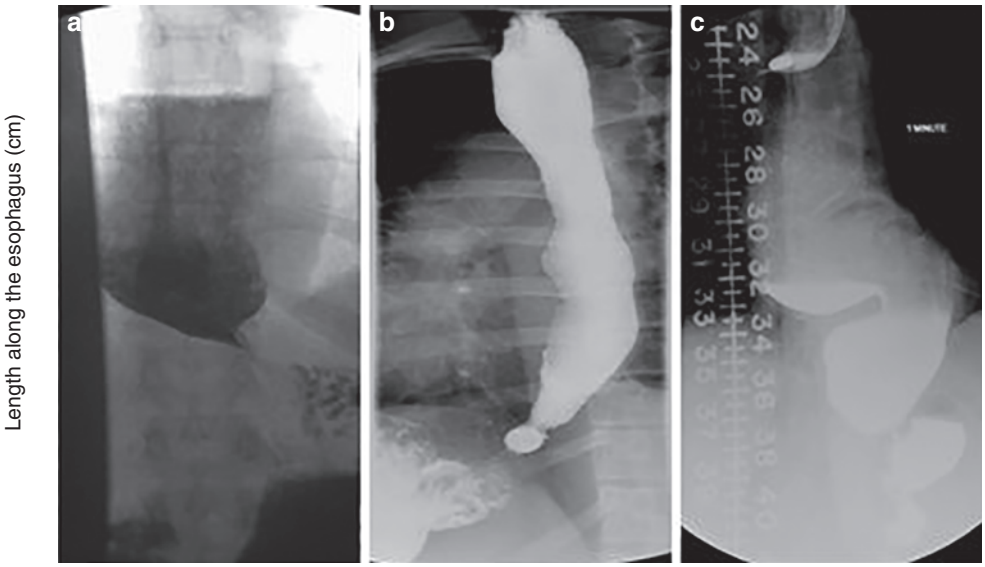

Fig. 32.2 Esophagram of achalasia. (**a**) Dilated esophagus with retention of fluid and bird's beak, (**b**) tortuous esophagus with retention of 13 mm tablet at esophagogastric junction. (**c**) Sigmoid esophagus

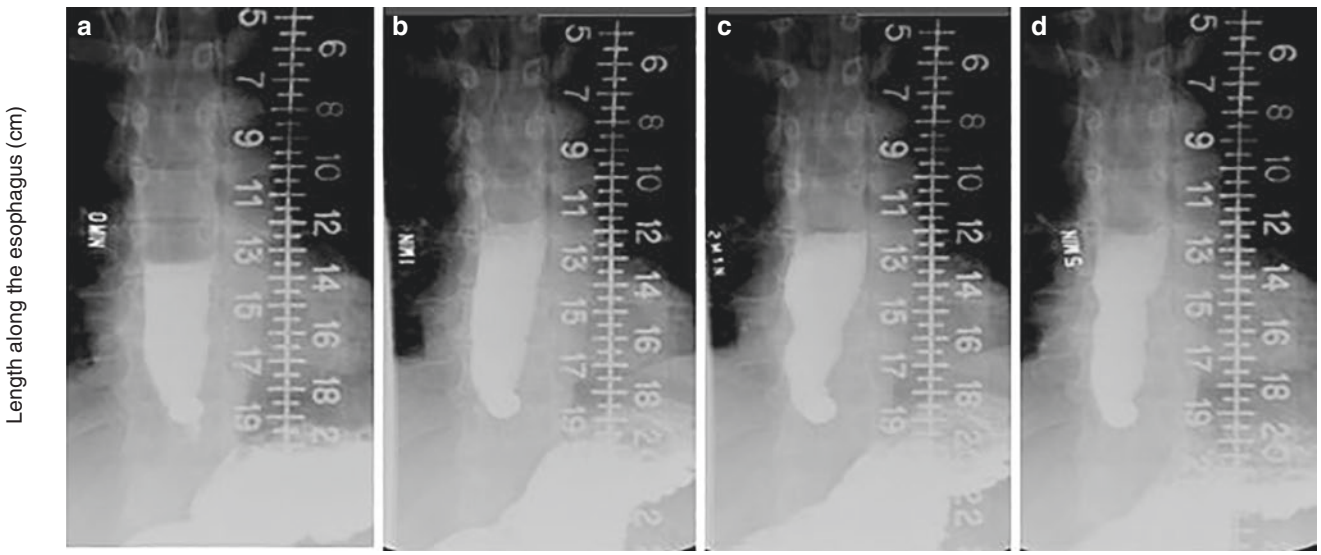

Fig. 32.3 Timed Barium Swallow esophagram of achalasia showing dilated esophagus with retention of fluid and 13 mm tablet at the esophagogastric junction. (**a**) Barium column at 0 min, (**b**) 1 min, (**c**) 2 min, (**d**) 5 min

Disorders of Peristalsis

Absent Contractility

Absent contractility is defined by normal GEJ relaxation in supine and upright position and 100% failed peristalsis (DCI <100,450 mmHg cm s) [4] (Fig. 32.4). It is most commonly found in patients with systemic sclerosis. It has been described in patients with other connective tissue disorders, myopathic disease, and non-rheumatologic disorders, including pulmonary disease.

Absent contractility is associated with poor bolus transit and erosive GERD. Symptomatic patients present with reflux, dysphagia, or both. However, it can be found in healthy, asymptomatic individuals and its clinical significance and role in dysphagia and reflux are not well understood.

The pathogenesis of absent peristalsis not associated with connective tissue disorders is uncertain. Pathophysiology in systemic sclerosis involves three stages: neuropathy, myopathy, and fibrosis [5, 6]. Clinical presentation of systemic sclerosis is discussed in a dedicated chapter.

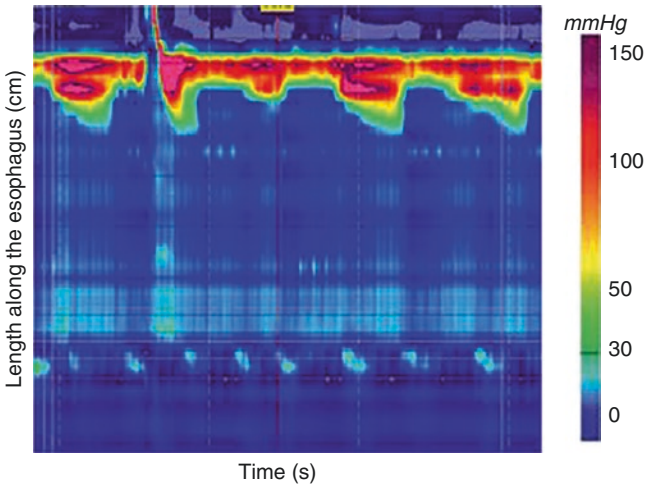

Fig. 32.4 High-resolution manometry of absent contractility with 100% failed peristalsis and normal of esophagogastric junction relaxation

Distal Esophageal Spasm

Introduction

Distal esophageal spasm (DES) is an uncommon, idiopathic disorder of peristalsis characterized by uncoordinated spastic contractions in distal esophagus.

Epidemiology

DES often goes unrecognized for years with a median time from onset of symptoms to diagnosis of 48 months. Prevalence has been estimated at 3–9% in symptomatic patients, with a mean age of 60 years and slight (55%) female predominance.

Pathophysiology

DES is believed to stem from an imbalance between inhibitory and excitatory pathway in the myenteric plexus. The increasing inhibitory gradient between the proximal and distal esophagus corresponds to gradual increase in duration of deglutitive inhibition as the peristaltic wave progresses along the esophagus. Several studies have suggested that malfunction in NO synthesis and/or degradation may play a role in dysfunctional inhibitory pathways. Impairment in inhibitory innervation leads to premature and rapidly propagated contractions in the distal esophagus. Spastic contractions may be generated by a reduction in NO, balanced by a central vagal cholinergic component that impacts timing and strength of peristalsis.

Data regarding the relationship between DES and GERD are conflicting. GERD and DES may coexist, although causality has not been proven. Pathological acid reflux has been demonstrated in 38% of patients with DES and patients' symptoms often improve with acid-suppressing treatments. DES and Type III Achalasia share similar pathophysiological mechanism, and there are case reports of patients with DES that progressed to achalasia. DES may also be linked to psychiatric conditions, as psychiatric diagnoses and medication use have been reported in a large portion of DES patients [7, 8]. Opioids appear to have acute and chronic effects on esophageal motility and chronic opioid use may interfere with inhibitory signals, resulting in spastic esophageal activity [9].

Clinical Features

Clinically, patients present with dysphagia to solids and/or liquids (55%) and non-cardiac chest pain (29%). Other symptoms may include regurgitation, heartburn, and weight loss. Symptoms are usually intermittent, lasting from seconds to hours, ranging from mild to severe in intensity. Symptoms are typically related to food or fluid intake but can occur spontaneously. The presentation is often nonspecific and the majority of patients presenting with dysphagia and chest pain do not have DES confirmed on HRM; therefore, more common and life-threatening cardiac diagnoses should be ruled out prior to an esophageal motility workup [7, 8].

Diagnosis

Manometric Testing

HRM is the gold standard for diagnosis of DES, as endoscopic and imaging findings are nonspecific. Chicago Classification version 3.0 (CCv3.0) classified DES as major motility disorder. It is characterized by premature contractions, defined as a distal latency (DL) <4.5 s in at least 20% of wet swallows, without impairment of relaxation of the esophagogastric junction (i.e., normal integrated relaxation pressure [IRP]) [10] (Fig. 32.5a). The definition of DES is purely manometric in CCv3.0; however, the manometric pattern of DES may be associated with GERD or opioid use, raising questions regarding the clinical significance of this manometric definition. CCv4.0 emphasized that the diagnosis of DES requires both clinically relevant symptoms (i.e., dysphagia and/or non-cardiac chest pain) and a conclusive manometric diagnosis of DES. The notion of major and minor disorders was eliminated in the newest iteration of Chicago Classification and DES is classified as a disorder of peristalsis. Caution is made to accurately localize contractile deceleration point and to distinguish contractile activity from other causes of pressure rise in the distal esophagus, such as intrabolus pressure and/or artifact, as failure to do so may lead to over diagnosis of DES [11].

Imaging

Barium esophagram may show retention of barium and/or tablet, tertiary contractions, and "corkscrew" or "rosary bead" appearance; however, this is neither sensitive nor specific for DES (Fig. 32.5b).

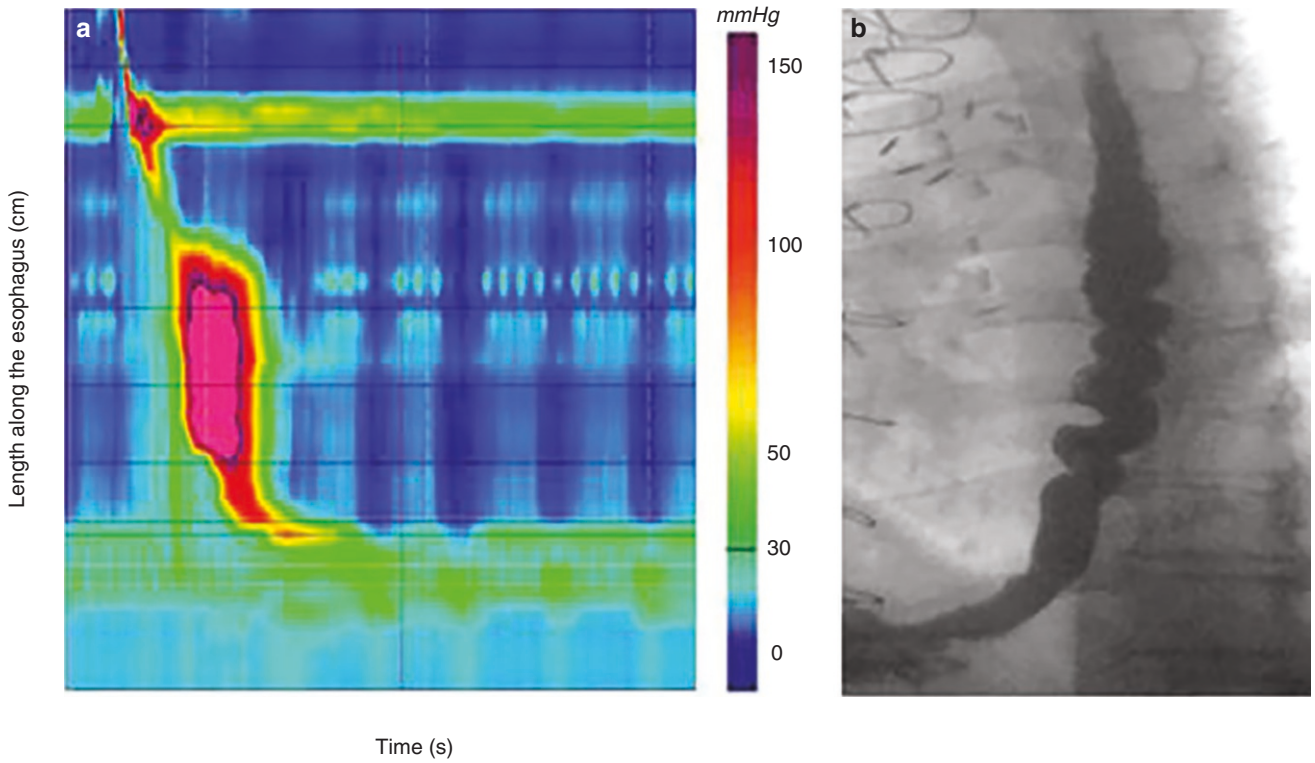

Fig. 32.5 (**a**) High-resolution manometry of distal esophageal spasm with premature contractions without impairment of esophagogastric junction relaxation, (**b**) esophagogram of distal esophageal spasm showing corkscrew appearance of esophagus

Endoscopy

Endoscopy may show spastic, uncoordinated contractions in distal esophagus. Fluid retention, esophagitis, and peptic strictures may be found.

FLIP

FLIP can identify EGJOO associated with spastic and hypercontractile esophageal motility disorders with normal LES relaxation on HRM, potentially altering the treatment plan. FLIP topography may show abnormal pattern of repetitive retrograde contractions or sustained occluding contractions during response to distention. More research is needed to define the role of FLIP in evaluation of DES [7, 8].

Hypercontractile Esophagus

Introduction

Hypercontractile esophagus (HE) is a heterogeneous major motility disorder of the esophagus that occurs in the presence of a normal median IRP, defined when at least 20% of supine wet swallows on HRM are hypercontractile or have a distal contractile integral (DCI) greater than 8000 Hg s cm, without a mechanical cause of obstruction. There are various recognized patterns of hypercontractility, including single-peaked and multi-peaked waves, LES-independent, LES-dependent, and repetitive powerful contractions are noted (Jackhammer) [12]. Of note, about half of HE patients with multi-peaked contractions experience episodes with respiration; the other half do not [13]. In light of this heterogeneity, defining best treatment practice and prognosis is somewhat limited.

Epidemiology

HE is a rare finding on HRM, making up only 1.5–3% of defined manometric abnormalities. It is of higher incidence in females and in those >60 years of age [14]. There is some increased incidence in morbidly obese patients, due to increased intra-abdominal pressures, and in patients following lung transplantation [13]. In the recently updated Chicago Classification version 4.0, it is recommended that HE be diagnosed only in the presence of both conclusive HRM findings and clinically relevant symptoms [12].

Pathophysiology

Increased cholinergic stimulation of the esophagus may contribute to asynchronous circular and longitudinal smooth muscle contractions that produce hypercontractile peristalsis seen either pre-peak or post-peak on HRM [13, 14]. While most HE is considered idiopathic, gastroesophageal reflux disease, eosinophilic esophagitis (EoE), esophageal visceral hypersensitivity, psychiatric comorbidities, opioid use, and early-stage achalasia have been identified as potential etiolo-

gies. HE can involve the esophageal body with or without the lower esophageal sphincter or even be limited to the LES alone. Increased thickness of the esophageal smooth muscle may be present, although this is likely secondary to HE as opposed to the inciting cause [14].

Clinical Features and Presentation

The two most common presenting symptoms of HE are dysphagia (32–100%) and chest pain (10–52%). Symptoms of gastroesophageal reflux are also common (17–58%), including heartburn and regurgitation [13]. While efficacy is controversial, a positive response to pharmacologic intervention to decrease contractility, such as nitrates, calcium channel blockers, and phosphodiesterase inhibitors, supports the diagnosis of HE.

Diagnosis

Manometric Testing

DCI of >8000 Hg s cm on greater than or equal to 20% of wet swallow-induced peristaltic sequences on HRM, with distal latency and IRP below the upper limit of normal, is diagnostic (Fig. 32.6). According to CCv4, HE is diagnosed only in the absence of achalasia, DES, or mechanical obstruction [5]. Provocative maneuvers including multiple rapid swallows (MRS) and rapid drinking challenge (RDC) can assist in diagnosis [14]. MRS will show incomplete esophageal body inhibition with exaggerated excitation and absence of contraction reserve compared to single swallow (SS) resulting in an MRS-DCI:SS-DCI ratio <1. RDC will reveal brief hyper-pressurization with IRP >17 mmHg as a predictor of HE [14].

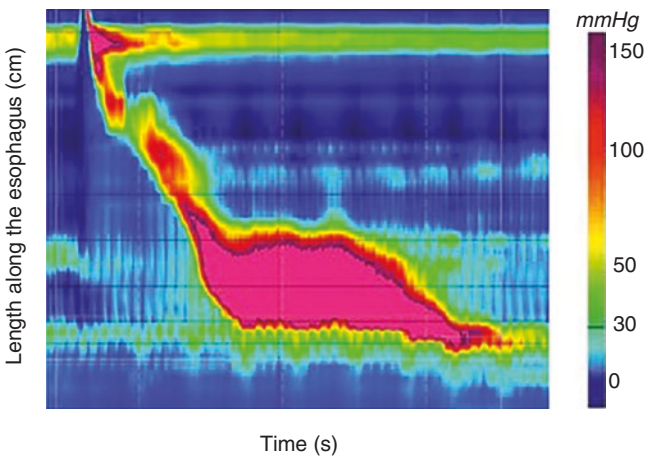

Fig. 32.6 High-resolution manometry of hypercontractile (jackhammer) esophagus with excessive peristaltic vigor and normal esophagogastric junction relaxation

Endoscopy

While structural abnormalities are infrequently noted, EGD is imperative to evaluate for and rule out causes of mechanical obstruction and assess for EoE. EGD and barium esophagram (BE) findings may not be significantly different than in normal controls.

FLIP

Flip may be normal, although excessive LES lift and sustained occluding contractions extending along the entire length of the distal esophagus have been noted in some patients; this may contribute to diagnosis but is insufficient alone [14].

Esophagogastric Junction Outflow Obstruction

Introduction

Esophagogastric Junction Outflow Obstruction (EGJOO) is a disorder of EGJ Outflow characterized by incomplete relaxation of LES in the absence of other defined peristaltic abnormalities. While some cases of EGJOO represent a primary LES motility abnormality with resulting dysphagia, manometric findings consistent with EGJOO are also commonly found incidentally during workup for other foregut pathologies. Clinically relevant diagnosis of EGJOO requires both manometric findings of outflow obstruction and clinically relevant symptoms, as well as supportive evidence of obstructive physiology on TBS and/or FLIP [15].

Epidemiology

EGJOO is diagnosed in up to 14% of HRM reports. It is more common in females than in males and typically occurs in individuals between 50–70 years old. Secondary EGJOO can occur from myriad causes of pressurization at the LES. There is increasing recognition of the relationship between HE and EGJOO; HE may be secondary to distal esophageal obstruction, and EGJOO may also result from the decreased inhibition seen in HE. Manometric evidence of EGJOO may also be related to effect of artifact.

Pathophysiology

A small subset of patients with EGJOO represent a variant of early achalasia. In these patients, loss of ganglionic cells in the myenteric plexus and interstitial cells of Cajal may be seen on pathologic review. EGJOO may also be due to any process interfering with the ability of the LES to relax, such as fibrosis, malignant infiltration, or opioids. Obstructive processes, such as esophagitis, EoE, Schatzki's rings, benign or malignant distal esophageal strictures, obstructing esophageal varices, external compression from the aorta, hiatal hernias, epiphrenic diverticulum, and post-surgical changes

such as fundoplication and bariatric lap-bands may also result in EGJOO [15].

Clinical Features and Presentation

Patients with clinically relevant EGJOO primarily present with dysphagia and/or non-cardiac chest pain.

Diagnosis

Manometric Testing

According to the most recent iteration of Chicago Classification (CCv4.0), EGJOO is considered clinically inconclusive. Manometric diagnosis of EGJOO is made when median IRP is elevated in the primary and secondary position, peristalsis is intact, and >20% swallows demonstrate elevated IRP in supine position. Outflow obstruction and pressurization during rapid drink challenge (RDC), outflow obstruction during solid meal test, and abnormal EGJ function following pharmacologic provocation can be used to support the diagnosis. EGJOO should be described in association with pattern of peristalsis (i.e., with spastic features, with hypercontractile features, with IEM, without evidence of disordered peristalsis). Maximum DCI >11,000 mmxHgxcmxs has a positive predictive value of clinically relevant symptoms that persist without intervention of 82%. Intrabolus pressure also appeared helpful, with a mean threshold of 40 mm Hg demonstrating a PPV of 75% and maximum threshold of 46 mm Hg a PPV of 70% [16, 17].

Imaging

TBS with a 13 mm tablet may show stasis of barium and/or retention of the 13-mm tablet, which can help distinguish between obstruction, achalasia, and manometric artifact [16]. CT scan can assist in the evaluation of contributing structural abnormalities.

Endoscopy

EGD may be unremarkable in primary EGJOO but is essential in evaluating for structural causes of obstruction as mentioned above. Endoscopic ultrasound may help identify infiltrative or vascular abnormalities at the GEJ.

FLIP

Distensibility of LES on FLIP can help differentiate true obstruction at GEJ (low distensibility) from a manometric artifact (normal distensibility).

Ineffective Esophageal Motility

Introduction

Ineffective Esophageal Motility (IEM) is characterized by ineffective or failed peristalsis. It is a manometric diagnosis that can be found in asymptomatic healthy individuals, and its clinical impact remains debatable.

Epidemiology

IEM diagnosed based on CCv3.0 has been reported in up to 30% of patients referred for esophageal motility evaluation but has also been frequently found in healthy subjects (up to 17% of healthy volunteers) [18]. IEM based on the latest Chicago Classification has been reported in 10% of healthy volunteers [19].

IEM has been reported in smooth muscle disorders (e.g., systemic sclerosis, other connective tissue disorders, and gastroparesis) and neurological disorders, such as Parkinson's disease. Use of phosphodiesterase inhibitors and skeletal muscle relaxants has been associated with reduction of contractile strength and IEM pattern on HRM. IEM, especially severe peristaltic dysfunction, is associated with GERD and esophageal mucosal injury [18].

Pathophysiology

The pathophysiology underlying IEM is incompletely understood. Low amplitude contractions observed in IEM are a result of a variety of neuronal and muscular factors. Esophageal smooth muscles are controlled by brain stem vagal nuclei, which are influenced by peripheral sensory input from esophagus and direct central input. Dysfunction at central and peripheral levels can contribute to ineffective peristalsis. Muscle dysfunction can also be a result of primary smooth muscle disorder, a consequence of GERD, or related to other factors, such as medications.

Secondary peristalsis triggered by esophageal distention has an important role in normal esophageal function and reflux clearance, especially during sleep. GERD patients with IEM have diminished secondary peristaltic response compared to matched controls. Severe peristaltic dysfunction (>70% ineffective swallows) is associated with abnormal acid exposure and esophageal mucosal injury, especially supine acid exposure. Peristaltic dysfunction may either be a contributor to GERD due to poor clearance of refluxate, or the motor abnormality may be a result of compromised mucosal integrity related to chronic acid exposure [18].

Clinical Presentation

Observational studies based on older IEM definition show that patients with IEM represent a heterogeneous group, with a range of intermittent symptoms, including dysphagia, heartburn, regurgitation, and chest discomfort or pain. Rates of symptoms, however, are similar between patients with and without IEM, with a lack of correlation between subjective symptoms of dysphagia and objective manometric findings. IEM, especially severe IEM, appears to contribute to supine and refractory GERD and nonobstructive dysphagia. In general, observational studies suggest that IEM appears to be

non-progressive without significant impact on quality of life and minimal long-term consequences [18–20]. Clinical significance of IEM based on latest Chicago Classification requires further investigation.

Diagnosis

Manometric Testing

CCv3.0 categorized IEM and fragmented peristalsis as minor motility disorders. IEM was defined as ≥50% ineffective sequences (DCI < 450 mmHg cm s), with normal IRP. Both weak (DCI (100–450 mmHg cm s) and failed (DCI < 100 mmHg cm s) swallows were considered ineffective. Fragmented peristalsis was defined as ≥50% fragmented swallows (DCI >450 mmHg cm s with ≥5 cm break) (Fig. 32.7).

CCv4.0 does not make a distinction between major and minor disorders, and fragmented peristalsis is included under the definition of IEM. The diagnostic criteria were made more stringent and require more than 70% ineffective swallows or at least 50% failed peristalsis (DCI <100 mmHg s cm).

The changes were implemented because of recent evidence that identified several shortcomings with respect to hypomotility disorders within CCv3.0. Fragmented peristalsis is rare but has a great impact on retention of swallowed bolus and reflux burden, hence it was incorporated into IEM. Failed sequences have a more profound impact on bolus transit and reflux exposure. Using a cutoff >70% ineffective swallows is more predictive of abnormal bolus transit and more severe reflux compared to 50–70% ineffective swallows and decreases the incidence to 10% among healthy volunteers. IEM can be further characterized using provocative maneuvers during HRM, including multiple rapid swallows, RDC, solid swallows, and solid test meal [19].

FLIP

FLIP distention can provoke secondary peristaltic response. Normal response to FLIP distention consists of repetitive anterograde contractions (RACs) and has been observed in 60% of patients with IEM (based on CCv3.0). Subjects with greater esophageal acid exposure were more likely to demonstrate absence of RAC pattern, indicating that secondary peristalsis may have clinical significance in GERD clearance. Complementary FLIP evaluation has potential to enhance evaluation of IEM; however, its diagnostic role in IEM requires further investigation [18].

Due to uncertainties outlined above, further research is needed to define the clinical significance and impact of IEM.

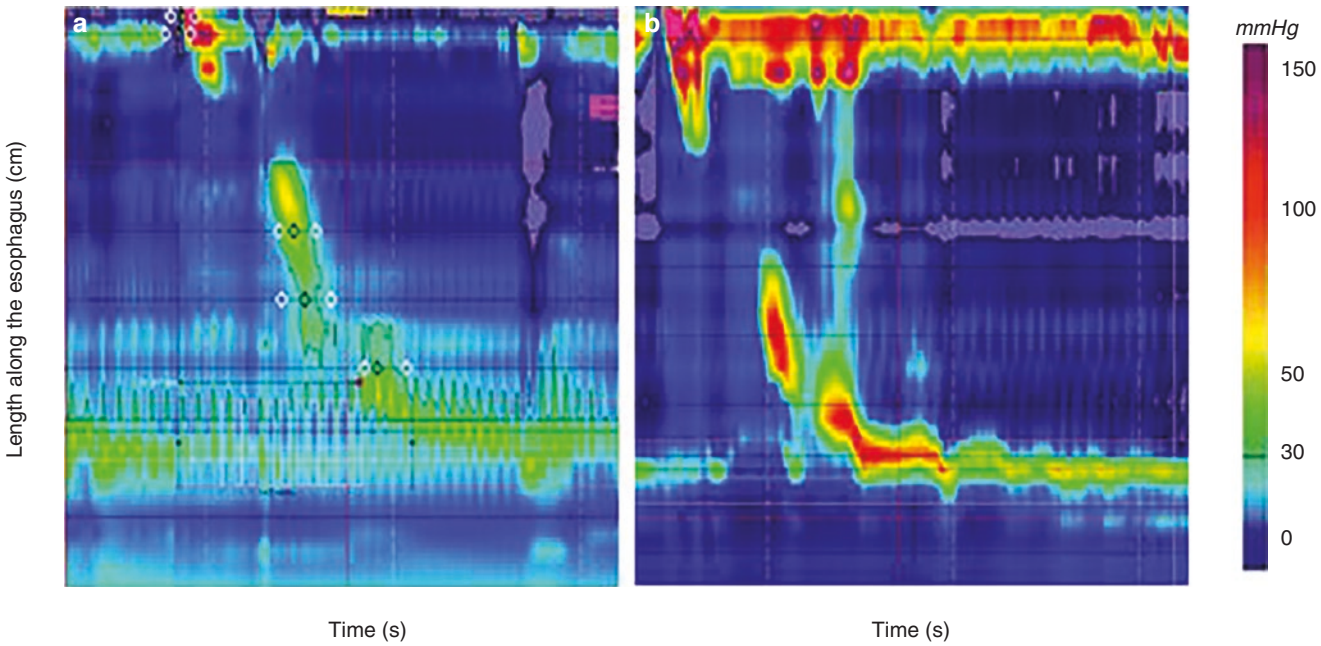

Fig. 32.7 High-resolution manometric patterns seen in ineffective esophageal motility (**a**) Weak swallows [DCI (100–450 mmHg cm s)], (**b**) fragmented swallows (DCI >450 mm cm s with ≥5 cm break)

Questions

1. Achalasia is associated with the following:
   A. Increased risk of esophageal squamous cell carcinoma
   B. Increased risk of esophageal adenocarcinoma
   C. Increased risk of esophageal squamous cell and adenocarcinoma
   D. Increased risk of gastric adenocarcinoma

Answer: C. The risk of squamous cell carcinoma is approximately 72 times higher and the risk of esophageal adenocarcinoma is 6 times higher in patients with achalasia compared to the general population.

2. Diagnosis of distal esophageal spasm can be made in the following scenario:
   A. Patient with dysphagia and EGD showing spastic, uncoordinated contractions in the distal esophagus
   B. Patient with heartburn and manometry showing premature contractions without impairment of esophagogastric junction (EGJ) relaxation
   C. Patient with heartburn and barium esophagram showing "corkscrew" appearance of esophagus
   D. Patient with dysphagia and manometry showing premature contractions without impairment of esophagogastric junction (EGJ) relaxation

Answer: D. Distal esophageal spasm is defined by premature contractions (evident by distal latency (DL) <4.5 s in at least 20% of wet swallows) without impairment of esophagogastric junction (EGJ) relaxation (normal integrated relaxation pressure [IRP]). Pattern of DES may be associated with GERD or opioid use, hence Chicago Classification version 4.0 (CCv4.0) emphasized that the diagnosis of DES requires both clinically relevant symptoms (dysphagia and/or non-cardiac chest pain) and conclusive manometric diagnosis of DES.

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Therapies for Spastic Esophageal Motor Disorders

33

Dustin A. Carlson, Reena V. Chokshi, and Ellen Stein

Objectives

1. Describe potential pharmacologic treatment options for spastic esophageal motility disorders
2. Describe outcomes related to endoscopic dilation and botulinum toxin injection for treatment of spastic esophageal motility disorders
3. Describe patient selection for utilization of esophageal myotomy for the treatment of esophageal motility disorders

Introduction

Spastic esophageal disorders have been variably defined over the years, but with the advent of high-resolution esophageal manometry (HRM) and esophageal pressure topography as well as the Chicago Classification, the term "spastic disorders" now refers to type III achalasia, distal esophageal spasm (DES), and hypercontractile esophagus (HE). Type III achalasia is notable for functional outflow obstruction and aperistalsis with premature contractions. DES also has premature contractions but no outflow obstruction. HE is characterized by increased esophageal body contractility. The Chicago Classification version 4.0 criteria for each of these disorders, as well as representative Clouse plots, are shown in Fig. 33.1. Overall, the spastic disorders represent a rare diagnosis seen on HRM. Recent studies have estimated achalasia prevalence at 18/100,000 in patients under 65 years and 162/100,000 in those over 65 years, and of the three subtypes, type II achalasia is thought to be the most prevalent. HE represents approximately 2–3% of manometric diagnoses, and DES likely another 3–4%. Progression from HE or DES to achalasia is uncommon but can occur. The exact pathophysiology of these disorders remains unclear but represents a neural imbalance in the form of decreased inhibition, excess contractile drive, or both. These affect the smooth muscle anatomy and/or function and lead to spasm. Clinically relevant disorders typically manifest with dysphagia, chest pain, regurgitation, and/or reflux. Because of their unclear pathogenesis and heterogeneity, treatment decisions should be guided and measured.

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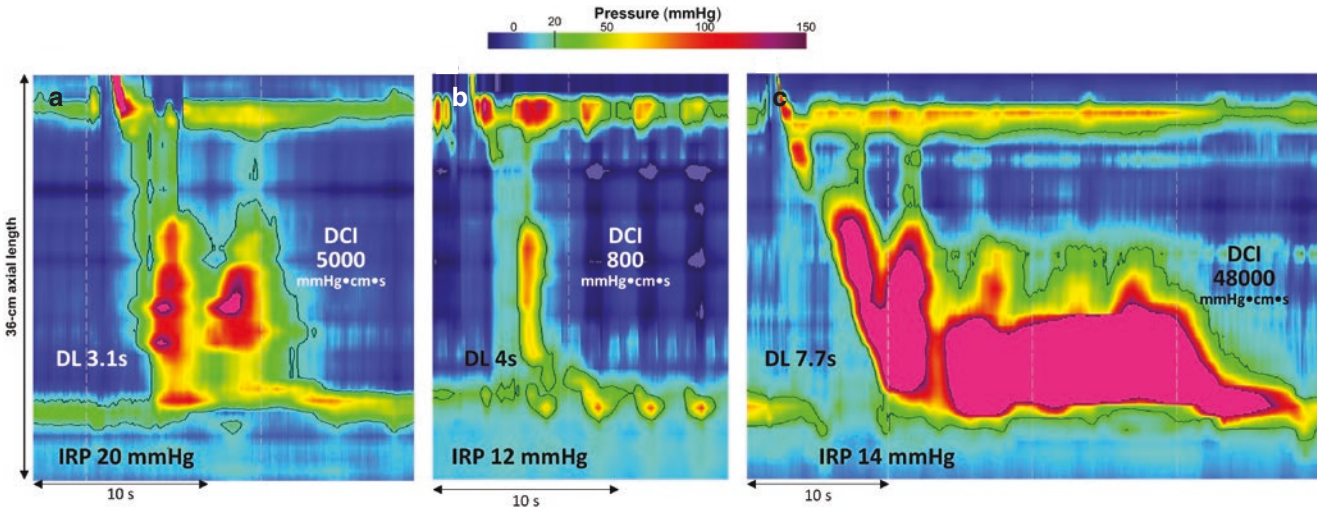

Fig. 33.1 Chicago Classification v.4.0 criteria and manometric representations of the spastic esophageal disorders. High-resolution manometry test swallows from three patients are displayed (**a**–**c**). (**a**) Type III (spastic) achalasia with esophagogastric junction (EGJ) outflow obstruction reflected by an elevated integrated relaxation pressure (IRP) in addition to the premature swallow reflected by the lower-than-normal distal latency (DL). (**b**) Distal esophageal spasm is represented by the premature swallow and normal EGJ outflow pressure. (**c**) Hypercontractile esophagus is represented by the hypercontractile swallow with greater-than-normal distal contractile integral (DCI), in addition to normal EGJ outflow pressure and normal DL

Approach to Management

The management of spastic esophageal disorders is multifaceted and depends upon etiology and pathogenesis, clinical symptoms, and objective data. For HE and DES, clinical symptoms must be present in order for the diagnosis to be considered clinically relevant. The primary reported symptoms are dysphagia, seen in 53–67% of HE and 32% of DES patients, and chest pain, seen in 29–47% of HE and 22% of DES patients. Atypical symptoms are also reported but should be approached with caution when making treatment decisions. Additionally, secondary causes of spasm should be assessed and ruled out. Considerations include gastroesophageal reflux disease (GERD), opiate use, and mechanical obstruction. Finally, in suitable patients with confirmed type III achalasia, management should be more aggressive than in HE or DES, as pharmacologic therapy alone is known to be the least effective achalasia treatment option.

Pharmacologic Therapy

Medications in treatment of spastic motor disorders are primarily used for HE and DES and are aimed at symptom reduction and reduction of contractile abnormalities. Treatment can be challenging due to the heterogeneity of etiologies but is typically initiated toward the primary presenting symptom. Perceptive symptoms, such as chest pain, may respond slightly better to proton pump inhibitors and/or neuromodulators, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), or trazodone. Mechanical symptoms, such as dysphagia, may respond better to therapies directed at relaxing the smooth muscle; however, notable overlap can occur. Overall, there are limited data for the treatment efficacy of any of the medications, as large, randomized, placebo-controlled studies are rare. In addition, some studies have suggested that esophageal motor abnormalities can change over time, thus creating variability in symptom persistence among patients. The various pharmacologic options are detailed below. Dosing and side effect profiles are noted in Table 33.1. Of note, many of the agents used for smooth muscle relaxation can worsen GERD if present.

Calcium Channel Blockers

Blocking L-type calcium channels leads to reduction of intracellular calcium, thus inhibiting smooth muscle contraction. This effect can decrease esophageal contractile amplitude and relax the lower esophageal sphincter (LES). A randomized, placebo-controlled study in achalasia showed that nifedipine and verapamil both decreased LES pressure, and nifedipine also decreased esophageal body contraction amplitude. Unfortunately, neither significantly improved symptoms. Nifedipine has thus been used with limited success in achalasia but may still be considered for treatment of

Table 33.1 Medications used to treat spastic esophageal disorders

Medication class	Proposed dose	Common adverse effects
Calcium channel blockers	Nifedipine 10–30 mg before meals, diltiazem 180–240 mg/day before meals	Headache, constipation; hypotension
Nitrates	Isosorbide dinitrate 5–10 mg before meals	Headache, flushing, dizziness, hypotension
PDE-5 inhibitors	Sildenafil 50 mg (can be multiple times per day)	Headache, dizziness, hypotension, pedal edema
Peppermint oil	10 mL peppermint oil in water; OTC peppermint tablets also used (2 tabs before meals)	Heartburn, allergic reactions
PPIs	Variable; treat as GERD	Headache, diarrhea, nausea, vomiting
TCAs	Amitriptyline 10–50 mg at bedtime (also used: nortriptyline, imipramine, desipramine, all at similar doses)	Drowsiness, constipation, dry mouth, tremor, jitteriness, QT prolongation
SSRIs	Sertraline 50–200 mg daily, paroxetine 5–50 mg daily, citalopram 20 mg daily	Nausea, dry mouth, bowel changes, headache, abnormal ejaculation, decreased libido, insomnia
SNRIs	Venlafaxine 75–150 mg daily	Sleep disturbances, nausea, anorexia, dry mouth, abnormal ejaculation
Trazodone (SARI)	100–150 mg daily	Dizziness, drowsiness, fatigue

Note off label use for listed medications as treatments of esophageal chest pain or dysphagia

HE and DES. Diltiazem is thought to have similar effects and is often considered for chest pain symptoms. Small trials of nifedipine and diltiazem in DES have been mixed with regard to effects on chest pain and dysphagia.

Nitrates and Phosphodiesterase (PDE-5) Inhibitors

Increased nitric oxide allows for LES relaxation and decreased contractility. Small trials have shown both manometric and symptom benefit of nitrates in non-reflux-related DES. However, large, controlled trials in either DES or HE are lacking. PDE-5 inhibitors block the degradation of nitric oxide, thus enhancing its inhibitory effects on the smooth muscle. Despite this, symptom improvement is not consistently reported among patients with motor disorders. Sildenafil was the first in this class to show improvement in LES pressure, esophageal contraction amplitudes, and symptoms in patients with spastic disorders. Similar results were seen for vardenafil and tadalafil, but cost and lack of insurance coverage can present a barrier for patients.

Peppermint Oil

Peppermint oil is a relatively safe and inexpensive option that can be used to reduce spastic contractions. Originally evaluated by Pimentel et al. peppermint oil was found to eliminate simultaneous contractions seen on esophageal manometry. Khalaf et al. expanded on this to show improvement in symptoms of non-obstructive dysphagia and chest pain in patients with esophageal motility disorders.

Proton Pump Inhibitors

Acid inhibition with proton pump inhibitors is thought to address the issue of concomitant GERD frequently seen in patients with spastic disorders. In cases of GERD confirmed by pH testing, PPIs can be considered a first-line therapy. Their use has also been shown to ameliorate perceptive symptoms of non-cardiac chest pain (NCCP), as GERD is by far the most common cause of NCCP. Some mechanical symptoms noted in this patient population may also be improved with PPIs. That said, the actual efficacy in DES and HE as currently defined has yet to be fully elucidated.

Neuromodulators

The role of neuromodulators in visceral hypersensitivity is well described, and both visceral hypersensitivity and psychiatric comorbidities have been suggested as mechanisms in patients with NCCP. In this population, TCAs have proven successful in up to 75% of patients who have incomplete response to acid-suppressive therapy. In one randomized, open-label trial of patients with NCCP, adding amitriptyline to rabeprazole improved global symptom score significantly more than doubling of the rabeprazole dose. Imipramine has also been shown to be effective at relieving NCCP in patients with esophageal motility disorders. Another well-designed trial of patients with hypersensitive esophagus showed improved symptoms with citalopram, a commonly used SSRI, versus placebo. Successful treatment of DES with SSRIs has also been demonstrated in smaller trials. The SNRI, venlafaxine, has shown some success in patients with functional chest pain. Finally, trazodone can help relieve NCCP and has also demonstrated superiority to placebo in patients with DES and the formerly-termed nutcracker esophagus.

Endoscopic Therapy for Spastic Esophageal Motility Disorders

Dilation

Endoscopic therapies for spastic motility disorders include esophageal dilation and botulinum toxin injection. As spastic motor findings on HRM can be associated with mechanical obstruction, evaluation should include a thorough endoscopic examination including biopsies to exclude eosinophilic esophagitis. However, even if an overt mechanical obstruction is not identified on endoscopy, a trial of esophageal dilation (≤20 mm) may be worth considering. It is worth noting that a previous sham-controlled, cross-over study of patients with "nutcracker esophagus" on conventional line tracing manometry demonstrated neither symptomatic nor significant manometric improvement following 54-French therapeutic bougie dilation.

Larger caliber pneumatic dilation may also be a consideration for treatment of spastic esophageal motor disorders. However, with regard to treatment of type III achalasia, pursuit of surgical myotomy is likely preferred over pneumatic dilation. In post-hoc analysis of the prospective European Achalasia study that randomized patients to pneumatic dilation versus laparoscopic Heller myotomy, the 18 patients with type III achalasia had better symptomatic outcomes when treated with Heller ($n = 8$), than with pneumatic dilation ($n = 10$) with positive outcomes in 86% vs 40%, respectively. However, another study demonstrated that benefit was reported following 30-mm (sometimes followed by 35 mm) pneumatic dilation in 14/20 patients with DES; however, an esophageal perforation also occurred. Therefore, with application of pneumatic dilation in spastic motor disorders, the consideration of lower potential for benefit (as compared with non-spastic achalasia) needs to be balanced with the small, but real, risk of perforation prior to advancing to pneumatic dilation.

Botulinum Toxin Injection

Botulinum toxin injection, which exhibits its inhibitory neuromuscular effect via cholinergic blockade, is also a potential therapeutic option. Symptomatic improvement following botulinum toxin injection into the LES +/− distal esophageal wall was reported in open-label case-series in patients with DES and/or hypercontractile esophageal disorders, as well as in a sham-controlled cross-over study in patients with DES or nutcracker esophagus. Additionally, a multi-centered, retrospective study of the safety of esophageal botulinum toxin injection found mild complications in 16% of 141 botulinum toxin injections among patients with non-achalasia spastic motility disorders. While chest pain was the most common "complication," there was report of a death following mediastinitis as the only major complication among 657 total botulinum toxin injections for all esophageal motility disorders.

However, another very important study from Mion et al. in this area was a sham-controlled, prospective trial of botulinum toxin injection for patients with type III achalasia, DES, or hypercontractile esophagus. In this study that randomized 10 patients to a sham endoscopy versus 13 patients to botulinum toxin injection and demonstrated significant symptomatic improvement in both arms, without a difference between treatment and sham. Further, HRM was repeated 3 months after randomization (in 21/23 patients) and notably, a spastic motor pattern was only observed on follow-up HRM in only 3 patients; this included resolution of the spastic HRM findings (i.e., HRM with normal motility or ineffective esophageal motility) in 75% (6/8) patients in the sham arm that completed follow-up HRM (Fig. 33.2). Therefore, while botulinum injection, or esophageal dilation, can be considered for patients with spastic motor disorders, the potential for both symptoms and manometric abnormalities to resolve with time and/or conservative management needs to be recognized. This is of particular importance prior to pursuit of invasive and irreversible interventions such as myotomy.

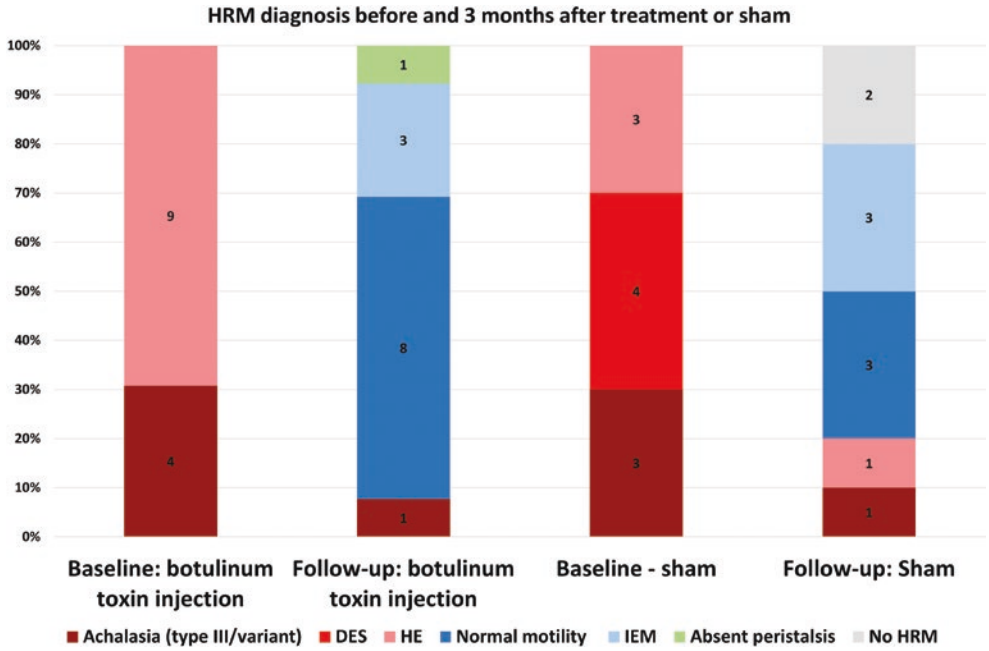

Fig. 33.2 High-resolution manometry (HRM) diagnoses at baseline and after treatment (botulinum toxin injection) or sham. "Follow-up" HRM was performed 3 months after treatment/sham. Data labels indicate the number of patients. Notably, resolution of the spastic manometric findings occurred in 6/8 patients that completed HRM in the sham arm. *IEM* ineffective esophageal motility

Surgical/Endosurgical Therapy for Spastic Esophageal Motility Disorders

Patient Selection for Surgical/Endosurgical Management

When conservative measures in the treatment of non-achalasia, primary spastic esophageal motor disorders have failed to provide sustained or meaningful relief of symptoms, more invasive measures may be considered. For patients with achalasia, especially type III achalasia, invasive measures may be considered as primary treatment. Given the known correlation between opioid medications and esophageal spastic disorders, time off opioids should be undertaken for several months before a major irreversible intervention. Even a brief history of opioid exposure or ongoing use of even mild opioid agents poses a risk of exacerbating spastic dysfunction. Myotomy can be done safely but is most valuable in symptomatic spasm patients. In the absence of symptoms, it would not be recommended to proceed with a surgical or endoscopic myotomy in most cases. Multidisciplinary care teams can help guide rational decisions.

Procedures: Laparoscopic Heller's Myotomy (LHM) and Peroral Endoscopic Myotomy (POEM)

As described for spastic esophageal disorders, LHM would include a myotomy extending at least 6 cm over the esophagus above the GE junction and at least 1.5 cm over the stomach and a fundoplication with at least a 180° closure to manage reflux. Per-oral endoscopic myotomy was originally described as a 2 cm longitudinal entry incision within the esophagus with tunnel creation followed by myotomy of the circular muscle fibers with a length of between 3 and 8 cm above the gastroesophageal junction and 2–3 cm below into the gastric area. Shorter myotomy was originally described for achalasia treatment, but when managing spastic types, longer and longer myotomies have been studied with increasing observed symptom relief noted by some interventionalists with length of myotomy. Theoretically, longer myotomy can be performed and tailored to the length of observed spastic motion in the esophagus (i.e., observed on HRM), although the benefits of longer myotomy are thought to be non-inferior in treatment of type II achalasia. There is less certainty in esophageal spastic dysfunction without achalasia.

Risks and Considerations

Myotomy carries a risk of worsening reflux, but in long myotomy some of the resultant peristaltic dysfunction, the outcome of extended myotomy is often absent peristalsis, contributes to problematic clearance of acid exposure. Thus, there may be an added risk of long myotomy to worsen total esophageal acid exposure time. When performing LHM, most surgeons can also perform a surgical fundoplication within the same session, reducing risk of long-term reflux. It

has not been possible until recently for fundoplication to be performed immediately with POEM. Recent work with transoral incisionless fundoplication and POEM has been looking at this possibility, but scant published data on the optimal patient selection for this procedure exists at this time. Not all POEM patients demonstrate abnormal acid reflux exposure, and therefore some patients will not require fundoplication. In studies of POEM without fundoplication, abnormal reflux was reported in 1 out of 5 patients studied.

Outcomes

Both LHM and POEM have effectiveness for symptomatic relief in spastic esophageal disorders and achalasia. Estremera-Arevalo and colleagues published a study showing that POEM has demonstrated an effectiveness for DES of 88% and JE of 70%. In a retrospective study of French patients at several motility centers, POEM with long myotomy (8 cm above the EGJ) was successful in improving symptoms including Eckhart score, dysphagia, regurgitation, and chest pain for patients with a variety of non-achalasia motor disorders. Response was noted at 3 months in approximately 80% and was persistent at 6 months in 63%. This study was limited by a substantial proportion of participants lost to follow-up. The benefits of POEM and LHM have been clearly demonstrated for achalasia I, II and III. Sustained relief after LHM reaches 67–85% for type I achalasia, 93% in type II, 86% in type III. For POEM, symptom improvement is similar and several meta-analyses have shown no difference in outcomes. With longer myotomy in POEM, some studies have found up to 96% of patients with improvement in type III achalasia, which is an improvement over LHM.

Cost Considerations

With respect to costs, POEM tends to be favored over LHM because it requires a shorter hospital stay, has higher clinical observed success reported in studies, a shorter operative time, and sustained symptom relief. There are only small series published regarding outcomes of relief of pain after treatment of spastic esophageal disorders, but many patients in those studies did experience pain relief. Dysphagia as measured by the Eckhart score was more reliably improved.

Concerns

The risks of POEM in spastic disorder were examined in a pooled study. Khashab et al. reported the main complications to be: pneumothorax, pulmonary embolism, capnoperitoneum, and bleeding. Rare reports of mucosectomy were listed as well. Most complications were able to be managed in real time with conservative measures. The rate of complications was 14% when being inclusive of all events, even those that required no measures of correction or change in length of stay. Other studies have quoted much lower rates of adverse events, only 7.5% in a group of 1826 subjects.

Conclusion: Surgical/Endosurgical Therapy for Spastic Esophageal Motility Disorders

Efficacy of LHM is comparable to POEM for achalasia. Efficacy is similar between methods for non-achalasia spastic esophageal disorders. POEM has known advantages in spastic disorders like type III achalasia as well as refractory non-achalasia spastic disorders like JE and DES. Ability to attain a longer myotomy appears to improve symptom outcomes. Long-term studies and more randomized studies will be needed to see if these results are maintained and to determine which methods are best to identify and control reflux long term.

Conclusions

A broad spectrum of therapeutic options that target alleviation of spastic esophageal motor activity are available for treatment of spastic esophageal motility disorders, including pharmacologic (smooth muscle relaxants), endoscopic (dilation or botulinum toxin injection), or (endo)surgical (LHM or POEM). However, it is also important to recognize that the HRM features and patterns that define these spastic disorders (i.e., type III achalasia, DES, and HE) can occur secondarily to other causes such as GERD, mechanical obstruction, or opioid use. Further, they may even carry a potential to spontaneously resolve, as evident in a sham controlled study that utilized HRM as a treatment outcome. Thus, while these treatment options can be effective, care should be taken to exclude alternative (secondary) etiologies for symptoms and "spastic" manometric abnormalities, and importantly: invasive, irreversible therapies should only be applied in carefully selected patients.

Question 1

1. **Which of the following can be an etiology for spastic motor findings on manometry?**
   A. Primary esophageal motility disorder
   B. Secondary effect of opioid use
   C. Secondary effect of mechanical obstruction
   D. Secondary effect of esophageal acid exposure
   E. All of the above

Answer: D.

Question 2

1. Which of the following was demonstrated to be more efficacious for treatment of type III achalasia than pneumatic dilation in a randomized controlled trial?
   A. Lower esophageal sphincter myotomy
   B. Botulinum toxin injection
   C. Peppermint oil
   D. Omeprazole

Answer: A.

Potential Competing Interests DAC: Medtronic (Speaking, Consulting); Phathom Pharmaceuticals (Consulting); RVC, ES: None.

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Pneumatic Dilation for the Treatment of Achalasia

34

Steven Clayton and Joel E. Richter

Objectives

1. To describe the role of pneumatic dilation in the treatment of achalasia
2. To detail, which patients are appropriate for treatment with pneumatic dilation
3. To instruct, on the proper technique of performing pneumatic dilation in the treatment of achalasia
4. To compare, the efficacy of pneumatic dilation in the treatment of achalasia with other available treatment modalities

Introduction

Achalasia is the quintessential form of esophageal dysmotility characterized by abnormal lower esophageal sphincter (LES) relaxation and aperistalsis. Dilation of the LES has been at the forefront of the treatment of achalasia since 1674 when Sir Thomas Willis described dilation of the LES performed with a whalebone [1].

Modern use of pneumatic dilation for achalasia works by disrupting the LES smooth muscle fibers by forcefully stretching them using air-filled non-compliant balloons. Pneumatic dilation was first described in the early 1960s by Vantrappen et al. Of historical interest, the original technique involved the patient swallowing a weighted bag of mercury tied to a string. A guidewire with an eye was passed over the string. Then, sequential dilating balloons were passed over the guidewire and positioned at the level of the LES using fluoroscopy. Dilations would range from 3–5 cm [2]. Thankfully, the advent of flexible fiber-optic endoscopes has made the practice of swallowing weighted mercury bags obsolete. Modern pneumatic dilation is performed with balloons made from a soft polyethylene polymer mounted on a flexible catheter. Most balloons are 10 cm long and come in three diameters (30, 35, and 40 mm). The balloon is not visible under fluoroscopy but has four radiopaque markers on the shaft that define the upper, lower, and middle borders—the last defined by two markers close together. These balloons are non-compliant and therefore do not inflate maximally beyond the designated diameter [3].

The aim of this chapter is to describe the indications, patient selection, procedure technique, and potential complications of performing pneumatic dilation to treat achalasia.

Definition, Incidence/Prevalence, Epidemiology, Pathophysiology/Mechanism

The term achalasia first appeared in the medical literature in an article by Arthur Hertz in 1915. He credits the name designation to his colleague, Sir Cooper Perry. The term "achalasia" (a, not; χαλάω, I relax) was used to describe the underlying pathophysiology of this esophageal disease where the LES fails to relax [4]. Our understanding of and ability to diagnose, characterize, and treat achalasia has increased greatly since 1915. Achalasia is an esophageal smooth muscle motility disorder that is the result of the LES failure to relax in response to deglutition, resulting in a functional obstruction at the gastroesophageal junction. Complicating matters, there is loss of the esophageal peristaltic function and/or disorganized peristalsis. The combination of a functional obstruction at the LES and aperistalsis results in esophageal bolus stasis, leading to symptoms of dysphagia and voluminous regurgitation.

Achalasia is a rare disease occurring with an annual incidence of approximately one per 100,000 people and a prevalence of 10 per 100,000. Achalasia afflicts humanity as a whole and does not have a preponderance for a particular

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age, race, and/or gender [1]. Achalasia presents with equal frequency in both males and females. Achalasia typically presents between the second to the fifth decade of life with a peak incidence between the ages of 30–60 years. Achalasia occurs in the pediatric population with an estimated annual incidence of 5% in children less than age 16 [5].

The pathogenesis of achalasia is not fully understood. The pathophysiology of achalasia results from the inflammation and degeneration of myenteric plexus ganglion cells that innervate the smooth muscle of the esophagus and LES. Within the myenteric plexus, there are two types of neurons: excitatory cholinergic and inhibitory neurons using nitric oxide (NO) and vasoactive intestinal polypeptide (VIP) as neurotransmitters. This degeneration preferentially involves the NO-producing inhibitory neurons. The cholinergic neurons affecting the tonic contraction of the LES are relatively spared. This loss of inhibitory innervation of the LES results in loss of deglutative reflexive relaxation of the LES. In the smooth muscle portion of the esophagus, the loss of ganglion cells results in disordered peristalsis and subsequent aperistalsis, ultimately resulting in esophagogastric junction outflow obstruction from a poor relaxing LES.

Also, contributing to pathogenesis of achalasia is the esophageal response to the esophagogastric outflow obstruction. Feline models show the development of hypertrophy, excitability, and eventually failed peristalsis following placement of pressure cuffs around the distal esophagus, creating esophagogastric outflow obstruction. This occurs in humans as the result of laparoscopic gastric bands, malignancy, and tight fundoplication [6–9].

The clinical presentation of achalasia can be variable but classic symptoms are bland, large volume regurgitation, progressive solid and liquid dysphagia, chest pain/fullness, varying degrees of weight loss, and sometimes retrosternal burning or heartburn. As patients with achalasia may present with regurgitation and/or heartburn, differentiation from gastroesophageal reflux disease (GERD) can be difficult. This leads to many patients being started on pharmacologic therapies such as proton pump inhibitors (PPI) and sometimes even treated with anti-reflux surgery. Undoubtedly, the similarity in symptoms between GERD and achalasia results in a delay in achalasia diagnosis. This has been addressed in recent guidelines from the American College of Gastroenterology, which recommend evaluating patients with refractory GERD for other diseases, including achalasia. They recommend evaluating for achalasia in patients suspected of having GERD but who do not respond to acid suppressive therapy [10].

Despite being a rare disease, achalasia is associated with significant health care costs. A study from 2017 by Wadwha et al. revealed that between 1997 and 2013, the frequency of achalasia-related hospital discharges increased by 108% (from 2493 to 5195) and the national expenditure for achalasia increased by 675.2% from $32,020,083 ± 3,424,012 in 1997 to $248,215,416 ± 19,066,436 in 2013 ($P < 0.001$). These hospitalizations and costs were primarily in patients 65–84 years of age. The authors speculated this rise in discharges and cost may be the result of the introduction and widespread use of high-resolution manometry resulting in better disease recognition [11].

Although, modern treatment of achalasia has advanced significantly from the days of whalebone esophageal dilation, achalasia is still a chronic condition without a cure. All current treatment modalities for achalasia aim to alleviate the functional obstruction created by poor deglutitive relaxation and hypertonicity of the LES. The aims of therapy are to reduce symptoms, improve esophageal emptying, and prevent the development of a megaesophagus. Modern treatment options for achalasia include pharmacologic, endoscopic, and surgical approaches. Pharmacologic therapy has been demonstrated to be the least effective treatment modality for achalasia and should be pursued in patients who are not candidates for endoscopic or surgical therapies. Endoscopic treatments for achalasia include pneumatic dilation, botulinum toxin injection, and per oral endoscopic myotomy (POEM). Surgical options include laparoscopic Heller myotomy, usually performed in conjunction with either a Dor or a Toupet fundoplication. The purpose of this chapter is to discuss the clinical utility of pneumatic dilation in the treatment of achalasia.

Indications

Pneumatic dilation is an important treatment option for any of the diseases of esophagogastric junction outflow obstruction. These disorders include the three subtypes of achalasia and clinically relevant esophagogastric junction outflow obstruction (EGJOO). It is contraindicated in patients with severe coagulopathy and/or poor cardiopulmonary function that would preclude surgery [10].

Patient Selection

The advent of high-resolution impedance manometry has refined the classification of esophageal dysmotility. Disorders with esophagogastric junction outflow obstruction by the Chicago Classification scale v4.0 have a functional esophageal obstruction as the result of a poorly relaxing LES with or without preserved peristalsis. In this category, achalasia is the best-known esophageal disorder but a new manometric

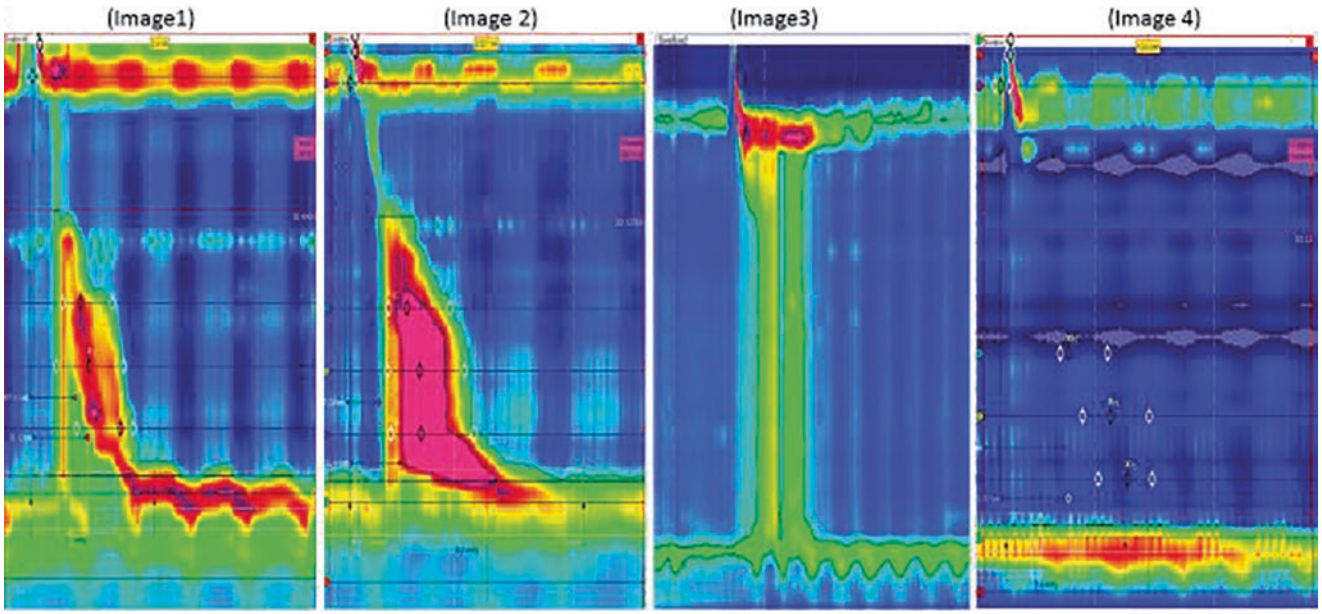

Fig. 34.1 Representative Clause plots representing the four subtypes of disorders of esophagogastric junction outflow obstruction. Image 1—Clinically relevant esophagogastric junction outflow obstruction. Image 2—Type III achalasia. Image 3—Type II achalasia. Image 4—Type I achalasia

diagnosis called esophagogastric junction outflow obstruction (EGJOO) has been defined as having an elevated integrated relaxation pressure (IRP >15 mmHg) with intact esophageal smooth muscle peristalsis [10]. High-resolution manometry allows for achalasia to be differentiated into three subtypes based on manometric patterns: type I (classic) with absent smooth muscle contractility in the esophageal body and an elevated IRP, type II with ≥20% of swallows of panesophageal pressurization and an elevated IRP, and type III (spastic) with shortened distal latency (<4.5 s), DCI >450 mmHg cm s and an elevated IRP. For the diagnosis of achalasia to be made, no identifiable peristalsis should be present. The achalasia subtypes are shown in Fig. 34.1. Subtyping achalasia is of paramount clinical importance as the three achalasia subtypes present very similarly but treatment response varies considerably between the three subtypes [11–13].

Patient selection should be made based upon the patient's cardiopulmonary functional status after high-resolution manometry has confirmed a disorder of esophagogastric junction outflow obstruction, and a balanced discussion about risks and benefits of the different surgical and endoscopic therapies available. In general, male patients less than 40 years of age and type 3 achalasia are better treated with surgical myotomy or POEM. However, this is a general rule of thumb and the authors would like to point out three clinical scenarios where pneumatic dilation may be preferable to surgery or POEM. These scenarios include patients who are morbidly obese (BMI >40), status post laparoscopic sleeve gastrectomy, and clinically relevant EGJOO. Symptomatic GERD is rare after pneumatic dilation (4–37%), compared with laparoscopic Heller myotomy with Dor fundoplication (8.8–26%) and POEM (17–41%) [14]. In a study comparing POEM to pneumatic dilation, 7% of achalasia patients developed post-procedure erosive esophagitis compared to 41% of the patients treated with POEM [15]. Therefore, pneumatic dilation may be a reasonable first procedure in patients with a high risk of post-myotomy GERD such as patients with morbid obesity or with sleeve gastrectomy anatomy. In the setting of EGJOO where peristalsis is routinely preserved, surgical intervention, especially POEM, seems overly aggressive as it creates a scleroderma-like esophagus (absent peristalsis with a hypotensive LES).

Preoperative Evaluation

All patients being considered for a pneumatic dilation need confirmation of a clinically relevant functional obstruction at the LES. Alternative obstructive etiologies should have been assessed for and ruled out with a prior upper endoscopy. These mechanical alternatives would include but are not limited to esophageal carcinoma involving the GE junction, tight fundoplication, esophageal stricture, and EoE [16].

Other endoscopic findings suggestive of achalasia are a rosette (puckered LES), retained secretions and/or food, and a dilated esophagus.

If feasible, all patients should undergo manometry prior to pneumatic dilation. We have stressed the importance of high-resolution esophageal manometry in subtyping achalasia. In general, type III achalasia patients do better with POEM compared with pneumatic dilation. Complementary tests to manometry are the traditional or timed barium esophagram (TBE) and EndoFlip® impedance planimetry. We would recommend obtaining these tests if they are available to help with the initial diagnosis and patient follow-up after treatment.

The TBE protocol begins with administration of 240 mL (8 oz) of low-density barium in the standing position; two-on-one spot films will be obtained at 1 and 5 min to assess liquid emptying. Barium column height and width will be measured from the GE junction to the top of the column that was recorded from each film. Next, the esophagus will be cleared with water, followed by ingestion of a 13-mm barium tablet. Tablet passage will be evaluated after 5 min with an abnormal test being tablet retention at EGJ. A TBE column height at 1 min of 5 cm and 5 min of 2 cm is used to discriminate between patients with achalasia/clinically relevant EGJOO and patients without disorders of EGJ outflow obstruction [17]. The EndoFlip® impedance planimetry system consists of a 24 cm long, 3 mm outer diameter catheter with a highly compliant balloon. The balloon surrounds 16 paired impedance planimetry sensors mounted on the catheter and a solid-state pressure transducer on the distal end of the catheter. EndoFlip® measures distensibility of the esophageal body and/or EG Junction. Reduced distensibility of the EG-junction is suggestive of LES dysfunction. The benefit of the EndoFlip® is that it can be done before and after an LES intervention to assess for improvement of the EGJ distensibility.

Technique

There are no clear guidelines for performing pneumatic dilation. Most centers in the world utilize an endoscopic approach with fluoroscopy. In Asia predominately, and in small centers without fluoroscopy, a purely endoscopic approach has been described [18]. For this chapter, the authors will describe their endoscopic approach using fluoroscopy, which has been used by the senior author for over 30 years. The most commonly used pneumatic balloon is the Boston Scientific Rigiflex™ balloon system, but other products are available. The Boston Scientific Rigiflex™ balloon system consists of a 10-cm long, non-compliant balloon on a flexible catheter with radiopaque rings defining the balloon location. The balloon system is available in 30, 35, and 40 mm diameters.

Prior to treatment, the authors recommend a complete endoscopic examination of the esophagus. The esophagus should be cleared completely of any retained secretions to minimize the risk of aspiration. Always inspect the cardia as pseudoachalasia from a tumor at the GE-junction is in the differential diagnosis. The initial balloon diameter selection is variable, but the authors tend to start with a 30 mm balloon and subsequently repeat pneumatic dilation with increasing balloon diameter size (35 mm and 40 mm) based on the persistence of symptoms after the initial pneumatic dilation. The pneumatic balloon catheter is advanced into the esophagus over a Savary guidewire. Fluoroscopic guidance is used to ensure appropriate positioning at the level of the LES. Next, the balloon is inflated slightly until a "waist" {a narrowing in the balloon under fluoroscopy representing the non-relaxing LES} (Fig. 34.2) is identified and balloon inflation occurs by increasing the PSI as measured with a sphygmomanometer until the "waist" disappears (Fig. 34.3). Dilation is used and held for 60 s after successful effacement of the "waist". After dilation, the patient is observed for 1–2 h, and we routinely obtain a post-procedure barium esophagram on all patients prior to leaving the endoscopy unit. The authors admit there is considerable variability in clinical practice.

The primary author routinely performs a pre-pneumatic dilation Endoflip®, endoscopic evaluation for perforation after every pneumatic dilation, and then performs a post-pneumatic dilation Endoflip; however, this is not practiced at all centers. The primary author also marks the rosette and the diaphragmatic hiatus with radio-opaque markers (Fig. 34.4). There is

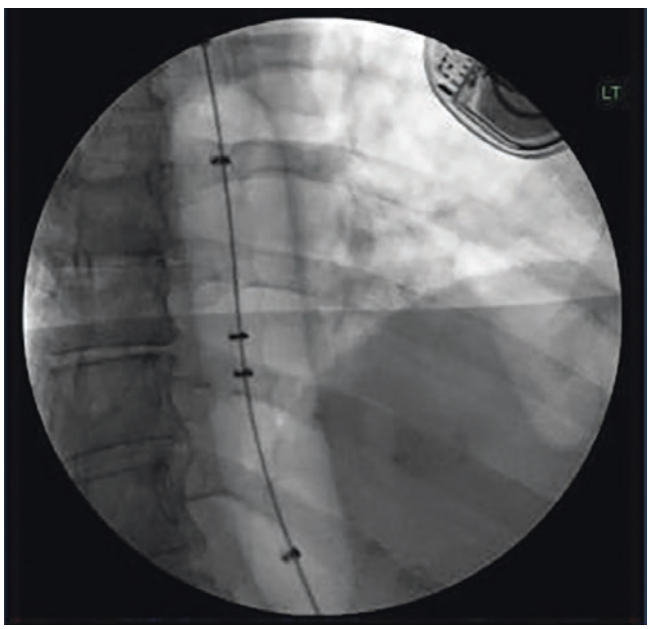

Fig. 34.2 Flattening of the "waist" following inflation of a 30 mm Rigiflex balloon

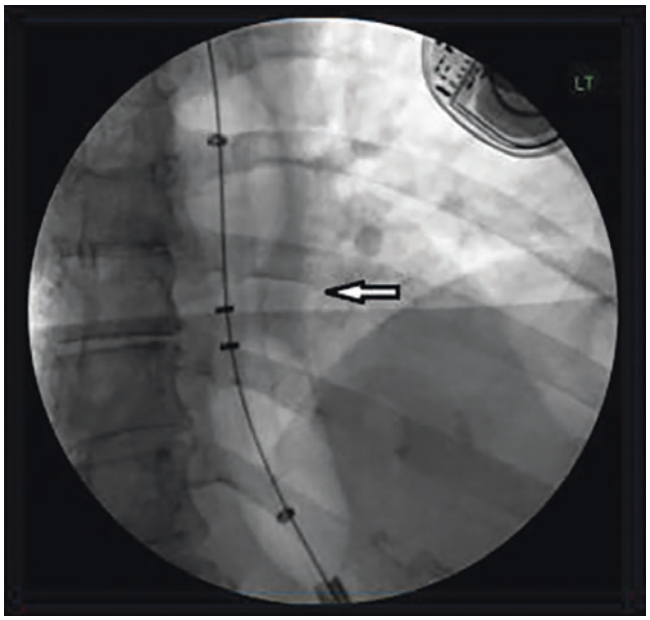

Fig. 34.3 Inflation of a 30 mm Rigiflex balloon revealing a "waist" at the EGJ. The waist is always on the left side of the balloon

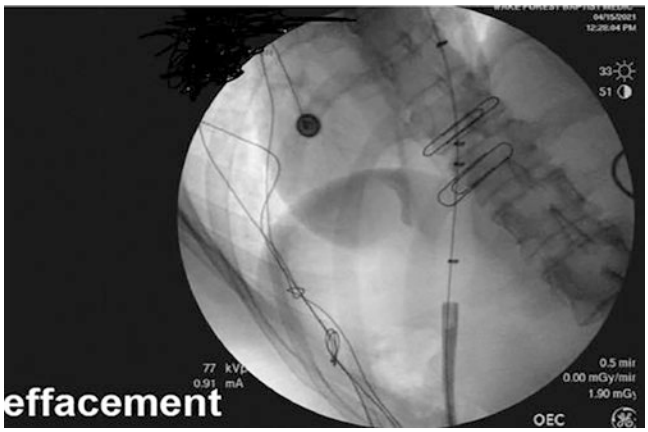

Fig. 34.4 Radiographic markers identifying the lower esophageal sphincter and the diaphragmatic hiatus

some controversy about the necessity of post-pneumatic dilation radiographic testing with gastrografin/barium esophagram to evaluate for perforation prior to discharge. The authors still routinely obtain an esophagram post-pneumatic dilation because esophageal perforation carries a high morbidity and mortality rate if not treated quickly and appropriately.

Outcomes

Pneumatic dilation is a safe and effective treatment for achalasia and should be part of any tertiary referral center's achalasia treatment armamentarium. Pneumatic dilation has proven clinical efficacy, resulting in good to excellent symptom relief with 3.0-, 3.5-, and 4.0-cm in 74%, 86%, and 90% of patients with an average follow-up of 1.6 years (range 0.1–6 years) [19]. As previously mentioned, the authors generally start with a 30 mm balloon for most patients, Pneumatic dilation can be repeated every 2–4 weeks in a sequential fashion with incremental increasing (30 mm–35 mm–40 mm) balloon size if persistence of symptoms necessitates. Serial pneumatic dilation has similar efficacy to laparoscopic Heller myotomy at two (85% vs 90%, respectively) and 5 years (82% vs 84%, respectively) [20], based on a large randomized control trial from Europe.

Patients that have the most optimal treatment response after treatment with pneumatic dilation include the following: older age (>45 years), female sex, narrow (non-dilated) esophagus, and LES pressure after pneumatic dilation of <10 mmHg [21]. Esophageal perforation is the most serious complication, with an overall rate, by experienced endoscopists, of 1–2.0%. The senior author has performed 680 pneumatic dilations over the last 25 years with 15 perforations (overall rate of 2.2%) The vast majority occurred with the 30 cm balloon and three with 35 cm balloons. Every patient undergoing pneumatic must be aware of the perforation risk and understand that surgical intervention is possible in the event of perforation [22]. In the last 10 years, we have successfully treated all perforations with an esophageal stent rather than surgery. In a large high-volume single-center study comparing complications and deaths after achalasia treatment, the authors reported significantly fewer complications in patients treated with pneumatic dilation compared to patients treated with laparoscopic Heller myotomy ($p = 0.02$) [23].

Healthcare Costs

Pneumatic dilation is highly cost-effective compared with both laparoscopic Heller myotomy and POEM. Patients undergoing Laparoscopic Heller myotomies are charged on average $44,839 and patients undergoing POEM are charged $41,730. Comparatively, an EGD with pneumatic dilation is $9190 per procedure. Therefore, pneumatic dilation remains the most cost-effective treatment, as long as the patient requires less than four dilations to achieve symptom relief [24].

In conclusion, pneumatic dilation remains a safe, effective, cost-efficient procedure to treat achalasia and should remain at the forefront for treating disorders of esophagogastric outflow obstruction, especially achalasia.

Questions

1. Which patient listed below would have the most favorable outcome after treatment with pneumatic dilation?
   A. 35-year-old male with type I achalasia
   B. 65-year-old female with type III achalasia
   C. 85-year-old male with severe COPD requiring high levels of supplemental oxygen and type II achalasia
   D. 50 year female with type II achalasia

Answer: D. Older patients, female gender, and narrow caliber esophagus tend to have more favorable outcomes when treated with pneumatic dilation. Pneumatic dilation should be avoided in patients who are poor surgical candidates. Type I and II achalasia patients can be treated effectively with pneumatic dilation. Type III achalasia patients should be considered for per oral endoscopic myotomy.

2. A 45-year-old female with type II achalasia presents for consultation to discuss treatment options for her achalasia. She is concerned about post-lower esophageal sphincter intervention risk of gastroesophageal reflux. Which of the following procedures is appropriate for the treatment of achalasia and has the lowest risk of post-treatment GERD?
   A. Nissen fundoplication
   B. Pneumatic dilation
   C. Laparoscopic Heller myotomy with Dor Fundoplication
   D. Per Oral Endoscopic Myotomy

Answer: B. Only 7% of achalasia patients develop post-pneumatic dilation erosive esophagitis, compared with 16% and 41% for laparoscopic Heller myotomy with Dor fundoplication and POEM, respectively. Therefore, pneumatic dilation may be a reasonable first procedure in patients with a high risk of either post-myotomy GERD, such as patients with morbid obesity or with sleeve gastrectomy anatomy. Nissen Fundoplication is an anti-reflux surgery and is not appropriate for the treatment of achalasia.

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Minimally Invasive Heller Myotomy

35

Melissa L. Desouza and Kevin M. Reavis

Objectives

1. Discuss common disease processes managed with Heller myotomy and fundoplication and objective preoperative workup
2. Review the technical aspects of laparoscopic or robotic Heller myotomy with partial fundoplication in detail
3. Present intraoperative and postoperative considerations and complications related to surgical myotomy
4. Review postoperative outcomes following minimally invasive surgical myotomy for achalasia

Introduction

In 1913, Ernst Heller performed the first transthoracic extramucosal cardiomyotomy, with combined anterior and posterior myotomies, revolutionizing the treatment of achalasia. In 1962, Dor added his eponymous fundoplication to Heller's technique in an effort to address post-myotomy iatrogenic gastroesophageal reflux [1]. Over time, modifications were made to these techniques, including adoption of a minimally invasive thoracoscopic approach first described thoracoscopically by Carlos Pellegrini and colleagues [2]. With some initial poor results, a laparoscopic approach ultimately became favored with improved dysphagia relief, less postoperative reflux, and shorter length of stay compared to its thoracoscopic counterpart [3, 4]. The gold standard approach to achalasia became a laparoscopic Heller myotomy performed with a single anterior cardiomyotomy and partial fundoplication.

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While less-invasive approaches to achalasia exist, such as pneumatic dilatation and botulinum toxin injection, myotomy is the most definitive form of treatment for the non-relaxing lower esophageal sphincter. Laparoscopic Heller myotomy has been shown to have better long-term outcomes than pneumatic dilation in treatment of achalasia, providing better quality of life, less retreatment, and better esophageal emptying on barium timed barium studies [5, 6].

Common Indications for Myotomy

Achalasia

Achalasia is a rare primary esophageal motility disorder that is characterized by the lack of relaxation of the lower esophageal sphincter (LES) combined with absent esophageal body peristalsis. The primary symptom of this disorder is dysphagia, however, disease progression can present with regurgitation of ingested food or saliva, aspiration of esophageal contents, malnutrition, chest pain, and sensation of heartburn [7] (Fig. 35.1).

There are three manometric subtypes of achalasia described as part of the Chicago Classification of esophageal motility disorders. Common to all three is incomplete or failed relaxation of the LES, defined as integrated relaxation pressure (IRP) at or greater than the upper limit of normal on high-resolution manometry (HRM). Additionally, all three require absence of normal peristalsis. Type I achalasia demonstrates absent esophageal body contractility, while in Type II, 20% of swallows demonstrate panesophageal pressurization. Type III achalasia demonstrates secondary or tertiary distal esophageal spasm in at least 20% of swallows, again without any evidence of normal peristalsis [8] (Fig. 35.2).

The esophageal aperistalsis of achalasia is currently irreversible, therefore the treatment of this disease is aimed at symptom palliation and attempts to prevent progressive esophageal dilation [9]. In considering surgical myotomy for

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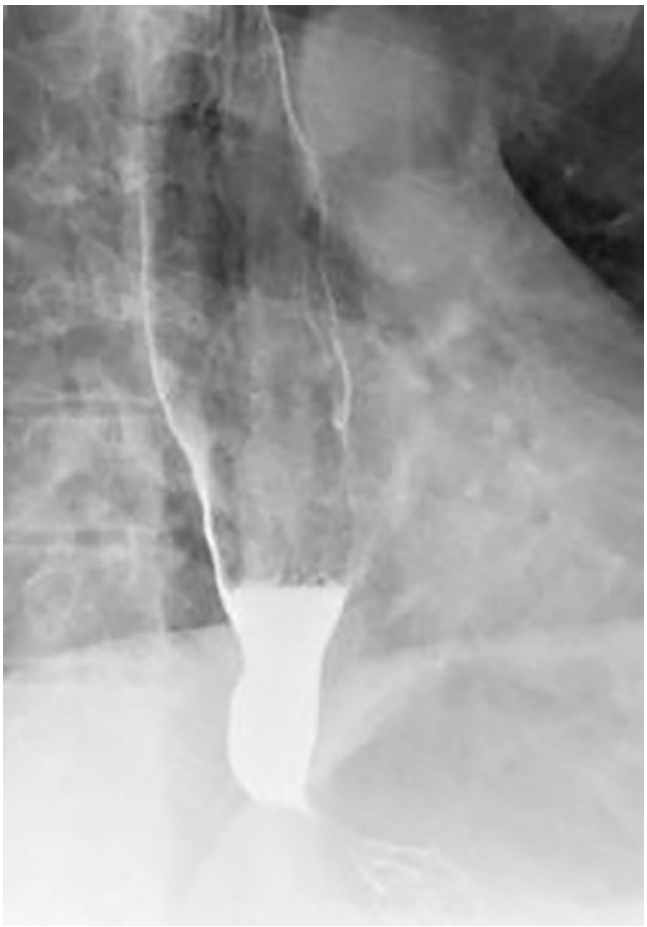

Fig. 35.1 Esophagram in a patient with achalasia demonstrating static column of barium and narrowing at the LES

achalasia, it has been demonstrated that patients with Type I and II achalasia have better outcomes than patients who undergo Heller for Type III achalasia [10].

Esophagogastric Junction Outflow Obstruction (EGJOO)

Increased use of HRM has demonstrated the vast range of esophageal motility disorder and LES dysfunction. Among them is esophagogastric junction outflow obstruction (EGJOO). Functional EGJOO is characterized by a poorly relaxing LES associated with a variable degree of preserved peristalsis that falls outside of classic achalasia criteria. Patients with functional outflow obstruction have no identifiable mechanical cause (malignancy, stricture, inflammation) but it is considered by some to be an early or incompletely expressed form of achalasia [11].

EGJOO is not a diagnosis of exclusion, as concurrent motility disorder has been reported in >60% of patients [12]. Symptomatic EGJOO may be treated similarly to achalasia with therapeutic dilation or myotomy. In the asymptomatic individual, follow-up with repeat HRM and timed barium swallow should be considered if symptoms develop or to evaluate for progression.

Epiphrenic Diverticulum

Epiphrenic pseudodiverticula are formed in the setting of pressurization of the distal esophagus against a closed LES

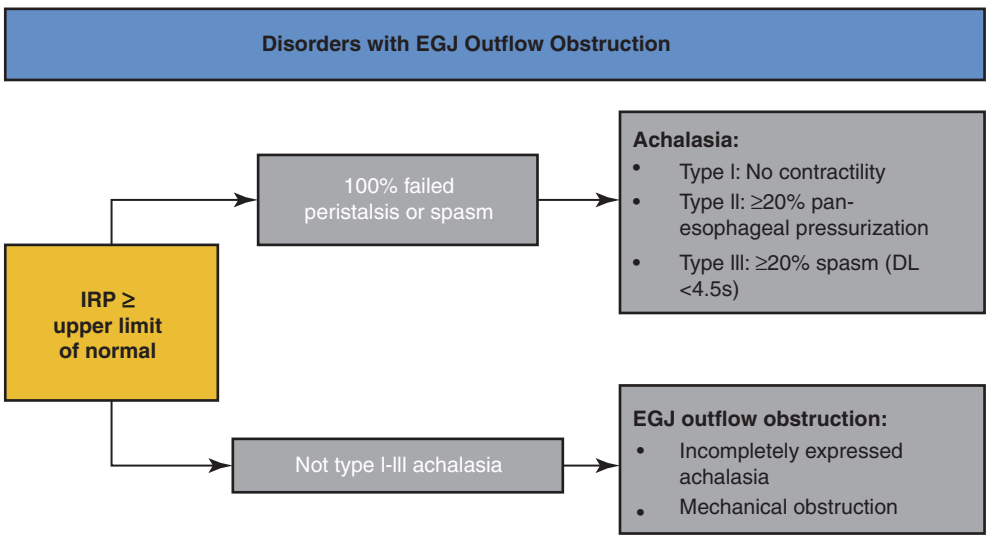

Fig. 35.2 Classification of disorders of esophagogastric outflow obstruction per Chicago Classification v3.0

in the setting of a weakened muscularis propria, resulting in lateral herniation of the esophageal mucosa and submucosa [13]. These are most commonly asymptomatic, but patients may present with dysphagia, regurgitation of undigested food, globus sensation, retrosternal chest pain, etc. Primary epiphrenic diverticuli are almost always acquired in the presence of underlying motility disorder with esophageal outflow obstruction or LES dysfunction. For this reason, myotomy is recommended during diverticulectomy, extending from at least the top of the neck of the diverticulum through the LES and onto the gastric cardia. Workup should include barium swallow, endoscopy, and manometry [14].

Preoperative Evaluation

Often, patients referred with dysphagia will have undergone initial barium esophagram or endoscopic procedure prior to presentation. Contrasted esophageal studies may demonstrate the classic "bird-beak" appearance of distal esophageal narrowing. The test of choice to confirm a diagnosis of achalasia is HRM, which demonstrates both the aperistaltic esophageal body component, as well as failure of the LES to relax [10].

For patients who have not yet undergone esophagram, or for whom further imaging is warranted, a timed barium swallow can provide more specific information. Timed barium swallow is an effective tool for objective evaluation of the severity of achalasia and a baseline to compare to postoperative outcome. The TBS study involves baseline radiograph followed by ingestion of 200 mL of barium with subsequent films taken at 1, 2, and 5 min following ingestion. The height and width of the barium column can then be recorded [9].

All patients with diagnosis of achalasia should additionally undergo upper endoscopy prior to surgical intervention. Endoscopic evaluation will rule out malignancy of the gastroesophageal junction as a cause of delayed emptying and allows for therapeutic dilation prior to surgery [9].

Specific Considerations

Difficulties following prior instrumentation: A careful approach should be taken in operating on patients who have had prior botulinum toxin injection or prior myotomy. Intramuscular Botox has been shown to result in submucosal fibrosis, which makes the planes more difficult to visualize and dissect in subsequent operations [15]. For this reason, Botox has been recommended only for poor surgical candidates or as a transient bridge to surgery if definitive treatment is not promptly available [10].

Patient Preparation

Given the nature of the disease, it is not uncommon to have retained ingested contents within the esophagus. For this reason, we recommend patients stay on a liquid diet for a minimum of 24 h prior to surgery to promote esophageal emptying prior to procedure.

Laparoscopic Heller Myotomy with Partial Fundoplication

Prior to induction, care should be taken in patients with achalasia or EGJOO to prevent aspiration. Use of a wedge or elevated head of bed may be considered, and rapid sequence intubation with cricoid pressure is often recommended. The patient is placed supine with arms out and a footboard is secured to the base of the bed. The vast majority of the procedure is performed with the patient in steep reverse Trendelenburg position, so patients should be fully secured to the operating room table. The authors' preferred approach has the operating surgeon standing to the patient's right, with the assistant on the patient's left side.

Standard laparoscopy equipment is employed with atraumatic graspers for tissue handling, ultrasonic shears for dissection, monopolar cord with a hook device, and laparoscopic Kittners. Five laparoscopic ports are used between the level of the umbilicus and costal margins, typically three 5 mm ports and two 11–12 mm ports, one for use of a 10 mm laparoscope and the other for passage of suture and surgical sponges. The authors prefer use of a flexible liver retractor placed through a lateral right subcostal port. All port sites are noted in Fig. 35.3. Varying sizes of bougie should be available for placement by anesthesia, though the authors standardly employ a 48 Fr. An anesthesiologist experienced with the procedure and bougie passage is recommended, as there are risks of perforation with passage. When in doubt, the operating surgeon or colleague may elect to place the bougie. A gastroscope is used intraoperatively to evaluate the anatomy before and after myotomy as well as to perform an endoscopic leak test.

Technical Procedure

Following access and port placement, the patient is placed in steep reverse Trendelenburg and the liver retractor is placed to facilitate visualization of hiatal structures. The three main components of laparoscopic Heller myotomy are hiatal dissection, esophagogastric myotomy, and fundoplication.

In patients without significant hernia, hiatal dissection can be kept to a minimum to preserve posterior esophageal attachments, which may play a role in the prevention of post-

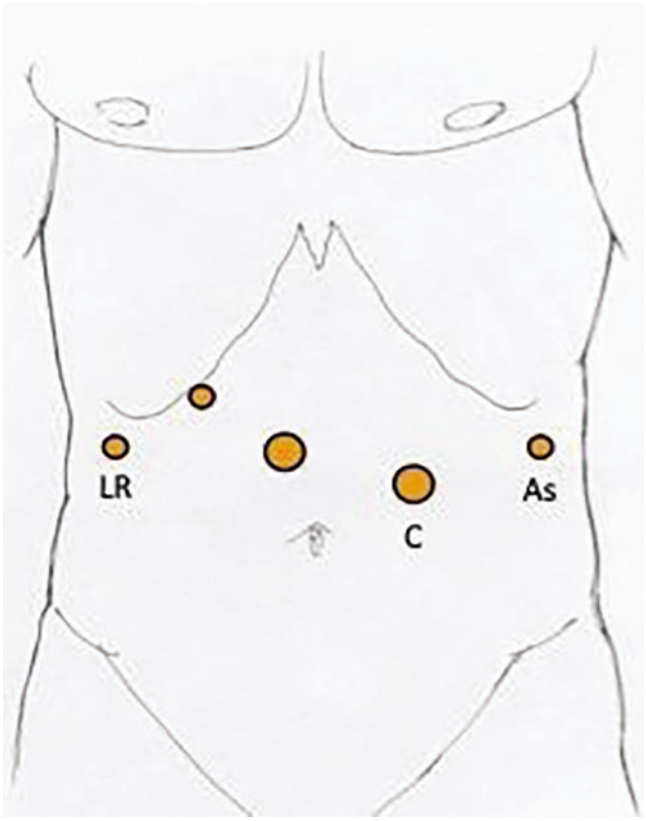

Fig. 35.3 Laparoscopic port placement, *C* camera, *LR* liver retractor, *AS* assistant

operative reflux development. For patients who have a notable hiatal hernia, we recommend complete 360° hiatal dissection and cruroplasty, followed by Toupet partial posterior fundoplication once the myotomy is complete. Hiatal exposure begins with opening of the phrenoesophageal ligament from 9 o'clock to approximately 2–3 o'clock. In the absence of a hiatal hernia, further hiatal dissection is avoided to preserve native posterior attachments. The anterior fat pad is mobilized to better visualize the gastroesophageal junction (GEJ), and the anterior vagus nerve is identified and isolated. The GEJ is identified using the Angle of His as an external landmark and may be confirmed on interoperative endoscopy.

Myotomy

A 48 Fr bougie is passed transorally. Electrosurgical coagulation is used to gently score the path of the planned myotomy anteriorly across the GEJ, taking care to retract the anterior vagus nerve to prevent injury. Two laparoscopic Kittners are used to tease apart longitudinal fibers and splay these laterally, starting just proximal to the GEJ. Circular fibers can be disrupted with a gentle rotational and sweeping motion of the tip of the device (Figs. 35.4 and 35.5). We have found this to

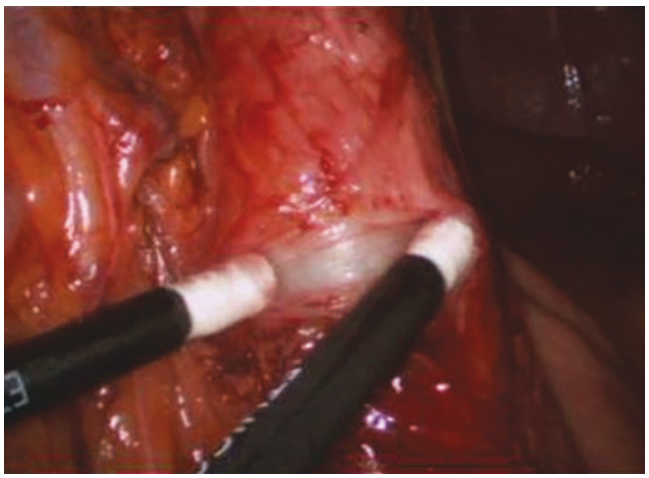

Fig. 35.4 Starting the myotomy using blunt Kittner dissection over a bougie

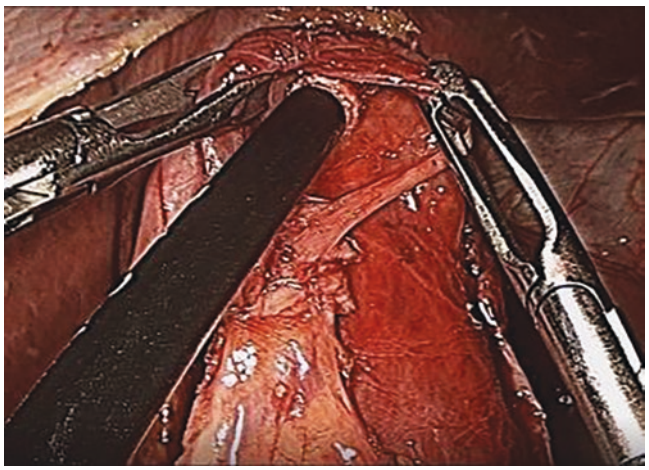

Fig. 35.5 Continuation of Kittner dissection above the vagus to elevate the esophageal muscle off the underlying mucosa

be an effective way to minimize the use of an energy device for manipulation of the tissue. Tenacious fibers and thick proximal esophageal mucosa can be carefully disrupted using hook monopolar device or ultrasonic shears with the dissecting blade placed away from the submucosa. The myotomy is continued for at least 2 cm onto the gastric wall and typically 5–6 cm onto the esophagus. The natural course of the anterior vagus is from patient's left to right as it courses from the thoracic cavity into the abdominal cavity. For this reason, it is often necessary to isolate the vagus and retract it laterally as one progresses proximally on the esophagus to prevent from spiraling the anterior myotomy.

There are several caveats to note while performing myotomy. Due to high risk of thermal injury, we recommend using gentle pressure with an intra-abdominal surgical sponge to initially control bleeding encountered during creation of the myotomy. Most bleeding will resolve with com-

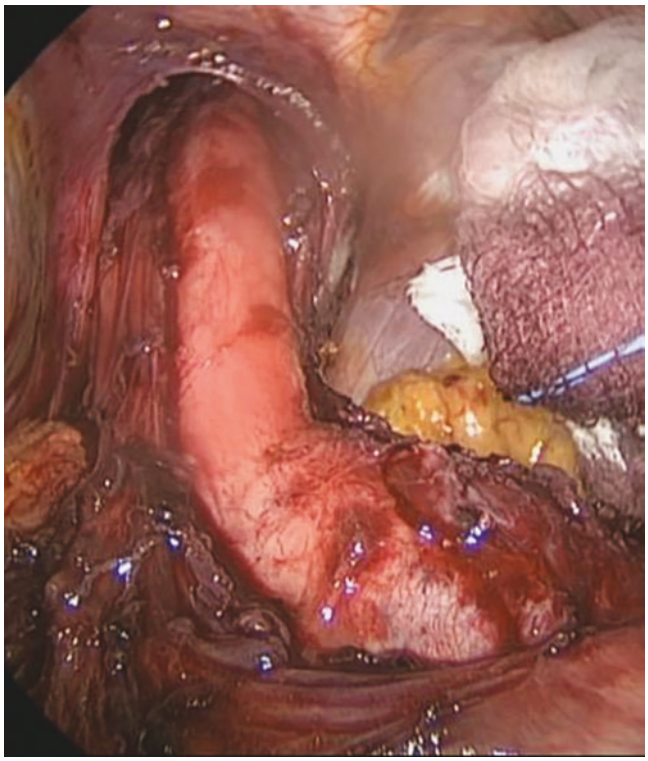

Fig. 35.6 Completed myotomy with 6 cm of esophageal length and 3 cm of gastric extension

plete transection of the muscle fibers. The most common location of incomplete myotomy is on the gastric side. This is also the region where perforation is most likely to occur in achalasia, as the gastric musculature is often less robust than that of the LES and distal esophagus.

Continuing myotomy above the level of the hiatus may result in subsequent development of a distal esophageal diverticulum. Due to the relative negative intrathoracic pressure, these diverticula may enlarge over time, giving a blown-out appearance to the distal esophagus and leading to pooling of esophageal contents. For this reason, care must be taken to avoid creation of unnecessarily long myotomy proximal to the hiatus. Following completion of the myotomy, the bougie is removed and an endoscopic leak test is performed (Fig. 35.6).

Partial Fundoplication

Fundoplication type is chosen based on presence of hiatal hernia and severity of dysmotility seen on preoperative manometry. In a prior multicenter randomized-controlled trial comparing Dor to Toupet partial fundoplication in patients with hiatal hernia of less than 5 cm, patients who underwent Dor fundoplication were more likely to have an abnormal postoperative 24-h pH test, but this difference was not found to be statistically significant [16]. In patients without hiatal hernia, our standard fundoplication of choice is a partial anterior fundoplication as described by Dor.

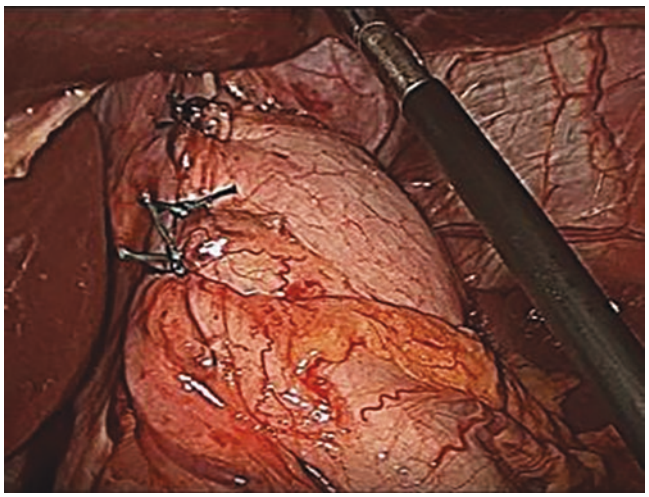

Fig. 35.7 Completed Dor fundoplication

In Dor's initial description, the short gastric vessels were preserved, however, to avoid tension on the wrap and myotomy, the uppermost vessels may need to be divided. The Angle of His is reconstructed with two to three 2–0 permanent sutures from the anterior fundus to the lateral myotomized edge, starting on the gastric side. The apex of the greater curvature is then sutured to the diaphragm at 1 o'clock. The remaining anterior fundus is rotated over the myotomy, and it is secured to the hiatus at 11 o'clock. The greater curvature of the fundus is then secured to the medial myotomized edge with two to three permanent sutures (Fig. 35.7). In the presence of a hiatal hernia or if a more robust fundoplication is desired, a posterior 270° partial fundoplication may be performed.

Robot-Assisted Heller Myotomy

Benefit Compared to Laparoscopic Approach

The primary advantages of the robotic system include increased degrees of movement with the use of articulating instruments, self-assistance (autonomy), and enhanced visualization. The robot also provides some additional degree of tremor reduction, which can be an asset when working with delicate fibers on the mucosal wall. There have also been described some advantages in terms of mediastinal reach with the robot, which can be beneficial if a longer esophageal myotomy is needed. Previous studies comparing the difference between robot-assisted and laparoscopic Heller myotomy demonstrate no differences in overall morbidity, and statistically no differences in operative time. Most robotic

series demonstrate longer initial operative times, which is suspected to be related to the learning curve associated with adoption of the technology [17]. One multicenter study and a subsequent meta-analysis reported decreased rate of intraoperative mucosal injuries with robotic approach [18, 19].

Technical Procedure

The patient is placed supine with both arms tucked and pressure points padded. A footboard is secured at the end of the table. Five ports are used between the level of the umbilicus and costal margins. An optical viewing robotic trocar is placed 10 cm below the xiphoid just off midline. Two additional robotic trocars are placed as noted in Fig. 35.8. Care is taken to place robotic trocars at least 8 cm apart to minimize collisions between arms. A 12 mm assistant port is placed on the left as indicated. This can be used to pass sutures, sponges, and mesh if required during hernia repair.

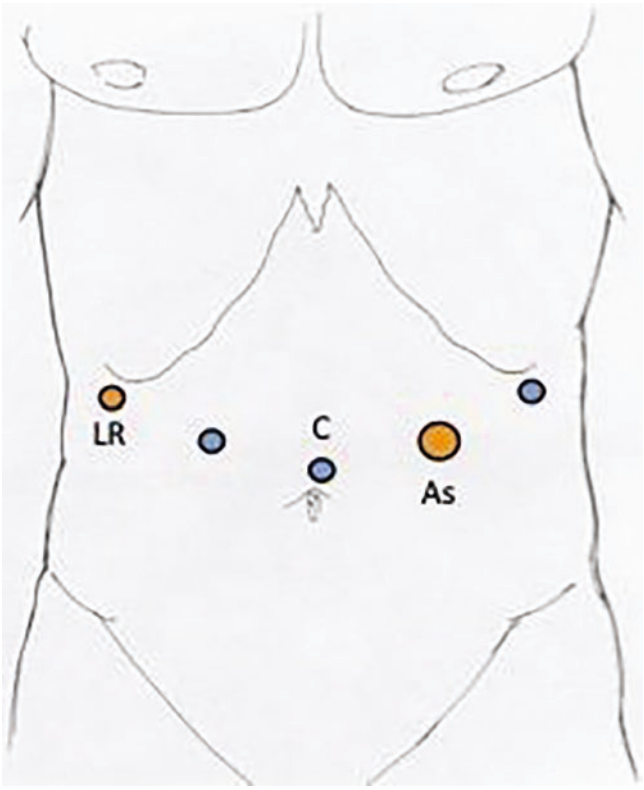

Fig. 35.8 Robotic port placement, *C* camera, *LR* liver retractor, *AS* assistant

The patient is placed in steep reverse Trendelenburg and then the robot is docked. For the DaVinci Xi device, this is typically from the patient's right shoulder. Initial instruments are vessel sealer in the right hand and either bipolar forceps or Cadiere forceps in the left hand. For surgeons who prefer the ultrasonic shears, there is a long Harmonic instrument available for the robot. Currently, this is not an articulating instrument and therefore does not provide the same freedoms as other wristed instruments on the robot platform. Dissection begins with the short gastric vessels starting at the lower pole of the spleen, taking them with the vessel sealer device, and then proceeding with anterior 180° dissection of the hiatus. In the presence of a hiatal hernia, a complete 360° dissection is performed. The anterior fat pad is mobilized and the anterior vagus is identified and isolated, after which a 48 Fr bougie is passed.

The vessel sealer is exchanged for a monopolar hook with effect set to 25. This is the portion of the procedure that is most benefitted by use of the robot, as fine movement can be made with the wristed hook instrument. Electrosurgical coagulation is used to mark the path of cardiomyotomy anteriorly, taking care to avoid the vagus. Myotomy is made starting on the esophageal side of the GEJ and is carried 6 cm from the GEJ onto the esophagus and 2–3 cm distally onto the gastric side. If the surgeon desires to avoid the use of electrosurgical coagulation near the mucosa, then the Cadiere forceps and fenestrated bipolar forceps can be used in tandem to tease apart muscle fibers. With the myotomy complete, the bougie is removed and an endoscopic leak test is performed.

The monopolar hook is exchanged for a mega suture cut needle driver, and a 2–0 permanent suture is inserted for use in Dor fundoplication. The assistant grasps the apex of the fundus and retracts it towards the hiatus to relieve tension while sutures are placed, as described in the preceding technical segment. For patients with hiatal hernia, similar consideration is made in reconstruction with posterior cruroplasty and use of a Toupet posterior partial fundoplication. In the setting of myotomy, the authors' preferred technique for Toupet is a posterior 270° greater curve to greater curve configuration. Permanent sutures between the apices of the fundoplication are secured from fundus to crura at 11 o'clock and 1 o'clock. Each myotomized edge is secured to the gastric wall with three interrupted 2–0 permanent sutures (Fig. 35.9).

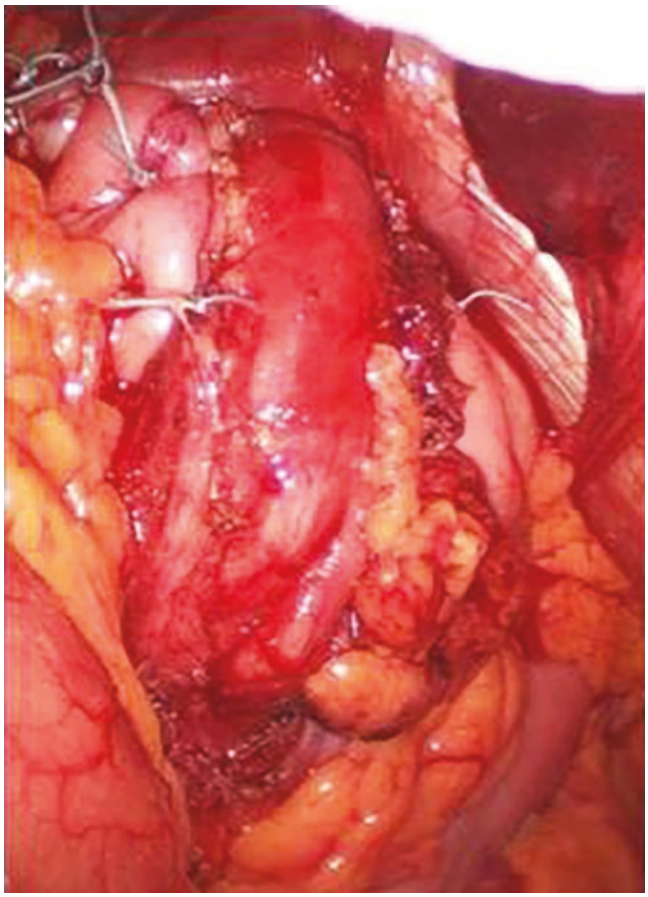

Fig. 35.9 Completed Toupet fundoplication

Fig. 35.10 Photo of the Endoluminal Functional Lumen Imaging Probe (EndoFLIP) catheter device, deflated

Intraoperative Functional Assessment

The Endolumenal Functional Lumen Imaging Probe (EndoFLIP™, Medtronic) is a balloon catheter device that uses impedance planimetry technology to provide a real-time assessment of LES distensibility, lumenal diameter, and esophageal body function [20]. Unlike HRM, which relies on an awake ambulatory patient, the functional lumen imaging probe is designed for use under sedation, allowing for a range of applications in the operating room and endoscopy suite (Fig. 35.10).

The probe uses the measurement of lumenal cross-sectional area and intra-balloon pressure to calculate a distensibility index. Larger distensibility values at the LES suggest a sphincter with less resistance or more "open" than a stiffer or "tighter" LES with a lower distensibility [20]. Normal values for LES distensibility index have been reported as greater than 2.8 mm^2/mmHg [21]. In patients undergoing myotomy for achalasia, the baseline distensibility is often less than 1.5 mm^2/mmHg. Prior studies have shown that the distensibility index more than doubles following myotomy (near 5 mm^2/mmHg) [22].

For best interpretation of functional intralumenal probe data, it is recommended that a standardized protocol be used to guide timing of recording measurements. Balloon volumes as well as table position can impact reading. Good protocol should involve separate measurements at baseline after induction, after hiatal dissection, after myotomy, and after fundoplication [22]. The probe should be confirmed to be centered across the LES such that the waist of the hourglass image on the monitor is in the center of the measurable balloon range [23] (Fig. 35.11).

Evaluation of myotomy length using the device has demonstrated no significant difference in distensibility with extension of myotomy onto the cardia to be 2 cm with both laparoscopic and endoscopic myotomy [24]. This finding is in contrast to prior prospective studies that recommended 3 cm extension onto the gastric cardia to improve outcomes [25]. Long-term results of tailoring fundoplication based on intraoperative distensibility data require further study, but it is a promising tool in providing real-time intraoperative metrics.

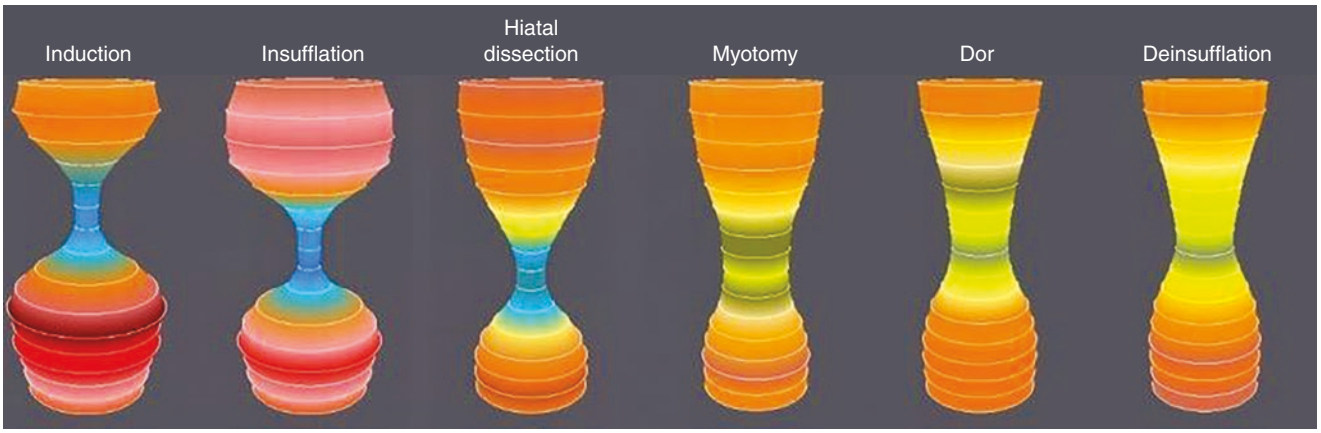

Fig. 35.11 Example of real-time images using EndoFLIP device at different stages of the operation. Note the change in the "waist" as the lumen opens with myotomy, then narrows slightly with fundoplication

Postoperative Care

It is the authors' practice to obtain an esophagram on postoperative day 1 prior to starting patients on a liquid diet. Patients continue on liquid diet with liquid or crushed medications for 2 weeks before slow diet advancement through pureed and soft foods into regular textures.

Endoscopy is performed routinely at 3 months postoperatively following myotomy to assess for the presence of esophagitis. Repeat endoscopy, TBS, manometry, and pH testing are performed 6 months to 1 year after surgery. Biopsies are taken on surveillance endoscopy to evaluate for microscopic changes at the GEJ, as well as screen for development of squamous cell carcinoma. Patients who present with complaint of heartburn, have a DeMeester Score >14.7 on pH testing, or have presence of esophagitis are started on oral antacid medication and consideration is made for revisional fundoplication. Patients with achalasia are known to be at increased risk of development of squamous esophageal carcinoma, and therefore, routine screening is recommended with upper endoscopy at least every 5 years following myotomy [26].

Complications

The most common complication during esophageal myotomy is mucosal perforation. Perforation is infrequent and is typically detected at the time of occurrence intraoperatively. Excessive use of electrosurgical coagulation may lead to delayed full-thickness injury thus energy devices should be used judiciously. If a full-thickness injury is identified intraoperatively, it can be closed with a fine interrupted absorbable suture and subsequently covered by the fundoplication. Delayed identification of a perforation can sometimes be managed with endolumenal treatments such as stenting, but in severe leaks, diversion may need to be considered.

The rate of esophageal perforation during primary laparoscopic Heller myotomy has been reported to range from 2.9 to 16% across several larger series, and for smaller series of robotic Heller myotomy, the rate of perforation has been reported from 0 to 2.7% [18, 27]. However, patients who had mucosal perforation repaired intraoperatively had similar outcomes to patients who underwent uncomplicated laparoscopic Heller myotomies [28].

Outcomes

Laparoscopic Heller myotomy has been demonstrated to have excellent early outcomes in dysphagia relief, with 80–96% reported as having no dysphagia within the first year following myotomy [29, 30]. Due to the progressive nature of achalasia, patients may develop recurrent or progressive dysphagia after 1 year, in spite of prior myotomy. However, up to 71% of patients endorse relief from dysphagia as late as 20 years out from myotomy [26]. For patients with recurrent dysphagia, pneumatic dilation has been shown to provide lasting relief in up to 75% of patients [31].

Post-myotomy gastroesophageal reflux has been reported on meta-analysis to occur in 1–44% of patients who had concurrent anti-reflux fundoplication and 60% of patients with symptomatic or objective reflux if no fundoplication is performed [30].

Conclusions

Minimally invasive Heller myotomy, performed laparoscopically or robotically, is the gold standard for surgical management of achalasia and can be applied to other disorders of esophagogastric outflow obstruction. Both procedures are safe and effective for treating dysphagia in the short and long term. Development of post-myotomy reflux disease can be mitigated by performing a partial fundoplication at the time of myotomy.

Questions

1. Which of the following patient is least likely to have dysphagia relief following minimally invasive Heller myotomy?
   A. HRM showing IRP >25 and panesophageal pressurization
   B. HRM showing IRP >55 and 60% preserved peristalsis
   C. UGI demonstrating a small hiatal hernia with lateral outpouching in the distal third of the esophagus
   D. UGI demonstrating a large diverticulum in the proximal third of the esophagus

Answer: D. Elevated IRP suggests failure of the LES to relax. This can be seen in achalasia or EGJOO, which may be an early or incompletely expressed variant of achalasia and may also benefit from Heller myotomy. Epiphrenic diverticuli are present in the distal third of the esophagus, just proximal to the LES. A diverticulum in the proximal third of the esophagus is more likely to be associated with a cricopharyngeal bar, in the case of Zenker's diverticulum or a traction diverticulum, and is not treated with distal esophageal myotomy.

2. Which of the following surgical techniques should be employed to minimize post-myotomy reflux disease in a patient with achalasia?
   A. Nissen fundoplication following myotomy
   B. Tailoring esophageal myotomy to 3 cm instead of 6 cm
   C. Performing a posterior 270° fundoplication
   D. Perform a truncal vagotomy at the time of myotomy

Answer: C. Either a Toupet or a Dor partial fundoplication may be used during minimally invasive Heller myotomy to prevent post-myotomy gastroesophageal reflux, though some patients may still develop this syndrome. A complete fundoplication (Nissen) is discouraged in patients with poor motility due to the relative outflow obstruction that is created. Tailoring the myotomy significantly or truncal vagotomy have not been shown to reduce postoperative GERD.

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Per-Oral Endoscopic Myotomy (POEM)

36

Kenneth J. Chang and Lee L. Swanström

Introduction, Background of POEM Procedure

The concept of POEM was first described in an animal study by Pasricha in 2007 [1] and the first human series was published by Inoue in 2010 [2]. Over the ensuing decade, the POEM procedure has proliferated and is available in most achalasia centers worldwide. Based on its safety and efficacy profile, per-oral endoscopic myotomy (POEM) can be considered to be a standard of care treatment for achalasia, at least in higher-volume esophageal centers.

Current Indications and Outcomes for POEM

Achalasia (Types 1, 2, 3) and Spastic Esophageal Disorders

The indications for POEM include all subtypes of achalasia. Other spastic esophageal disorders, such as Jackhammer esophagus, diffuse esophageal spasm (DES), and clinically significant esophagogastric junction outlet obstruction (EGJOO), are also emerging indications for POEM [3, 4]. In patients with achalasia, the treatment options include medical therapy, injection of Botox into the lower esophageal sphincter (LES), pneumatic dilation and surgical myotomy.

Clinical Outcomes—Relief of Dysphagia

The key clinical outcome of POEM is the rate of successful treatment of dysphagia. In general, this has been measured by the reduction of the Eckhardt score to ≤3. Over the past decade, since POEM was first described, there have been a number of single center [3, 5–12] and multicenter [13–15] studies reporting short, intermediate, and long-term outcomes of clinical success in the range of 80–90%.

Outcomes by Achalasia Subtypes

Type 1 achalasia patients have no peristalsis or esophageal pressurization. They tend to over time develop a more dilated or sigmoid esophagus as compared to the other types. Therefore the response to myotomy may be slightly less among Type 1 patients, especially in more advanced stages. Type 2 achalasia patients typically have the best outcomes with either LHM or POEM for relief of dysphagia. One caveat is that a subset of patients with Type 2 achalasia present with symptoms of esophageal spasm and these spastic regions may be identified on barium esophagram, endoscopy, manometry, endoFLIP, or even EUS. If this Type 2 variant is not properly identified, the patient may have relief of dysphagia but still have residual spasm symptoms. Therefore, if a Type 2 patient (confirmed by manometry) reports significant spasm-type symptoms in addition to dysphagia, we will assess carefully with all the above modalities to assess whether a more extended myotomy (proximal) should be considered. Type 3 achalasia patients typically have significant spastic symptoms and usually require a more extended myotomy. While Type 3 patients have been shown to do better with POEM than LHM [7], the clinical outcomes of POEM for all 3 achalasia subtypes appear to be similarly high [14, 16], especially at high-volume centers.

Outcomes of Other Spastic Esophageal Disorders (Jackhammer, DES, EGJOO)

While the clinical success of POEM for all types of achalasia is in the high 90% range, the clinical outcomes for other spas-

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tic esophageal motility disorders (SEMD), including Jackhammer esophagus (JHE) and distal esophageal spasm (DES), are slightly lower and less predictable [3, 4, 17, 18]. A retrospective multicenter study was conducted among five French university centers in which 90 patients were analyzed [17]: 30 patients with SEMD (13 jackhammer esophagus, 6 spastic esophageal disorders, 4 nutcracker esophagus, and 7 esophagogastric junction obstruction), 30 patients with type 1–2 achalasia, and 30 patients with type 3 achalasia. The 3-month response rates were 80% (24/30), 90% (27/30), and 100% (30/30) in SEMD, type I–II achalasia, and type III achalasia, respectively ($p < 0.01$). Eckardt scores improved from preoperative baseline in all groups (median scores 2.0 after POEM vs. 6.5 before POEM, 1.3 vs. 7.2, and 0.5 vs. 6.1 in SEMD, type I/II and Type III, respectively). The 6-month response rates were 63.2% (12/19), 95.5% (21/22), and 87.0% (20/23) in SEMD, type I–II achalasia, and type III achalasia, respectively ($p = 0.03$). A recent meta-analysis and systematic review of POEM for spastic esophageal disorders analyzed 9 studies with 210 patients and found the pooled rate of clinical success for POEM was 89.6% (95% CI 83.5–93.1, 95% PI 83.4–93.7, $I2 = 0\%$) and pointed out that the length of the myotomy did not seem to predict outcomes [4].

Long-Term Outcomes

There have been a handful of published studies with long-term outcomes data among POEM patients [7, 9, 14, 16] (see Table 36.1). The Shanghai Fudan University group reported on 564 patients followed over 4 years and showed that clinical success of POEM was achieved in 94% of achalasia patients at year 0–1 and 87% at year 4–5 [9]. The NYU-Winthrop group recently published their 10-year experience with POEM including 610 patients and showed clinical success of POEM of 98% at year 1 and 91% (for 29 patients) at year 7 [16]. This is somewhat better than our 10-year results for 52 patients that were recently presented at the European Society of Endoscopic Surgery, where 88% of patients at mean follow-up of 118 months had an Eckhardt score of <3 and 18% reported a secondary intervention (endoscopic dilation) in the interval. This confirms that within expert centers, the clinical success of POEM is in the 90% range and the durability reaches out to 10 years.

Table 36.1 Long-term outcomes POEM studies

Author/senior	Year	#Patients	Median follow-up (mo)	Achalasia type	%Prior Rx	Clinical success	AE rate	GERD
Li [9] Zhou	2018	564	49	–	–	Years 0–1: 94% 1–2: 92% 2–3: 91% 3–4: 89% 4–5: 87%	–	37.1%
Podboy [7] Huang	2020	55	47	1 (13) 2 (23) 3 (15) Other (2)	71%	72.7% Subtypes: 1 (69%) 2 (87%) 3 (53%)	–	Sxs: 44.9%
Brewer [14] Khashab	2020	146	55	1 (41) 2 (70) 3 (9) Non-Sp (26)	28%	Subtypes: 1: 95% 2: 93% 3: 95% 4: 95%	5.5%	Sxs: 32.1% Reflux Esoph: 16.8% + pH: 47.5%
Modayil [16] Stavropoulos	2021	610	60	1 (160) 2 (307) 3 (93) Unknown (25) Non-achalasia 23	47.9%	90% Years: 1: 98% 2: 96% 3: 96% 4: 94% 5: 92% 6: 91% 7: 91%	3.4%	Sxs: 20.5% +pH: 232/406 (57%) Reflux Esoph: 218/438 (50%) Mostly mild

Post-POEM GERD

While the clinical efficacy of relieving dysphagia with POEM is high, the other side of the double-edged sword is the rate of post-POEM GERD. Post-POEM GERD is assessed by GERD symptoms, objective pH testing for esophageal acid exposure time (AET), and the presence of esophagitis on endoscopy. In general, 30–50% of patients may have post-POEM GERD symptoms, 45–60% have abnormal pH studies, and 20–50% have reflux esophagitis. In the largest single-center experience (610 patients) with very tight follow-up, only 20% of patients had GERD symptoms more than once per week, 58% had abnormal AET, and 50% had reflux esophagitis, mostly mild (34% LA-A, 12% LA-B, 3% LA-C) [16]. The other way to consider post-POEM GERD is to follow the percentage of patients who become refractory to PPI therapy and subsequently underwent trans-oral incisionless fundoplication (TIF) or other anti-reflux procedures. In our own series of 145 consecutive POEM patients, we were able to analyze 132 cases [19]. There were 115 patients (87%) with achalasia (43 type I, 61 type II, and 11 type III), 9 patients with SEMD including jackhammer esophagus and diffuse esophageal spasm, and 8 achalasia of unknown type. Twelve patients (10%) had severe GERD that was PPI refractory. They were offered an anti-GERD intervention and subsequently all had a TIF (66.7% female, mean age 52.5, mean BMI 25.34 + 6.18). The mean distensibility index on EndoFLIP at 60 cc at the completion of POEM was 3.87 + 1.52. Eight of the 12 patients had ambulatory pH monitoring after their POEM and the mean DeMeester score was 53.85 (SD?). The majority had type I achalasia ($n = 7$) and one patient each had type II, type III, achalasia subtype unknown, jackhammer esophagus, and diffuse esophageal spasm. The risk of significant post-POEM reflux requiring TIF was highest for spastic disorders (22.2%), followed by achalasia type I (16%), type III (10%), and achalasia type II (1.6%).

POEM vs LHM: Clinical Outcomes

While both POEM and LHM achieve similar goals (myotomy of distal esophagus and proximal stomach) with fairly similar outcomes, there are differences in the level of invasiveness and post-myotomy GERD. LHM without fundoplication has a post-procedure GERD rate (by pH analysis) of approximately 41–48%, as compared to 9–15% when a fundoplication is added [20, 21]. Therefore, the vast majority of LHM today are performed together with a concomitant partial fundoplication, and in this chapter, the term LHM implies LHM plus fundoplication unless specifically noted.

A recent systematic review published in 2018 performed an analysis on 53 studies which included 5834 LHM patients, and 21 studies which included 1958 POEM patients [22]. The predicted probabilities for improvement in dysphagia at 12 months were 93.5% for POEM and 91.0% for LHM ($P = 0.01$), and at 24 months were 92.7% for POEM and 90.0% for LHM ($P = 0.01$). Patients undergoing POEM were more likely to develop GERD symptoms (OR 1.69, 95% CI 1.33–2.14, $P < 0.0001$), GERD evidenced by erosive esophagitis (OR 9.31, 95% CI 4.71–18.85, $P < 0.0001$), and GERD evidenced by pH monitoring (OR 4.30, 95% CI 2.96–6.27, $P < 0.0001$). They concluded that short-term results show that POEM is more effective than LHM in relieving dysphagia, but it is associated with a higher incidence of pathologic reflux.

Subsequently, the long-awaited prospective multicenter, randomized trial of LHM (with Dor's fundoplication) vs POEM was published in 2019 and included 221 patients with symptomatic achalasia [23]. The primary endpoint was clinical success, defined as an Eckardt symptom score of 3 or less (range 0–12, with higher scores indicating more severe symptoms of achalasia) without the use of additional treatments, at the 2-year follow-up; a noninferiority margin of −12.5% points was used in the primary analysis. Secondary endpoints included adverse events, esophageal function, Gastrointestinal Quality of Life Index score (range 0–144, with higher scores indicating better function), and gastroesophageal reflux. The 221 patients were randomly assigned to undergo either POEM (112 patients) or LHM plus Dor's fundoplication (109 patients). Clinical success at the 2-year follow-up was observed in 83.0% of patients in the POEM group and 81.7% of patients in the LHM group (difference 1.4% points; 95% confidence interval [CI] −8.7 to 11.4; $P = 0.007$ for noninferiority). Serious adverse events occurred in 2.7% of patients in the POEM group and 7.3% of patients in the LHM group. Improvement in esophageal function from baseline to 24 months, as assessed by measurement of the integrated relaxation pressure of the lower esophageal sphincter, did not differ significantly between the treatment groups (difference −0.75 mmHg; 95% CI −2.26 to 0.76), nor did improvement in the score on the Gastrointestinal Quality of Life Index (difference 0.14 points; 95% CI −4.01 to 4.28). At 3 months, 57% of patients in the POEM group and 20% of patients in the LHM group had reflux esophagitis, as assessed by endoscopy; at 24 months, the corresponding percentages were 44% and 29%. As summarized descriptively, high-grade esophagitis (Los Angeles Classification Grade C or D) was observed at 3 months in 6 of 100 patients (6%) in the POEM group and 3 of 96 patients (3%) in the LHM group and at 24 months in 4 of 87 patients (5%) in the POEM group and 5 of 78 patients (6%) in the LHM group.

Esophageal pH monitoring showed similar proportions of patients with abnormal reflux at both time points (at 3 months, 41 of 93 [44%] in the POEM group and 27 of 82 [33%] in the LHM group, and at 24 months, 21 of 70 [30%] in the POEM group and 17 of 56 [30%] in the LHM group). The authors concluded from this randomized trial that POEM was noninferior to LHM plus Dor's fundoplication in controlling symptoms of achalasia at 2 years. Although GERD was more common among patients who underwent POEM, the rates of severe esophagitis and abnormal esophageal pH were similar between the two groups at 2 years. As an aside, the hospital length of stay for POEM ranges from 1 to 3 days, which is quite similar to LHM and in the majority of cases, is one overnight stay [24–26].

Indications for LHM vs POEM

In the context of current medical evidence and our clinical experience, we propose clinical scenarios where a laparoscopic Heller myotomy with partial fundoplication (LHM) is preferable, where a POEM may be more suitable, and where either is equally beneficial (Table 36.2). In our opinion, the LHM is a better option for patients with the presence of a hiatal hernia or an open diaphragmatic hiatus (Hill Grade 3, 4). Although this occurs in a minority of cases, these patients are more likely to develop post-POEM gastroesophageal reflux disease (GERD) and which would necessitate a laparoscopic hernia repair as well as partial fundoplication if they were symptomatic. In our practice, if this profile is discovered during the pre-operative work-up, a laparoscopic approach is recommended to treat both the achalasia and the hernia in a single procedure. Another scenario where a laparoscopic approach may be preferable is in patients with advanced sigmoid esophagus, the so-called type S-2 esophagus, defined as an esophagus that is very dilated and severely tortuous with U-turns in a proximal direction and a double lumen as identified on some transverse CT slices. The POEM procedure in patients with advanced sigmoid esophagus is technically more difficult due to the potential of misdirecting (spiraling) the tunnel direction and sharp angled turns that can lead to inadvertent mucosal defects [27, 28]. A LHM with special attention to dissecting and straightening out the esophagus is considered by many as the first-line approach. Of course, patients that require a laparoscopic procedure for another indication (gallstones, gastroparesis, etc.) would be best served by a laparoscopic Heller and partial fundoplication at the same time. A very rare indication for a hybrid laparoscopic/POEM approach is for patients with a hiatal hernia (primary or secondary) and need for a long myotomy, e.g., type III achalasia of DES-related chest pain. A two-team approach can approach both "ends" of the problem during a single procedure.

The clinical scenarios where POEM may be advantageous include spastic esophageal disorders, including Type 3 achalasia, where the length of myotomy may need to be significantly longer (proximal extent) and well beyond the reach of a laparoscopic approach. In a retrospective cohort study, Podboy et al. reported that LHM and POEM were equivalent in clinical success, except among patients with type III achalasia, where POEM was superior to LHM in long-term success rate (53.3% vs 44.4%, $p < 0.05$) [7]. In addition, achalasia patients who have had prior myotomy (LHM or POEM) may be better candidates for revisional POEM [29–31]. This is based on the flexibility of POEM to create a myotomy anywhere around the circumference of the esophagus and LES. This is in contrast to a re-do LHM which is best done in an anterior approach, with its associated issues of adhesions and scar formation. For example, the typical strategy for performing POEM on a patient with a prior LHM is to perform a posterior myotomy. In addition, a patient with a prior fundoplication can have a POEM without the need to take down the wrap [32]. Finally, patients who have had prior resection of the gastric fundus (ex. prior gastric bypass or sleeve gastrectomy, or other upper abdominal surgeries that might create a "hostile abdomen") are better served with POEM.

Outside of these special populations, both LHM and POEM are largely felt to be equivalent as discussed earlier.

Table 36.2 LHM vs POEM clinical scenarios

Favor LHM with partial fundoplication	Favor POEM	Equivalent
Presence of hiatal hernia or hill 3 anatomy	Type 3 achalasia Spastic esophageal disorder (Jackhammer, DES)	Type 1 achalasia Type 2 achalasia
S-2 sigmoid esophagus	Prior myotomy	
	Prior fundoplication	
	Prior resection of gastric fundus (gastric bypass, sleeve gastrectomy)	

Failed Prior Interventions (Heller, Botox, Pneumatic Dilation, POEM)

The LHM has a high clinical success rate, but studies show a failure rate (persistent or recurrent dysphagia) of approximately 10–20%. POEM as a salvage procedure after failed LHM has been reported in initial case series [33, 34], as well as larger pooled analysis [35–39]. A recent meta-analysis compiling 9 studies involving 272 patients with achalasia has been published [38]. POEM was successfully performed in 270 (99.3%) patients after previous HM. Clinical success was achieved in 90% and the Eckardt score, lower esopha-

geal sphincter pressure, and IRP were significantly lowered. The pooled rates of postoperative symptomatic reflux, esophagitis, and abnormal pH monitoring were similar to naïve POEM: 36.9%, 33.0%, and 47.8%, respectively. The authors concluded that POEM is a safe and effective treatment for patients with achalasia with previous LHM. These case series and pooled data certainly advocate for POEM as perhaps the best primary salvage procedures for recurrent or persistent dysphagia. However, the POEM proceduralist must first step back and ask the question—what is the likely cause of the patient's dysphagia? A recent publication looking at the surgical approach to such patients developed a comprehensive checklist of possible etiologies of the patients' dysphagia and made a convincing argument for the personalized approach to intervention [40]. They included these six mechanisms with a tailored approach: (1) Incomplete myotomy—consider pneumatic dilation, Botox, POEM, or re-do Heller myotomy; (2) Periesophageal/hiatal scarring/cicatrix—consider dilation (savory, balloon, pneumatic), adhesiolysis with/without re-do Heller myotomy and reversal fundoplication; (3) Acid reflux induced stricture—consider dilation (savory or balloon) with acid-reducing medication, revision of fundoplication; (4) Obstructing fundoplication—consider dilation (savory or balloon), reversal of fundoplication with/without re-do Heller myotomy; (5) Functional dysphagia—consider reassurance, promotility medication.

And (6) End-stage achalasia—consider conservative management with/without dilation, or esophageal resection based on esophageal morphology. We would add one additional mechanism—(7) Formation of esophageal diverticulum with the presence of a hypertrophied muscular septum [41, 42]. These patients may benefit from a focused septal myotomy performed either in conjunction or separate from the standard POEM protocol (Fig. 36.1) [42].

While there may be variability among surgeons and proceduralists regarding the specific treatment of choice for each scenario, these seven mechanisms should all be considered in achalasia patients with dysphagia after prior LHM. If the etiology is likely to be #1 (incomplete myotomy) or #7 (proximal diverticulum with identifiable septum)—then POEM is a very reasonable, if not preferable, approach given its access endoscopic approach, the ability to tunnel along the posterior aspect of the esophagus/GE junction (avoiding

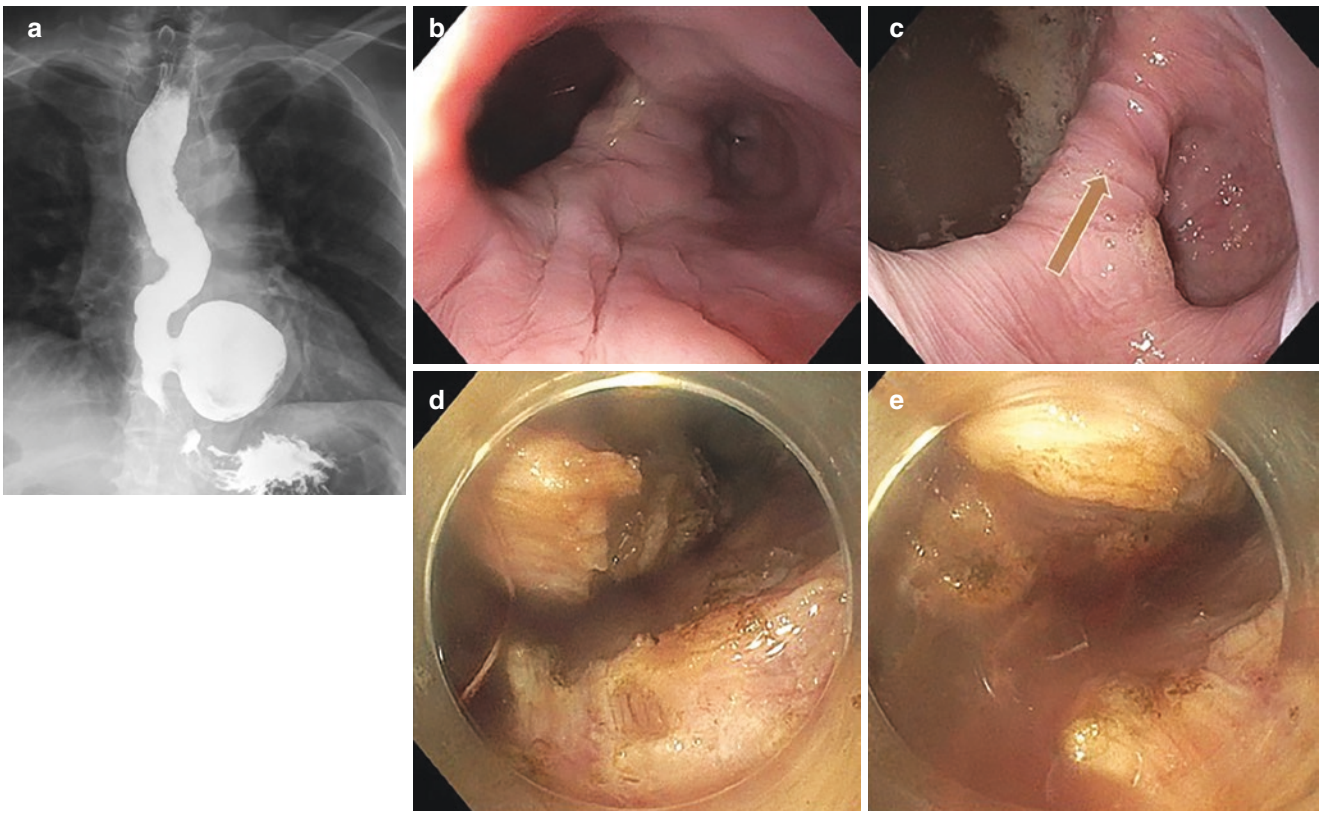

Fig. 36.1 Patient with Achalasia Unknown type with a epiphrenic diverticulum, s/p Heller Myotomy 2012 with partial symptom response. (**a**) Esophagram showing large epiphrenic diverticulum in addition to bird-beak narrowing of distal esophagus. (**b**) Diverticulum on left with distal esophageal lumen on right. (**c**) Residual fluid in diverticulum with muscular septum (arrow). (**d**) After standard myotomy, the muscular septum is exposed through the same tunnel with submucosal tunnel extension on esophageal and diverticular side of septum, followed by septal myotomy. (**e**) Myotomy of septum "meets" esophageal myotomy within the tunnel

the anterior scarred area), and extending the myotomy either more proximally in the esophagus, more distally along the proximal stomach, or isolated to the diverticular septum.

For achalasia patients with prior pneumatic dilation, POEM appears safe and effective, but technically more challenging due to prior scar resulting in a longer procedure time [43]. The same is true for prior endoscopic botulinum toxin injection into the lower esophageal sphincter. Studies looking at POEM performed without vs with prior endoscopic interventions show no difference in clinical outcomes or adverse events [37, 44]. Finally, we have come of age where some preliminary data is available to examine the strategy of re-do POEM after failed POEM [45, 46]. A recent international multicenter retrospective study at 16 tertiary centers followed a total of 3144 consecutive POEM patients and found clinical failure after the procedure in 99 patients (3.1%). Among these 99 patients (mean Eckardt score of 5.4), 32% were managed conservatively, 33% had repeat POEM, 30% had pneumatic dilation, and 7% underwent laparoscopic Heller myotomy (LHM). During a median follow-up of 10 months, clinical success was highest in patients who underwent repeat POEM (76%), followed by pneumatic dilation (60%), and LHM (29%). They concluded that repeat POEM and pneumatic dilation achieved acceptable clinical success with excellent safety profiles. In our experience, the early post-POEM failures are less than 5% and are most likely due to incomplete myotomy (either distally into the cardia; or in patients with esophageal spasm—proximally to the full extent of spastic muscle), presence of diverticula with septum, and end-stage achalasia.

Pre-procedure Evaluation

The routine pre-procedure evaluation of patients prior to POEM includes (1) Endoscopy (2) High-resolution esophageal manometry (HREM) (3) Timed Barium Esophagram (TBE) (Fig. 36.2). We both also routinely use an endoscopic functional lumen imaging probe (EndoFLIP) immediately pre and post POEM—both to obtain a confirmatory baseline distensibility index (DI) <2.0 pre-POEM and a repeat DI >3.0. In most cases, the 3 pre-POEM studies are in concordance (high 4 s IRP on HREM, retained column of contrast >5 cm at 5 min on TBE, EndoFLIP DI less than 1.5). However, if there is missing data or inconsistency, the EndoFLIP may be the final arbiter of whether or not POEM is performed. EndoFLIP is routinely performed at both our centers immediately pre and post POEM. Studies have shown that a thresh-

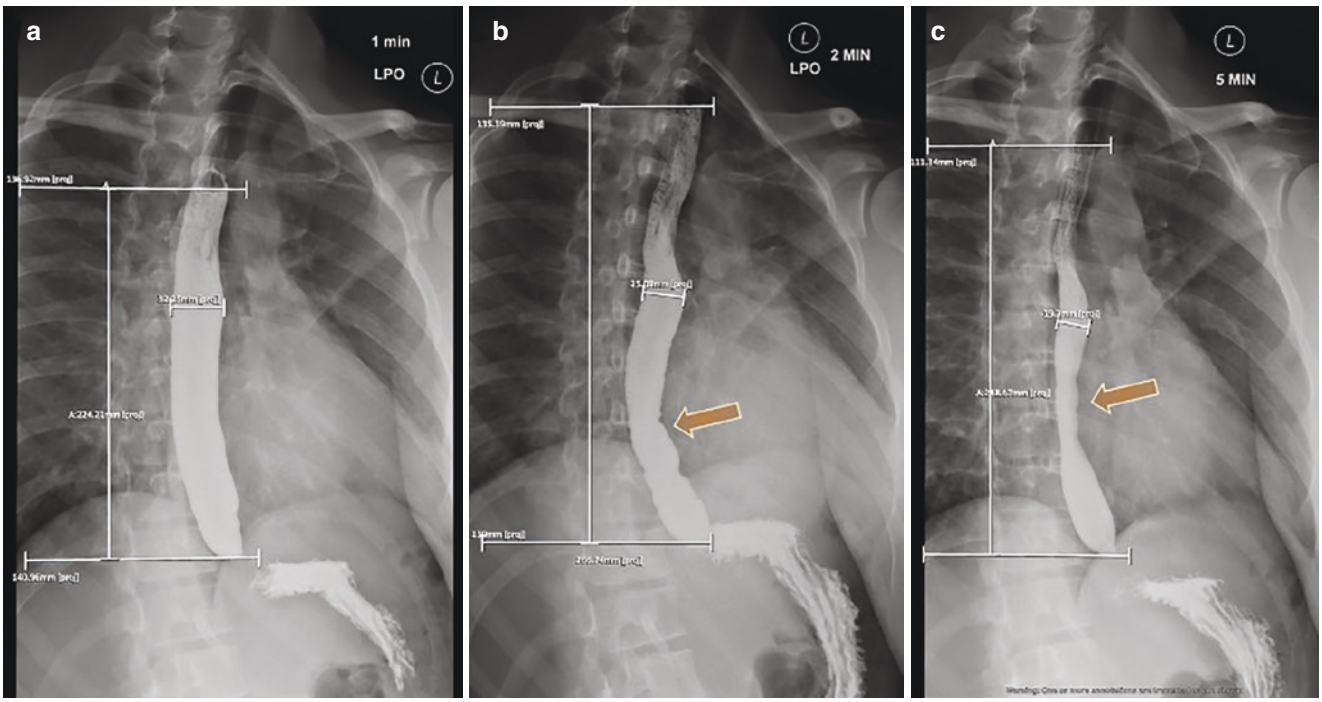

Fig. 36.2 Timed Barium Esophagram in patient with Type 2 Achalasia with symptoms of dysphagia and esophageal spasms. (**a**) At 1 min column of contrast measures 13.6 × 3.2 cm. (**b**) At 2 min column of contrast measures 13.5 × 2.5 cm, with evidence of spasm (arrow). (**c**) At 5 min column of contrast measures 11.1 × 1.9 cm, with spasm (arrow). Based on this, a more extensive myotomy was performed to include the spastic region

old increase in the EGJ diameter, cross-sectional area as well as the distensibility index (DI) is predictive of both clinical outcomes as well as risk for post-POEM GERD [16, 47–49]. Although the most predictive parameter and the threshold criteria is still uncertain, many POEM proceduralists utilize the cut-off of DI >2.9 to predict clinical success and a DI >6.0 to predict post-POEM GERD [16].

Technical Considerations (Fig. 36.3)

On average, it takes 45–90 min to perform the procedure. General anesthesia with endotracheal intubation and prophylactic intravenous antibiotics are routine. The patient is usually placed in the supine position to allow access to the abdomen during the procedure.

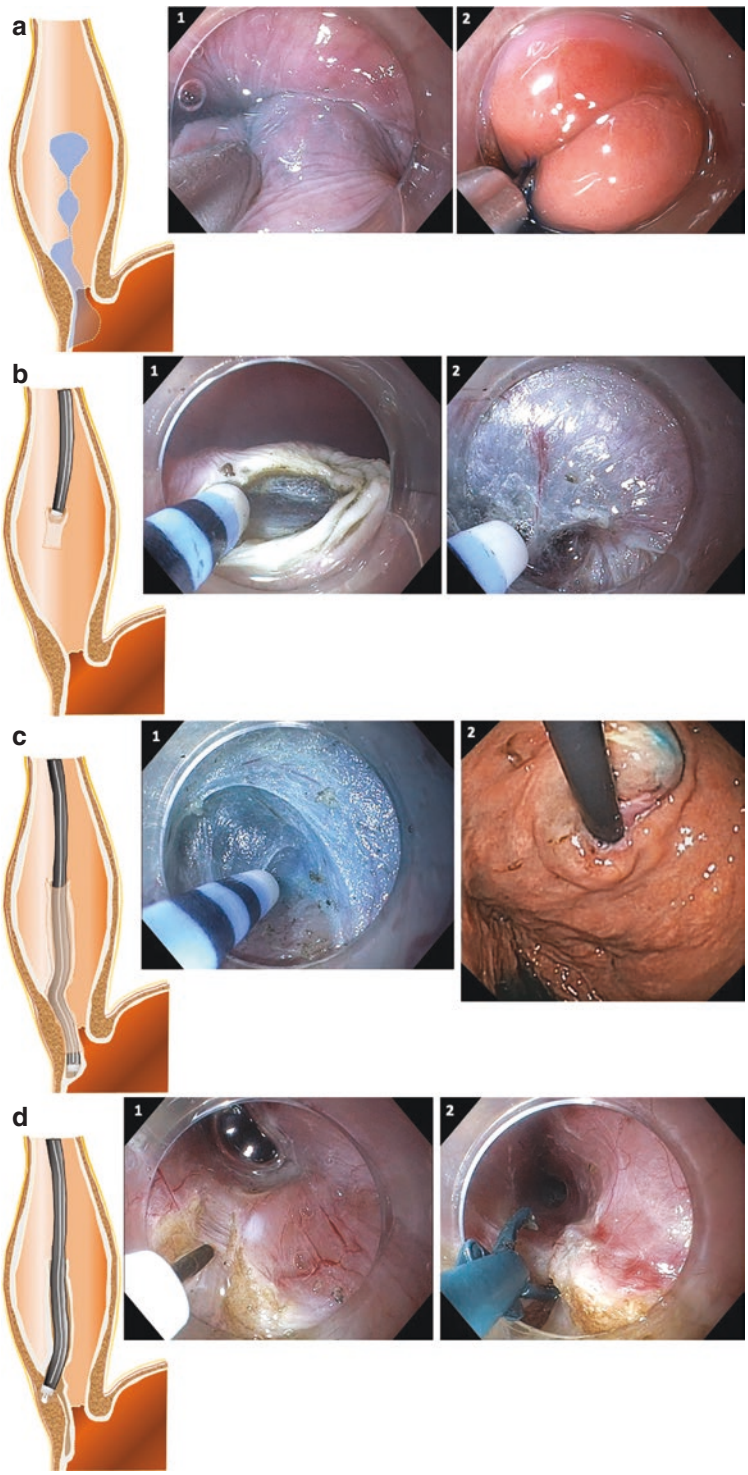

Fig. 36.3 Technical considerations for POEM procedure. (**a**) Navigational tunnel—pre-injection of lifting solution in strategic locations starting from posterior (1) and finishing in the lesser curve of the cardia (2). (**b**) Horizontal incision (1) and beginning of submucosal tunnel (2) with vessel management by prophylactic coagulation followed by ligation. (**c**) Furthest extent of the tunnel determined by prior navigational injection (1) and placement of thin scope into stomach (2) with thin scope light showing on the lesser curve approximately 1.5 cm distal to GEJ. (**d**) Myotomy performed from proximal to distal, beginning with circular muscle only (1) using Hybrid I-knife, then finishing with circular and longitudinal muscle (2) using SB scissor-type knife

Anterior vs Posterior Approach

There have been three randomized controlled clinical trials [24, 50–52] and three meta-analysis [53, 54] comparing the anterior vs posterior approach. The anterior approach has been advocated as a preferred strategy as it theoretically may result in decreased post-POEM GERD due to less disruption of the gastric sling fibers, which are important for maintaining the gastro-esophageal flap valve mechanism. The posterior approach has been advocated as an approach with theoretically less chance of cutting branches of the left gastric artery, and also because the angle of the scope channel is more in line with the posterior aspect of the esophagus, creating an easier angle of approach. However, all 3 RCTs as well as the meta-analysis studies have similarly concluded that the anterior and posterior approaches seem comparable to each other in terms of clinical success, GERD, and adverse events and that the total procedure time with posterior myotomy seems to be shorter than with anterior myotomy. At UCI, we started with the anterior approach, then quickly transitioned to the posterior approach due to ease of use. In Portland, and Strasbourg France, we still mostly perform the tunnel/myotomy anteriorly—though do not hesitate to do it posteriorly if it is indicated. Our technique of optimizing relief of dysphagia while minimizing post-POEM GERD will be discussed later.

Vertical vs Horizontal Mucosal Incision

POEM proceduralists are fairly evenly split between vertical vs horizontal mucosal incision. The advantage of a vertical incision is the fact that clip closure upon completion of the myotomy is easier to perform due to the alignment of the mucosal edges to the vertical clip formation. The disadvantage of a vertical incision is the possible inadvertent "zipper" effect where the scope can mechanically separate the wound edges during tunneling, resulting in a longer than desired opening. The horizontal incision has the advantage of allowing for easier endoscopic suture closure and it is less likely to zipper open (Fig. 36.3b). The disadvantage is that clip closure is slightly more challenging due to the need for vertical closure to a horizontal opening and may require a suture closure.

Extent of Tunnel/Myotomy

The "standard" POEM myotomy was adapted from the LHM, where the myotomy is extended for 8 cm in the esophagus and 3 cm in the stomach in order to ensure complete LES disruption in the face of absent external landmarks. This protocol has been challenged and the trend is towards shorter myotomy in both esophagus and stomach, with some individualized considerations. At UCI, for type 1 and 2 achalasia patients without clinical signs or symptoms of esophageal spasm (which can occur in a subset of type 2 patients, see Fig. 36.2), we perform a 6 cm myotomy in the esophagus and 1.5–2.0 cm in the stomach (Fig. 36.3c). For type 3 achalasia, and in type 2 with spasm, we will extend the myotomy proximally based on (MREM), barium esophagram, endoscopic observance of spasm, or EUS measurement of muscle thickness. In Portland/Strasbourg, we currently tailor the myotomy in type 1 and 2 according to intraoperative EndoFLIP measurements with the aim of doubling the cross-sectional area (CSA) and improving distensibility between 50 and 100%. The length of the myotomy is according to the mapped narrowing of the planimetry nomogram and our current average is 4.5 cm (3 cm on the esophagus and 1.5 on the stomach).

Full Thickness vs Circular Myotomy

While most experts agree that the circular muscle of the esophagus is most responsible for the dysphagia and spasm symptoms among achalasia patients and that the longitudinal muscle serves a role in the anti-reflux mechanism of the GE flap-valve, there is still strategic variability in which muscle layer to cut and where. Circular only compared to modified full-thickness myotomy has shown minimal difference in outcomes, but shortened procedure time in the latter [55]. Complete full-thickness myotomy may lead to eventual "blow-out" diverticulum formation and increases the risk of injury of mediastinal structures. Circular only is certainly more difficult to perform around the GEJ where the fiber orientation is more diffuse. In Portland/Strasbourg, we perform circular-only myotomy using either the traditional "TT" (triangle tip) knife or the Hybrid Knife from Erbe but have a 22% incidence of full-thickness breaches, particularly around the LES. At UCI, we routinely adopt the modified full-thickness myotomy, which starts with circular only but full thickness is applied starting 3–5 cm proximal to the LES and into the cardia. While there are a number of knives that are excellent for performing the circular myotomy, we prefer using the Olympus stag beetle (SB) knife (Fig. 36.3d) for the full-thickness myotomy, as in our opinion, it decreases the rate of spontaneous bleeding (from vessels arising from the MP) and therefore is more expedient [56].

Managing Esophageal Diverticulum

Epiphrenic diverticula are pulsion-type diverticula most commonly located in the distal 10 cm of the esophagus. They are usually associated with esophageal motility disorders,

and are not uncommon in achalasia patients. An achalasia patient with concurrent epiphrenic diverticulum needs special attention as the standard myotomy approach may [57] or may not be sufficient to relieve the patient's dysphagia [42]. Classic treatment is to perform a laparoscopic transhiatal diverticulectomy using an endoscopic stapler and then, importantly, perform a myotomy across the LES and typically add a partial fundoplication. A more recent strategy, particularly for patients at high risk for more invasive surgery, or whose diverticulum is too proximal to access laparoscopically, is to perform a septotomy at the same time, and through the same tunnel as myotomy over the LES, called D-POEM, has been reported [41, 58–61]. The muscles forming the thick septum may be distinct from the LES and can cause dysphagia even if the LES is severed. It is our routine practice to perform a complete septotomy in these cases at the time of the POEM procedure (Fig. 36.2).

Reflux Prevention Strategies

Reflux prevention strategies include consideration of how much to cut and where to cut. The more distal the extent of myotomy into the cardia, the higher the risk of GERD. Modifying the cardia myotomy to 1.5–2.0 is likely the "sweet" spot. Regarding the location of the cardiac myotomy, it is important to appreciate the concept that the lower esophageal sphincter extends into the gastric cardia by way of the sling fibers. These fibers do not appear to contribute to dysphagia in achalasia patients but cutting them disrupts the normal GE Flap-valve mechanism, which is involved in preventing GERD. While the anterior aspect may have less sling fibers than the posterior side, the lesser curve has the very least. Thus, our strategy is to end up, whether starting posterior or anterior, tunneling (spiral from posterior to lesser curve) onto the lesser curve of the cardia and performing the myotomy at this location (Fig. 36.3b, c). This can be facilitated using a "navigational pocket" technique [62] (Fig. 36.3a).

Confirmation of adequate extension into the stomach can sometimes be challenging, and simple fluid injection into the tunnel with subsequent retroflexed viewing in the stomach may not always be accurate. We routinely insert a 5 mm slim scope alongside the gastroscope (which remains in the tunnel) and advance into the stomach in retroflexed position. The slim scope light can be turned off, allowing the light from the gastroscope within the tunnel to be easily confirmed.

Post-procedural Complications

A recent multi-center, international study of 1826 POEM patients found 156 adverse events (AEs) occurred in 137 patients (7.5%). A total of 51 (2.8%) inadvertent mucosotomies occurred [63]. Mild, moderate, and severe AEs had a frequency of 116 (6.4%), 31 (1.7%), and 9 (0.5%), respectively. Multivariate analysis demonstrated that sigmoid-type esophagus [odds ratio (OR) 2.28, $P = 0.05$], endoscopist experience <20 cases (OR 1.98, $P = 0.04$), use of a triangular tip knife (OR 3.22, $P = 0.05$), and use of an electrosurgical current different than spray coagulation (OR 3.09, $P = 0.02$) were significantly associated with the occurrence of AEs. A smaller European multi-center study reported among 241 POEM procedures, 3 patients had severe AEs (SAE rate, 1.2%); 1 case of pneumothorax required intra-procedural drainage, and 2 patients had delayed SAEs (1 ischemic gastric cardia perforation and 1 hemothorax, both leading to surgery). The overall rate of minor AEs was 31.1%, mainly prolonged intra-procedural bleeding (>15 min hemostasis) and defects of the mucosa overlying the tunnel; none led to clinically relevant signs or symptoms [64]. In the largest US single center cohort of 610 patients, accidental mucosotomies occurred in 64 patients (10.5%) and clinically significant adverse events in 21 patients (3.4%): 3 (0.5%) asymptomatic tunnel-opening dehiscences without leak, 8 (1.3%) delayed bleeds [3 inside tunnel and 5 at tunnel closure suture puncture sites, 10 (1.6%) other] [16]. No adverse events led to death, surgery, interventional radiology interventions/drains, or altered functional status.

Conclusions

POEM is a safe and effective treatment for dysphagia in patients with all subtypes of achalasia, as well as other spastic esophageal disorders. A thorough pre-procedure work-up and careful consideration of technical aspects of the procedure to maximize relief of dysphagia while minimizing risk of post-POEM GERD is of utmost importance. POEM and LHM have quite similar outcomes with overlapping and individualized indications for each.

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Scleroderma

37

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Objectives

1. To review the pathophysiology and clinical manifestations of SSc in the foregut
2. To detail the current options for diagnosis—focusing on endoscopy, manometry, barium studies, impedance planimetry, reflux testing, and scintigraphy
3. To describe the treatment options available for maximizing quality of life in affected patients—focusing on lifestyle modification, medical therapy, and endoscopic/surgical options

Introduction

Scleroderma is a chronic connective tissue disorder with multisystem involvement, and the gastrointestinal (GI) tract is affected in >90% of patients. Gut involvement has a major impact on patient quality of life, and when severe, is associated with a high mortality. Symptoms vary based on the location of involvement and degree of impairment; however, dysphagia, reflux, nausea, vomiting, abdominal pain, diarrhea, constipation, fecal incontinence, and weight loss are all commonly reported.

While the esophagus is the most widely described site of GI involvement, SSc can affect any site within the GI tract from the mouth to anus. This chapter will focus on the foregut manifestations of SSc, ranging from the mouth to stomach, with an emphasis on both motility and bleeding. We will review pathogenesis, clinical manifestations, diagnostic options, and treatment considerations.

Pathophysiology

The pathogenesis of dysfunction in SSc is still not entirely clear and several potential mechanisms have been described. Approximately 30 years ago, Sjogren proposed a progression of GI SSc involvement comprised of three steps: (1) vascular damage, (2) neurogenic impairment, and (3) replacement of normal smooth muscle by fibrosis and atrophy. However, this model remains speculative and to a certain extent, controversial as causal progression has never been demonstrated and competing theories exist. For example, circulating autoantibodies directed against muscarinic receptors negatively impact communication between enteric neurons and smooth muscle, thereby blocking smooth muscle contraction in a small subset of patients with rapidly progressive GI disease in SSc. Autoantibodies targeting the soma of enteric neurons are also reported among subsets of SSc patients, although the antigenic targets, their role in SSc GI disease, and the SSc clinical phenotype with which they are associated remain unclear. A recent study examining esophageal tissue from SSc patients reported both proliferative and inflammatory molecular gene expression subsets, suggesting that such signatures may also contribute to defining SSc GI phenotypes. To a certain extent, even the hypothesis that SSc leads to progressive gut fibrosis is controversial, as two classic studies from Johns Hopkins University evaluating autopsies of patients with advanced SSc demonstrated GI atrophy in the vast majority of studied patients, without advanced fibrosis. Taken together, these data imply that SSc gut involvement is not a homogenous process but rather may be a conglomeration of distinct disease subsets leading to common phenotypic expression.

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Clinical Manifestations

The GI tract is the largest internal organ system and, not surprisingly, is almost always affected in SSc. Whether related to fibrosis or atrophy, symptoms relate to lack of propulsion and disruption of normal gut motility, resulting in stasis, impaired clearance, mucosal injury, and malabsorption. In addition, bleeding can be a frequent concern due to both mucosal injury and SSc-related vascular involvement.

Oropharyngeal Cavity

Oropharyngeal manifestations of SSc are not well studied, with estimates of involvement ranging from 20 to 80%. Sclerosis of the oropharyngeal mucosa as well as muscles associated with mastication and salivary glands can lead to difficulty in chewing and swallowing. Reported symptoms include head and neck numbness; tongue, hard palate, and soft palate fibrosis; microstomia; oral mucosal damage; perioral skin injury; xerostomia; periodontal ligament fibrous thickening; bone resorption; oral telangiectasia; trigeminal neuropathy; and significant dental caries. In addition, *sicca* symptoms are reported in at least 20% of SSc patients and the associated decreased salivary gland activity is typically associated with at least mild oropharyngeal dysphagia due to lack of food bolus lubrication. Significant perioral skin involvement can also reduce the size of the oral aperture and restrict food intake.

Treatment options are often limited to dietary modifications using small bolus size, soft foods, increased use of liquid supplements, and salivary replacement therapies. Close follow-up with a dentist or oral specialist (with expertise in pediatric care due to decreased oral aperture) is recommended, as is optimal oral hygiene. To date, there are no good data that suggest that oropharyngeal manifestations of SSc respond to specific medical therapy. Anecdotally, we often use over-the-counter oral moisturizers and have at times employed swallow therapy with some benefit in selected patients.

Esophagus

The esophagus is the most commonly affected organ in the GI tract, with involvement seen in over 90% of patients via both pathology and symptom assessment. Symptoms are related to dysmotility and commonly consist of heartburn, regurgitation, and dysphagia. Gastroesophageal reflux (GERD) is of particular concern due to multiple contributing mechanisms, including peristaltic dysfunction, decreased lower esophageal sphincter (LES) pressure, delayed gastric emptying, autonomic dysfunction, and frequently associated hiatal hernias. Equally important to the loss of the LES as an anti-reflux barrier is the loss of reflux clearance mechanisms, including secondary peristalsis and a reduction in salivary bicarbonate secretion in SSc patients affected by Sicca syndrome. Furthermore, medications used to treat other SSc manifestations, including calcium channel blockers and phosphodiesterase inhibitors, can further impair LES function. Dysphagia is often related to decreased or absent esophageal peristalsis; however, despite the degree of functional impairment of esophageal motility, dysphagia is generally mild and intermittent owing to gravity as a facilitator of bolus transit. Furthermore, many patients—up to 40% in some series—are asymptomatic despite well-documented esophageal dysmotility.

Esophageal SSc involvement can be associated with significant complications. Stricture formation is particularly prevalent and may be related to multiple potential etiologies—including reflux, pill-induced injury, and candida infection. Historically, the prevalence of esophageal strictures in the context of SSc has been estimated to be as high as 29%; however, the frequent administration of proton pump inhibitors has almost certainly reduced this prevalence in recent decades. According to one large case-control study evaluating risk factors for erosive esophagitis and stricture, a concurrent SSc diagnosis was associated with an odds ratio of 6.1 for erosive esophagitis and 12.3 for esophageal stricture. While stricture and esophagitis are classically described with reflux in this population, candida esophagitis deserves special consideration given the multiple potential risk factors involved, including esophageal stasis, chronic acid suppression, and frequent use of immunosuppressive agents and antibiotics. In one study evaluating SSc patients, candida colonization/infection rates were reported to be 15%, with strictures present in all cases.

Whether Barrett's esophagus (BE) is increased in SSc patients remains to some extent controversial, with conflicting data. However, prevalence of BE has been reported to be as high as 37% in one series, and a recent publication from the Mayo Clinic Scottsdale reported a prevalence of 12.8% in female SSc patients. While other data have been contradictory, the prevalence of BE likely exceeds that of the general public given the multiple reported anti-reflux mechanisms involved.

The potential relationship between esophageal involvement and pulmonary disease deserves specific discussion. Reflux may contribute to pulmonary disease through two mechanisms: (1) microaspiration leading to direct lung injury and (2) vagal stimulation leading to bronchoconstriction. In addition, pulmonary disease can potentially contribute to reflux through alteration of esophageal/gastric pressure dynamics, use of medications that lower LES pres-

sure, and potentially hernia formation. Several studies to date have suggested a correlation between esophageal reflux/dysmotility and SSc lung disease; however, causality has not been established and there are no data at present to prove that treatment of reflux in patients with SSc has any effect upon long-term pulmonary function. Nevertheless, in practice, treatment of reflux is often escalated in SSc patients with pulmonary disease as it is a potentially modifiable association.

Stomach

Gastric manifestations of SSc are highly variable and stem from both dysmotility and vascular ectasia. Symptoms of gastric dysmotility are seen in approximately 50% of patients and include nausea, bloating, epigastric pain, early satiety, and postprandial fullness. In addition, gastric dysfunction also contributes to GERD and may manifest only as traditional reflux symptoms such as heartburn and regurgitation. GI bleeding is also a consideration for the foregut practitioner and is reported in up to 15% of SSc patients. Gastric antral vascular ectasia (GAVE), also referred to as Watermelon Stomach, is classically described in association with SSc but is not pathognomonic and can be seen in multiple other conditions, including diabetes mellitus, cirrhosis, chronic renal failure, heart disease, and other autoimmune conditions. The true prevalence of GAVE in SSc is likely low, estimated to be between 1 and 6% in recent publications. From a clinical standpoint, this is more common among SSc patients with anti-RNA polymerase-3 antibodies and often presents as an asymptomatic iron-deficiency anemia, often without history of overt bleeding. In addition, bleeding can relate to telangiectasia, which can be present in the stomach or at more distal points in the gut. The presence of these bleeding diatheses does not correlate with GI dysmotility.

Diagnostic Evaluation

Given the high prevalence of SSc-related GI dysmotility and the absence of data suggesting that early diagnostic intervention affects the natural history of GI complications, we believe that empiric treatment is a reasonable first-line approach for most SSc patients with classic esophageal and gastric symptoms. However, if symptoms continue despite empiric treatment, if concern exists for potential complications, or if clinical presentation is unusual, then diagnostic evaluation is warranted.

Esophagus

Multiple diagnostic modalities exist to evaluate esophageal function, each with their relative risks and benefits. Traditionally, a barium esophagram was often the initial test of choice as it could provide a rough evaluation of both esophageal structure and function; however, fluoroscopy is less sensitive than endoscopy for detection of esophagitis and does not allow therapeutic considerations such as dilation. Similarly, fluoroscopy is less sensitive than manometry for detection of dysmotility. While fluoroscopy still has a role in evaluation of the symptomatic SSc patient, its position now is more nuanced and most authorities do not recommend it as the initial test of choice in the absence of severe dysphagia. In contrast, endoscopy should be considered as a first-line study in SSc patients presenting with esophageal symptoms, especially those who do not respond to initial histamine-receptor blockers or proton pump inhibitors (see Fig. 37.1). Esophagitis has been reported in 77% of SSc patients; however, multiple studies have suggested that symptoms do not necessarily correlate with esophageal injury and that even SSc patients with no symptoms can have significant esophageal damage. In addition, candida and Barrett's esophagus are both clinical concerns and both require endoscopy to secure a diagnosis. Furthermore, endoscopy provides the opportunity to dilate a stricture and thereby improve symptoms if present. For these reasons, some authorities recommend early endoscopy for all patients with SSc; however, at present, there are no data to suggest that this approach improves outcomes, and we believe that the decision to pursue endoscopy needs to be individualized given the relative risks and benefits of intervention.

Esophageal manometry is considered the gold standard for motility assessment and abnormalities are detected in up to 90% of SSc patients even in the absence of symptoms (see Fig. 37.2). Typical findings on manometry include loss of contractile reserve, low-amplitude contractions in the distal esophagus, and in more advanced cases, absent contractility with a hypotensive LES. Classically, contractile forces are maintained in the proximal esophagus and the upper esophageal sphincter is uninvolved. Similar to the story with endoscopy, there are some authorities who recommend early manometry for SSc patients; however, there are no data to suggest that this approach impacts long-term outcomes and in our practices, we generally pursue manometry only when it will impact clinical care (such as persistent symptoms or consideration for lung transplantation). It is also worth noting that the manometry findings described above are not pathognomonic for SSc. Recently, the Functional Lumen Imaging Probe (FLIP) has been utilized for assessment of esophageal

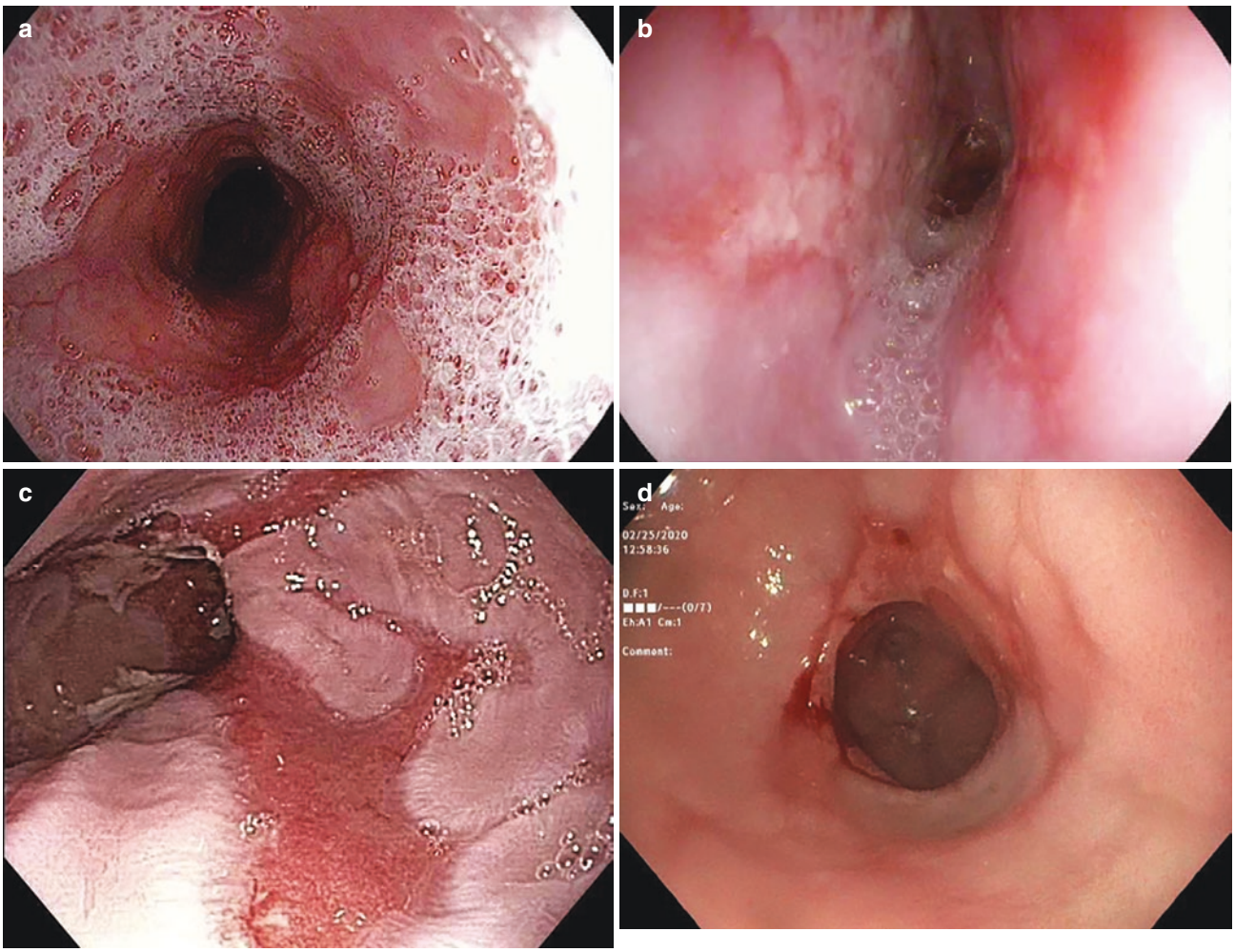

Fig. 37.1 Scleroderma can present with a variety of endoscopic phenotypes. Image (**a**) shows mild esophageal dilation with a patulous appearance and frothy secretions—which is a classic pattern for SSc patients undergoing endoscopy. Image (**b**) shows severe esophagitis in a SSc patient off PPI therapy. Image (**c**) shows Barrett's esophagus and superimposed esophagitis. Image (**d**) shows severe esophagitis with a peptic stricture

function in SSc; however, data are lacking at present with regards to how this technology impacts diagnosis and management. In our practice, we may employ this technology on a case-by-case basis, but usually only when there is a specific clinical question that is being asked with regards to diameter and/or distensibility. Finally, formal reflux testing, via ambulatory pH-impedance or wireless pH testing—has a clear role in the evaluation of select SSc patients with suspected reflux or continued symptoms despite medical therapy. Data clearly demonstrate that SSc patients may be less responsive to conventional medical reflux therapy and these tests may be helpful to optimize acid suppression. In our practice, we generally perform these studies on medical anti-reflux therapy given the high pre-test probability for GERD.

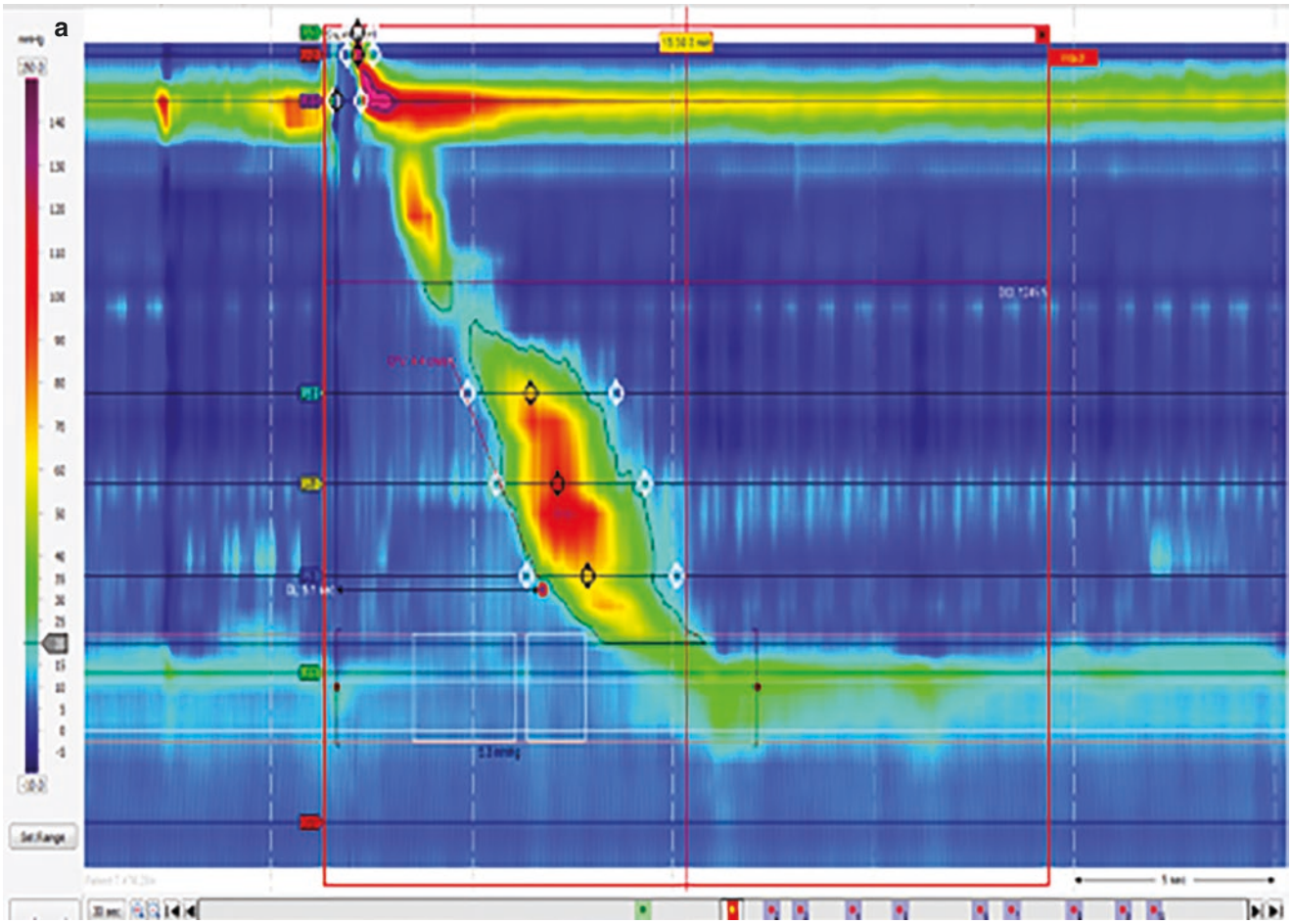

Fig. 37.2 While >90% of SSc patients have esophageal involvement, manometric patterns for SSc are heterogeneous. Figure (**a**) shows a patient with active SSc and esophageal symptoms but no manometric evidence of dysfunction on routine wet swallows. Figure (**b**) shows a patient with weak peristalsis, a hypotensive lower esophageal sphincter, and a small hiatal hernia. Figure (**c**) shows a patient with absent contractility and a hypotensive lower esophageal sphincter. This combination is often referred to as a classic "scleroderma pattern" but is not seen in all patients with scleroderma and, when present, is not pathognomonic for the disease

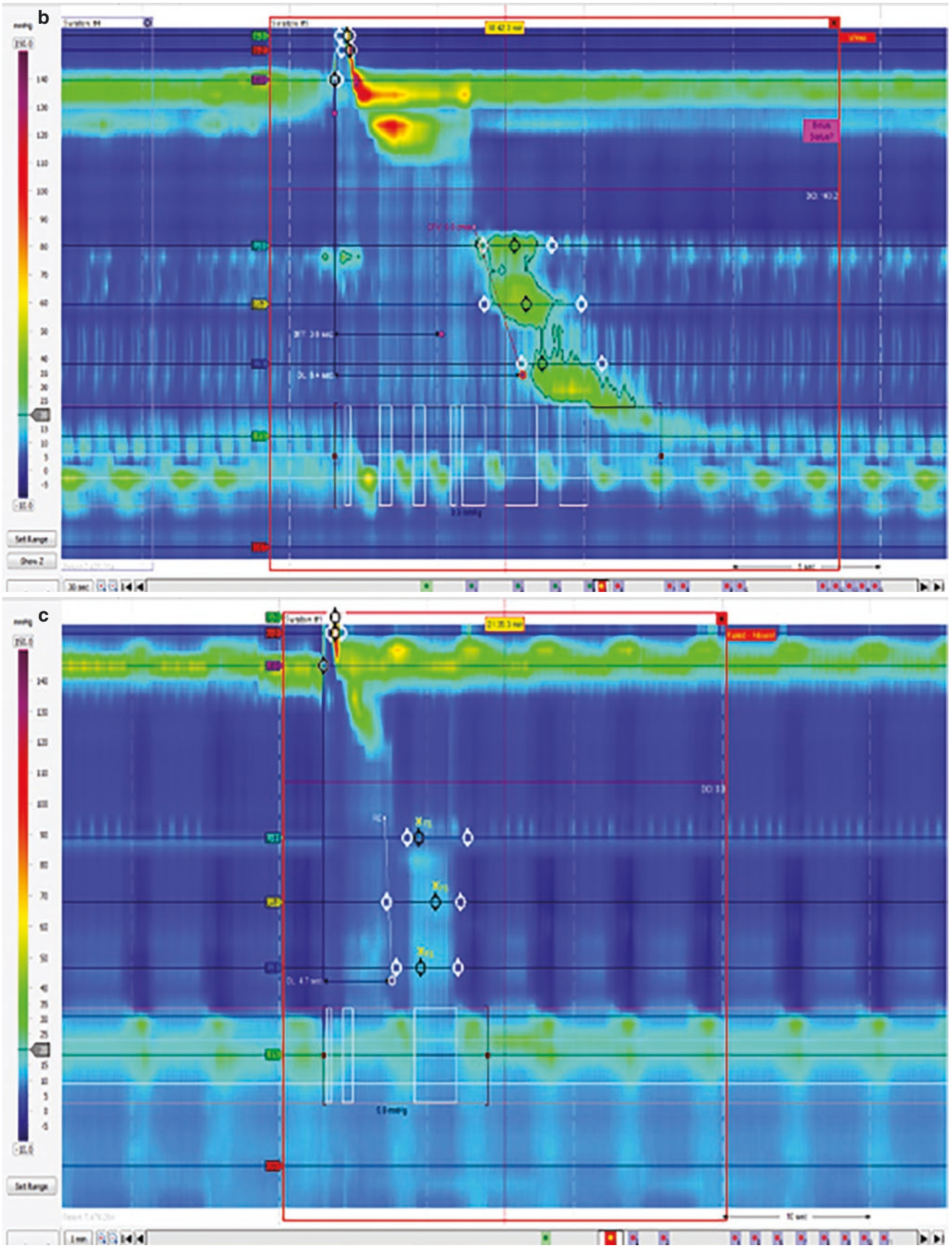

Fig. 37.2 (continued)

Stomach

There is no consensus regarding the best initial study to screen for suspected gastric dysmotility in SSc. From a historical standpoint, barium studies were often employed, but their sensitivity as a motility test is limited. Endoscopy is often performed for other indications and may be suggestive of dysmotility if food retention is seen despite an adequate fast; however, the absence of food retention does not exclude significant dysmotility. In practice, scintigraphy is often employed in the United States for formal assessment of gastric emptying—although wireless motility capsule and C^{13} breath testing are also FDA-approved options with more limited availability. The only modality that allows accurate assessment of gastric bleeding at present is endoscopy. This allows direct mucosal visualization plus the potential for therapeutic intervention.

Treatment Considerations

Given the high prevalence of gut involvement in SSc, empiric treatment is typically recommended as a first-line approach before diagnostic evaluation; however, diagnostic evaluation as detailed above can better define involvement and help lead to tailored treatment options.

Esophagus

Initial treatment of SSc esophageal involvement mimics conventional treatment of GERD. Diet and lifestyle are often the first therapies employed, with a particular emphasis on adequate time between meals/sleep and raising the head of the bed, given the known impairments in secondary peristalsis present with SSc. After maximization of diet/lifestyle interventions, acid suppression is typically the next step in care. In our practice, we advocate use of proton pump inhibitor (PPI) therapy as first-line anti-reflux medical therapy in the SSc population. This approach is supported by expert consensus (European League against Rheumatism Scleroderma Trials and Research Group; UK Scleroderma Study Group). We usually start once a day before meals and then increase to twice a day (or higher) every 2 weeks if symptoms continue. It is well-documented that SSc patients may require higher than typical acid-suppressive doses, which perhaps is not surprising given the multiple physiologic impairments at play in this population. In addition, delayed gastric emptying and small intestinal bacterial overgrowth may also contribute to decreased bioavailability of PPI therapy and may impact decisions regarding PPI dose and formulation. For this reason, anecdotally, dexlansoprazole may be a nice option for reflux control in this population given its dual-release formulation. Other antireflux medical options including antihistamines and alginates have been employed in select patients; however, their efficacy in this population seems to be more limited and they likely have, at best, a modest additive effect.

If symptoms progress despite high-dose acid suppressive therapy and lifestyle modification, then other potential medical therapies include (a) addition of a prokinetic, (b) trial of buspirone, or (c) trial of baclofen. While the effects of prokinetics on esophageal function in SSc are likely minimal, prokinetics may improve reflux through augmentation of gastric emptying. Limited data in SSc support at least short-term efficacy of cisapride, domperidone, erythromycin, metoclopramide, pyridostigmine, and prucalopride—although it should be emphasized that long-term data are lacking and side effects with these therapies are not insignificant. In our practice, pyridostigmine and/or prucalopride are often employed as first-line prokinetics given data to support use in SSc in tandem with FDA approval and good safety profiles. Buspirone is another consideration for refractory reflux in SSc patients. Buspirone is an oral 5-HT_{1A} agonist which affects receptors in the esophagus and fundus, leading to enhanced fundic accommodation. Investigators in Greece have shown improvement in peristalsis and LES pressure in SSc patients treated with this agent for both acute and short-term administration—and these data combined with European data evaluating buspirone for functional dyspepsia and esophageal dysmotility make this a reasonable treatment option to consider. Baclofen exerts action through modulation of GABA receptors and also has been found to increase LES pressure, although this agent has not been studied specifically in SSc. As it can be associated with short-term fatigue, it may be a nice addition for nocturnal breakthrough symptoms despite head elevation and antacid agents.

For those SSc patients with continued reflux symptoms or complications despite maximal medical therapy, surgical options can be considered. However, care needs to be taken as the risk of post-operative dysphagia may be significant. As surgery would be considered a salvage option and performed for quality of life, it is imperative that patients understand the potential risks and benefits thoroughly and their expectations should be managed accordingly. These conversations should include the patient, surgeon, gastroenterologist, rheumatologist, and other key stakeholders on the treatment team. If, in this shared decision-making model, surgical therapy is being considered, the surgery would ideally be performed by an experienced surgeon with expertise in all of the requisite surgical procedures.

Partial fundoplication would be the easiest and least invasive option. Care must be taken to recreate a flap valve that is competent but minimally restrictive. We have found the use of FLIP to be particularly helpful. The goal is not to stop all reflux, but rather to construct a barrier with minimal outflow obstruction. In our practice, Dor, Toupet, and Watson fundoplications are all performed—and we have

found significant improvement in patient quality of life for those patients who are carefully selected. Roux-en-Y (RNY) procedures are an escalation in both complexity and morbidity with the added potential for nutritional deficiencies and need for long-term surveillance; however, these operations do have the added benefit of improved reflux and dysphagia rates as compared to fundoplication. Some investigators advocate RNY procedures to be first-line therapy, although that is not our approach as it can be performed if fundoplication fails. Finally, for the most severe cases, esophagectomy may be entertained, but the patient's quality of life must be severely diminished to justify the morbidity and mortality associated with this intervention. Typically, esophagectomy would be reserved for patients with long-segment fibrotic strictures failing dilation.

Minimally-invasive endoscopic anti-reflux therapies have some appeal in this population but to our knowledge, there are no published data as of yet. In our practices, we have offered SSc patients anti-reflux therapy with generally good clinical outcomes (generally partial fundoplications), but we should emphasize that the patients have been very highly-selected and the surgeries themselves should be performed by expert surgeons to obtain the best outcomes.

Stomach

Treatment of gastric SSc-related dysmotility can be a challenge given the limited range of treatment options. Dietary modification is generally the first-line approach, with recommendation of a low-particulate gastroparesis diet. Liquid emptying may be preserved in some cases, and liquid nutritional supplements may be of benefit in that context. After maximization of diet and lifestyle modification, prokinetic agents have typically been the next step and should be considered the mainstay of treatment for gastric dysmotility in the context of SSc. Data are relatively limited, but this approach is endorsed by expert consensus. Metoclopramide is the only medication FDA-approved for gastroparesis at present but is associated with significant side effects, including tardive dyskinesia, that limit long-term use. Other agents that can be considered include domperidone, cisapride, erythromycin, pyridostigmine, prucalopride, and bethanechol. In our practices, pyridostigmine and prucalopride are often the first-line approaches given published data in SSc in tandem with favorable side effect profiles. Pyridostigmine is an acetylcholinesterase inhibitor with a whole gut prokinetic effect that is FDA-approved for treatment of dysphagia in the context of myasthenia gravis. While the main site of action appears to be in the small/large bowel, there is some gastric effect present. Similarly, prucalopride is a selective serotonin 5-HT_4 agonist with a whole gut prokinetic effect that is FDA-approved for constipation. However, it has documented gastric effects and is mechanistically similar to cisapride with a more favorable safety profile. Complementary and alternative therapies have been employed for SSc-associated gastric dysmotility and are worth consideration, given the drawbacks of conventional medical therapy. Herbal options include ginger and Iberogast. Several publications have shown benefit with acupuncture and this is also worth consideration for interested patients.

Endoscopic and surgical options can be considered in select patients. Botulinum toxin has been investigated for gastroparesis but there are no data to support use in SSc. Gastric per-oral endoscopic myotomy has gained popularity for treatment of gastroparesis, but data employing this technique for SSc are at present limited to one case report detailing benefit in two SSc patients. Decompression gastrostomy and/or feeding jejunostomies are occasionally performed but data are limited and in our practices, these are last-resort options that are rarely performed. Other surgical options that have been proposed for impaired gastric emptying include pyloric myotomy, subtotal gastrectomy, gastric bypass, and gastric electrical stimulation; however, at the present time, there are no data to support the use of any of these procedures for SSc-associated gastric dysmotility.

Treatment of GI bleeding in the context of GAVE or telangiectasia can be challenging. For mild cases, iron supplementation alone may be sufficient; however, endoscopic treatment is the mainstay of therapy for most affected patients (see Fig. 37.3). Multiple endoscopic ablative therapies have been employed, including argon plasma coagulation, cryotherapy, and radiofrequency ablation. Success rates for all three modalities are relatively high (approximately 80%); however, multiple treatment sessions are usually required (generally 3–4) and this has to be factored into the management equation. In select patients, the addition of medical therapy can be considered and case reports suggest that cyclophosphamide, hormonal therapy, and/or octreotide may be beneficial. Surgical management is reserved as a final option for refractory GAVE patients who have failed endoscopic and medical therapy. Antrectomy has been the most common procedure performed, but there is significant morbidity and mortality associated with this procedure in the SSc population, with one series reporting a mortality rate of 7%. Given these data, we recommend surgical resection only as a last resort when all else has failed.

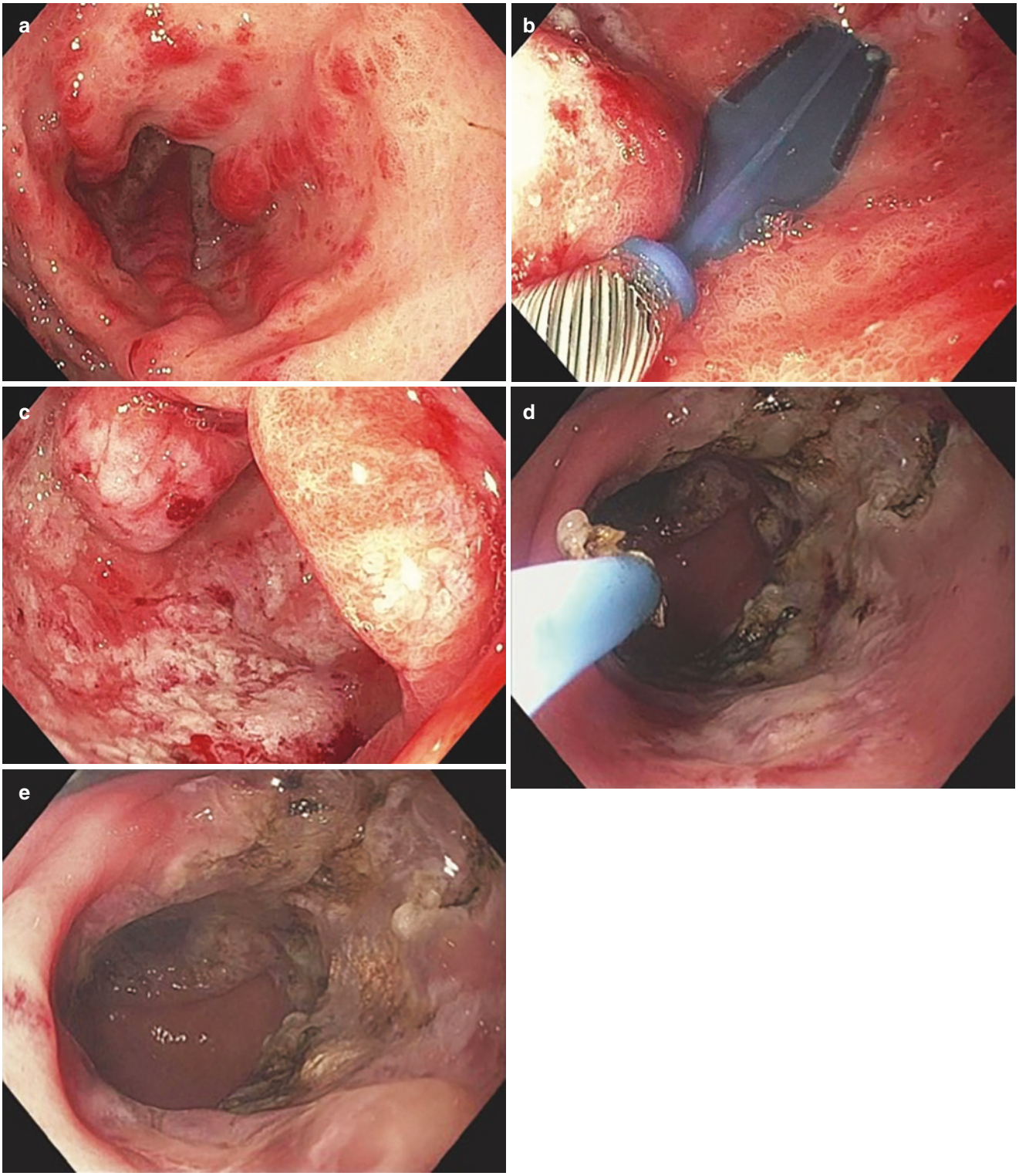

Fig. 37.3 Gastric antral vascular ectasias (GAVE) is seen in between 1 and 6% of SSc patients but is the classic GI endoscopic manifestation. Figure (**a**) shows a SSc patient with untreated GAVE. Figures (**b**, **c**) show the same patient during and after treatment with radiofrequency ablation. Figures (**d**, **e**) show the same patient at a later date during and after treatment with argon plasma coagulation

Conclusion

Management of GI SSc manifestations can be challenging and a multidisciplinary approach involving nutrition, rheumatology, gastroenterology and at times surgery can optimize care in this population. Unfortunately, available therapies directed at the slowing or reversal of SSc progression have not demonstrated efficacy to date from a GI perspective—and existing therapies are leveraged to manage complications of GI dysmotility and hemorrhage. With that caveat, there is a large arsenal of diagnostic and therapeutic options available which can help improve the quality of life of our patients with SSc.

Clinical Case Questions

1. A 57-year-old woman with longstanding scleroderma presents to clinic to see you with reflux symptoms despite diet and lifestyle modification. A prior endoscopy showed Los Angeles B esophagitis but no signs of Barrett's esophagus or stricture formation. Which of the following is the best next step in her care?
   A. Famotidine 40 mg nightly
   B. Alginates after each meal and nightly
   C. Dexlansoprazole 60 mg daily
   D. Metoclopramide 10 mg before meals and nightly

Answer: C. Scleroderma is often associated with refractory reflux symptoms and often requires higher PPI doses than typical to control symptoms and inflammation. A histamine receptor blocker or alginates would not be successful in this patient with known scleroderma and documented esophagitis. Metoclopramide would also likely have a modest effect.

2. A 70-year-old woman with advanced scleroderma on home oxygen with pulmonary hypertension presents to see you in clinic with asymptomatic iron-deficiency anemia. Prior colorectal cancer screening was unremarkable, as was an endoscopy 3 years ago. She denies any GI symptoms at the present time. What is the most appropriate next step?
   A. Start iron supplementation
   B. Treat for small intestinal bacterial overgrowth
   C. Upper endoscopy for evaluation and bleeding control
   D. Begin hormonal therapy

Answer: A. This is a classic presentation for gastric antral vascular ectasia (GAVE), which is present in a small minority of scleroderma patients but classically presents with asymptomatic iron deficiency. While other causes of blood loss or malabsorption cannot be excluded, her prior evaluation in tandem with her high risk for any endoscopic procedures would make iron supplementation a reasonable first step in this particular case.

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Benign Lesions of the Esophagus

38

Sanjay M. Salgado, Daniela Jodorkovsky, and Nitin K. Ahuja

Objectives

1. Review basic descriptions of several types of benign epithelial and subepithelial esophageal lesions
2. Identify endoscopic, ultrasonographic, and histologic features that characterize these benign esophageal lesions
3. Understand the general management of these benign esophageal lesions

Introduction

Benign esophageal lesions subsume a wide range of endoscopic findings but have low detection rates overall, as the majority of these lesions are small in size and never manifest clinical symptoms. Symptomatic benign esophageal lesions frequently present with dysphagia or chest or epigastric discomfort. Understanding the basic endoscopic and ultrasonographic appearance of these lesions can often yield a diagnosis in the absence of histologic evaluation. The purpose of this chapter is to outline the endoscopic and histologic features of a range of benign epithelial and sub-epithelial esophageal lesions alongside general guidelines for appropriate management.

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Epithelial Lesions

Glycogenic Acanthosis

Glycogenic acanthosis is one of the most common benign esophageal conditions and is present in approximately 20–40% of the population, with increased prevalence in males and with advancing age. While glycogenic acanthosis can be identified throughout the esophagus, its density tends to be greater in the middle and lower third. Endoscopic evaluation reveals raised white-to-gray nodules or papules, which are typically less than 1 cm in diameter (see Fig. 38.1). Chromoscopy demonstrates slightly elevated iodine-positive areas. Histologically, these lesions are characterized by thickened epithelium caused by the proliferation of glycogen-filled squamous cells. Although the exact pathogenesis is unknown, these lesions have been associated with gastroesophageal reflux, celiac disease, and Barrett's esophagus. Glycogenic acanthosis is asymptomatic and does not require intervention.

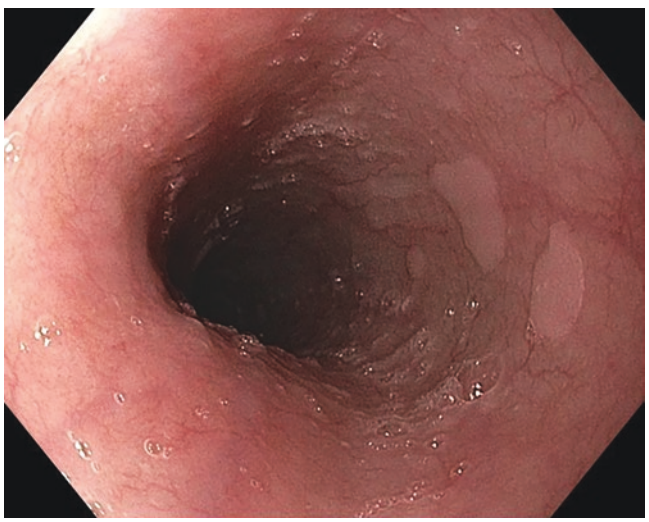

Fig. 38.1 Glycogenic acanthosis. Endoscopic appearance characterized by raised, white-to-gray papules

N. T. Nguyen et al. (eds.), *The AFS Textbook of Foregut Disease*, https://doi.org/10.1007/978-3-031-19671-3_38

Inlet Patch (Heterotopic Gastric Mucosa)

An inlet patch is an area of heterotopic gastric mucosa that is most often found in the proximal esophagus immediately distal to the upper esophageal sphincter. Studies evaluating the prevalence of inlet patches have yielded discordant results, with prevalence ranging from under 1 to 70%, with a general consensus that endoscopic evaluation tends to underdiagnose this condition in relation to its true prevalence [1]. Endoscopically, these lesions consist of round or ovoid areas of salmon-colored mucosa that can be flat, slightly raised, or slightly depressed (see Fig. 38.2). Inlet patches are generally considered a congenital condition arising from incomplete squamous epithelization of the esophagus during development. Histologically, inlet patches often consist of fundic-type gastric mucosa containing parietal cells, although antral patterns (with few parietal cells and absent chief cells) have also been observed. Inflammation in the adjacent esophageal squamous mucosa can develop due to acid secretion from ectopic parietal cells. Clinically, inlet patches are usually asymptomatic, but very rarely the associated acid secretion can lead to chronic inflammation, risking the formation of esophageal strictures and webs. Symptomatic inlet patches can manifest with cough, hoarseness, dysphagia, and odynophagia, though proving causality remains difficult given its high prevalence and non-specific presentation. Symptomatic lesions can be treated with proton pump inhibitor therapy, while secondary strictures and webs are generally responsive to endoscopic dilation. Inlet patches are generally regarded as benign lesions, but there are rare case reports of malignant transformation to adenocarcinoma.

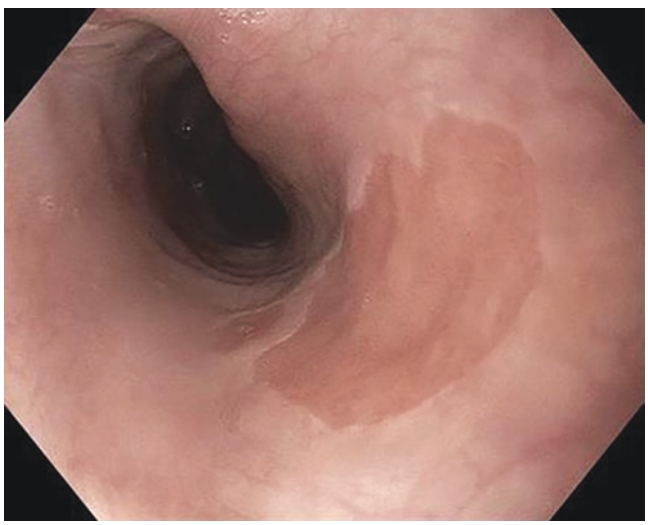

Fig. 38.2 Inlet patch. Endoscopic appearance is characterized by round or ovoid areas of salmon-colored mucosa that can be flat, slightly raised, or slightly depressed

Squamous Papilloma

Esophageal squamous papillomas are benign epithelial tumors most often found in the distal esophagus [2]. Their etiology is unclear, although links have been proposed to irritation from esophageal reflux, direct trauma, or human papillomavirus (HPV) infection. Most published reports of esophageal squamous papilloma have originated from Europe and suggest a higher prevalence in northern Italy. These lesions are usually asymptomatic but have been associated in some case reports with pyrosis and dysphagia. Endoscopically, squamous papillomas are characterized as small (2–6 mm in diameter), raised, white-to-pink verrucous lesions. While there are a few reports of multiple lesions, generally, squamous papillomas are solitary and can be removed endoscopically without demonstrable recurrence. Histology reveals characteristic finger-like projections lined by an increased number of squamous cells and a fibrovascular core containing small blood vessels. Notably, there is conserved cellular orientation and normal differentiation without signs of cytological atypia, with little evidence to suggest that esophageal squamous papilloma have the potential for malignant transformation [2].

Hyperplastic (Inflammatory) Polyp

Hyperplastic polyps are the most commonly identified benign esophageal polyp, hypothesized to represent an exaggerated response to mucosal injury. More common in males, hyperplastic polyps are characterized endoscopically as small (under 5 mm in diameter), solitary, nodular lesions most often located in the distal esophagus and at the gastroesophageal junction. Their exact pathogenesis is poorly understood, although their presence has been associated with chronic acid reflux, hiatal hernias, and HPV. Histologically, these lesions are characterized by a proliferation of hyperplastic gastric-type foveolar epithelium, hyperplastic squamous epithelium, or a mixture of both, with varying degrees of inflamed stroma [3]. Hyperplastic polyps are generally asymptomatic and do not require resection.

Fibrovascular Polyp

Fibrovascular polyps account for 1% of all benign esophageal tumors. These lesions are thought to originate from submucosal tissue near Laimer's Triangle, the area between the inferior cricopharyngeus muscle and the proximal esophagus. It has been hypothesized that this area, which has increased mobility due to an anatomic lack of muscular support and redundant tissue, becomes enlarged with the

repeated stress of esophageal peristalsis over the course of decades [4]. Incidence is higher in older males, especially those over 50 years of age. Fibrovascular polyps, if symptomatic, generally present with dysphagia and respiratory symptoms, although case reports have also noted regurgitation, weight loss, chest pain, bleeding, and asphyxiation. Larger polyps can cause mediastinal widening and anterior bowing of the trachea, identifiable on chest radiography. Endoscopic evaluation generally demonstrates a polypoid mass in the cervical esophagus. Radiographic imaging can play an important role in the identification of fibrovascular polyps as some studies have suggested that up to 25% of these polyps are missed at the time of endoscopy. Histologically, these lesions arise from submucosal mesenchymal tissue, with varying amounts of associated fatty and fibrous tissue. The treatment of symptomatic lesions is primarily surgical, as large lesions are difficult to endoscopically snare and retrieve.

Inflammatory Fibroid Polyp

Inflammatory fibroid polyps (also known as eosinophilic granulomas, inflammatory pseudotumors, or polypoid myoendotheliomas) are rare, generally solitary, benign polypoid tumors of the digestive tract. They are most often found in the stomach, although there are sporadic reports of esophageal involvement, which can present with dysphagia, bleeding, or reflux symptoms. The incidence and pathogenesis are unknown, although it has been hypothesized that their development may be related to a reactive response to mucosal ulceration [5]. Diagnosis of an inflammatory fibroid polyp is based on histologic evaluation and is characterized by connective tissue stroma with eosinophilic infiltration. Appropriate therapy depends on lesion size and structure, but it can usually be managed endoscopically.

Hamartoma

Esophageal hamartomas are extremely rare, slow-growing tumors, with fewer than two dozen cases reported in total. They are generally found in children and are thought to be formed by a congenital disorder of primitive mesenchymal tissue. Symptoms can include dysphagia, dyspnea, and chest pain. Endoscopic ultrasound has been suggested as the most accurate diagnostic imaging modality, with usual findings consisting of a hypoechoic septated cystic lesion [6]. Histologically, hamartomas can contain a mixture of smooth muscle, adipose tissue, and connective tissue, with immunohistochemical positivity for S100, CD117, and alpha smooth muscle actin. The safety and feasibility of endoscopic resection depend on lesion size and layer of origin, with lesions originating from the first to third layers of the esophageal wall being more amenable to endoscopic resection.

Polypoid Bacillary Angiomatosis

Bacillary angiomatosis is a vasoproliferative lesion caused by the gram-negative bacilli *Bartonella henselae* and *Bartonella quintana*. Classically, bacillary angiomatosis has been associated with acquired immune deficiency syndrome (AIDS), although it has also been identified in other immunosuppressed patients, including those with a history of organ transplants and those undergoing chemotherapy. Mucocutaneous manifestations of the oral and anal mucosa are common, and involvement of the rest of the gastrointestinal tract is rare. Case reports have noted esophageal involvement presenting with friable, polypoid lesions. Histology is notable for vascular proliferation mixed with an inflammatory infiltrate, with clusters of bacilli identified on Warthin–Starry stain. Resolution is expected with appropriate antimicrobial treatment.

Pyogenic Granuloma

Pyogenic granulomas are lobular hemangiomas that rarely develop in the esophagus, with fewer than two dozen cases reported in the literature. Pyogenic granulomas have been described in patients in the second through eighth decades of life. Symptoms most commonly include dysphagia and retrosternal pain, although weight loss and bleeding have also been described. On endoscopic evaluation, pyogenic granulomas appear as red, pedunculated, polypoid lesions with a white coating and occasional ulcerations. They tend to be found in the distal third of the esophagus, and their appearance can be mistaken for malignant vascular tumors. Endoscopic ultrasound generally demonstrates a lesion confined to the mucosa, characterized by homogenous hyperechogenicity that underscores increased vascular proliferation. Endoscopic biopsy should generally be avoided given the risk of significant bleeding [7]. Histologically, these lesions are characterized by proliferating capillaries in a unique lobar architecture, surrounded by inflammatory cells in connective tissue stroma. Resection can be successfully accomplished with snare polypectomy.

Ectopic Sebaceous Glands

Ectopic sebaceous glands of the esophagus are rare, often incidental findings on endoscopy, appearing in the middle to distal esophagus as yellowish papules or nodules with an

irregular surface, with or without a central protuberance. They generally present in the sixth decade of life and have equal prevalence in men and women. Macroscopically, these lesions can appear similar to xanthomas, although careful examination with narrow band imaging can identify the circular microvessels which surround the sebaceous excretory ducts to confirm the diagnosis [8]. Histology reveals large, polygonal clear cells with vacuolated cytoplasm within the squamous epithelium. The pathogenesis of these lesions is unclear, although they are most likely related to congenital predisposition or metaplastic change. Endoscopic intervention is not warranted.

Esophagitis Dissecans Superficialis

Esophagitis dissecans superficialis is a desquamative disorder of the esophagus, characterized endoscopically by a vertical sloughing of the superficial mucosa with normal underlying tissue, resulting in a "striped" appearance of the esophagus. In rare cases, this can result in the formation of esophageal casts that can present with obstructive symptoms. While the exact pathogenesis is unknown, esophagitis dissecans superficialis has been associated with systemic conditions like celiac disease and pemphigus vulgaris, as well as a number of medications, such as psychoactive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and bisphosphonates [9]. On histology, esophagitis dissecans superficialis is characterized by parakeratosis, often with a distinct necrotic edge and concurrent basal cell hyperplasia. Most reports describe complete and spontaneous recovery without specific intervention.

Schatzki Ring

A Schatzki ring is a membrane consisting of both mucosa and submucosa that generally forms at or near the squamocolumnar junction of the distal esophagus. The pathogenesis is thought to be related to gastroesophageal reflux, and these lesions are often associated with hiatal hernias. They are relatively common lesions; while the overall prevalence has not been confidently established, Schatzki rings are found in 6–14% of barium radiographs and are the most frequent cause of food impactions in adults [10]. Histologically, the upper surface consists of squamous epithelium while the lower surface is composed of columnar epithelium. Schatzki rings notably do not contain a muscularis propria. Treatment consists of proton pump inhibitors for the treatment of reflux and endoscopic disruption of the ring, either with biopsy forceps or endoscopic dilators, although 2-year recurrence is as high as 65% [11].

Subepithelial Lesions

Duplication Cyst

Duplication cysts arise from incomplete vacuolization of the gastrointestinal tract in early embryonic life. These lesions can develop anywhere along the gastrointestinal tract, with 10–15% of them occurring in the esophagus. The overall prevalence of esophageal duplication cysts is under 0.1%, with a 2:1 male predominance [12]. Up to 80% of these lesions are diagnosed in childhood, with a majority found in the distal third of the esophagus. Symptoms of upper esophageal lesions include stridor and cough, while lower esophageal cysts more often present with dysphagia, emesis, or epigastric discomfort. On endoscopy, duplication cysts generally present with extrinsic luminal compression with normal overlying esophageal mucosa and can be difficult to distinguish from other submucosal lesions (see Fig. 38.3a).

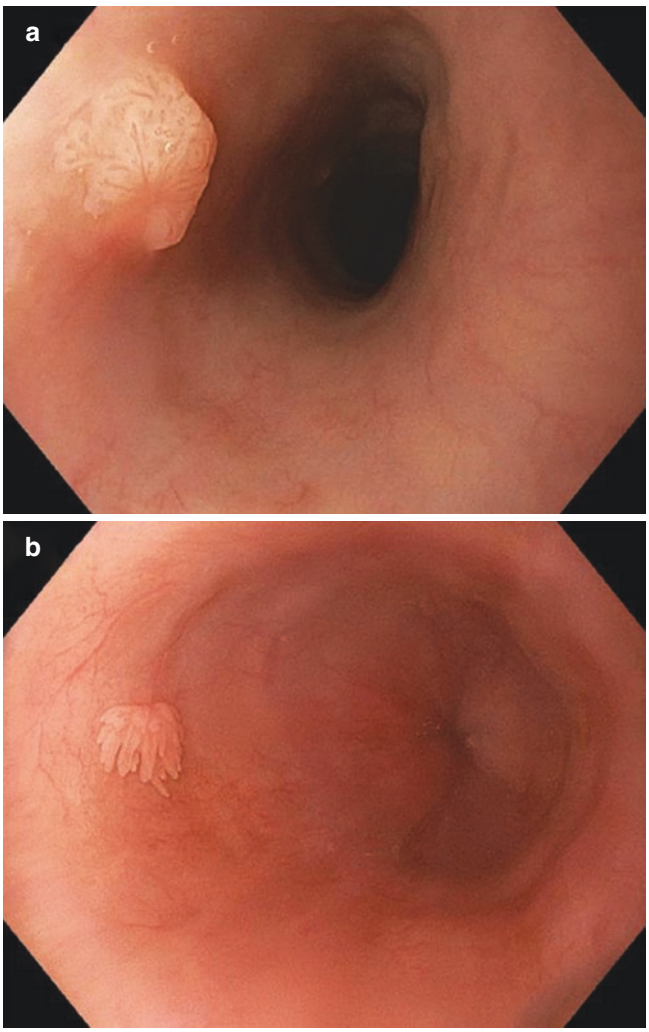

Fig. 38.3 (**a**, **b**) Squamous papilloma. Endoscopic appearance is characterized by small (2–6 mm in diameter), raised, white-to-pink verrucous lesions

Histologically, esophageal duplication cysts have a double layer of surrounding smooth muscle lined with squamous or enteric epithelium. Endoscopic ultrasonography often demonstrates a periesophageal homogenous hypoechoic mass with a multi-layered wall and well-defined margins (see Fig. 38.3b). If central fluid is present, endoscopic ultrasound findings appear similar to an anechoic cyst. Endoscopic ultrasound-guided fine needle aspiration has been associated with high infection rates and ideally, should be performed only if the diagnosis is in doubt and there are competing concerns for malignancy. The treatment of symptomatic duplication cysts is surgical removal.

Pancreatic Rest

Pancreatic rests consist of aberrant ectopic pancreatic tissue and are typically localized to the foregut. Pancreatic rests are often discovered incidentally and far more often in the stomach than the esophagus. On cross-sectional imaging, they sometimes appear as an ovoid mass with an ill-defined border and endoluminal growth pattern. Endoscopic evaluation classically reveals a submucosal nodule with central umbilication, signifying the presence of a draining duct. Endoscopic ultrasound demonstrates a hypoechoic heterogenous mass arising from the third or fourth echoic layer with anechoic structures, which correspond to ducts. Treatment varies based on symptoms and location but can include endoscopic surveillance, surgical resection, or in rare cases, esophagectomy.

Xanthoma

Gastrointestinal xanthomas are rare, benign lesions with incidence rates under 1%. They are generally found in the stomach but have been less commonly found in the esophagus and duodenum. Endoscopic evaluation reveals small (1–2 mm diameter), well demarcated, raised, white or yellow lesions with irregular borders. Magnifying endoscopy sometimes demonstrates characteristic areas of tortuous microvessels. Histologically, these lesions manifest with aggregated nests of large periodic acid-Schiff (PAS) negative cells with small nuclei and foamy cytoplasm [13]. The etiology of gastrointestinal xanthomas remains unclear but may be associated with mucosal injury or *Helicobacter pylori* infection. While gastrointestinal xanthomas are benign, their appearance on endoscopy is similar to lesions associated with poorly differentiated carcinoma and opportunistic infections (including cytomegalovirus and *Mycobacterium avium intracellulare*) and so should be sampled for further evaluation.

Lipoma

Lipomas are well-circumscribed nodules of adipose tissue that can occur at any region of the gastrointestinal tract. These lesions are easily identifiable by the characteristic endoscopic appearance of a smooth yellowish submucosal lesion and the distinctive "pillow sign," in which an indentation is elicited with forceps or similar accessory, and the "tenting sign," in which the mucosa can easily be pulled away from the underlying submucosal tumor. Endoscopic ultrasound shows a hyperechoic, homogeneous lesion arising from the third echoic layer, a finding which is essentially diagnostic. That said, diagnosis can be confirmed with tunneled biopsies, which will cause extrusion of the underlying adipose tissue, dubbed the "naked fat sign." Lipomas are benign and generally do not warrant surveillance or excision unless symptomatic. Rarely lipomas can ulcerate, which can lead to hemorrhage or obstruction, requiring removal. Careful consideration of endoscopic resection should be considered for lipomas over 2 cm, as the use of cautery in these lesions has been associated with an increased risk of perforation [14].

Leiomyoma

Leiomyomas are firm, submucosal lesions that account for two-thirds of benign esophageal tumors. If symptomatic, patients generally present with obstructive symptoms. Computed tomography (CT) imaging is generally characterized by a smoothly contoured, homogenous mass with low attenuation. Endoscopic evaluation usually reveals a protruding mass with normal overlying mucosa. Obtaining biopsies to diagnose leiomyomas is controversial, with some studies reporting complications including infection, bleeding, increased subsequent intraoperative difficulties, and perforation. Endoscopic ultrasound is perhaps the most accurate diagnostic imaging modality and demonstrates a well-circumscribed lesion arising from the fourth (or rarely second) ultrasonographic layer. While leiomyomas are benign, if the lesion contains cystic spaces, disrupts tissue planes, or has enlarged associated lymph nodes, malignant leiomyosarcoma should be considered [15]. Histologically, leiomyomas are paucicellular, with fascicles of spindle cells without nuclear atypia or frequent mitoses. Immunohistochemical analyses reveal positive immunoreactivity for desmin and smooth muscle actin and negative reactivity for c-kit and CD34. Surgical removal should be considered for lesions over 2 cm in diameter. Esophageal resection is often necessary for larger tumors or those located at the gastroesophageal junction. For smaller, asymptomatic lesions, endoscopic ablation, endoscopic resection, or conservative management with serial endoscopic ultrasounds can be considered.

Granular Cell Tumor

Granular cell tumors are nodular neuroendocrine tumors that account for 0.5% of soft tissue tumors. Granular cell tumors can occur at virtually any location but are most commonly seen in the skin and gastrointestinal tract, of which lower esophageal involvement is most prevalent. Endoscopy can reveal solitary or multiple lesions, which are characterized as firm, smooth, and yellowish in color, with hemispherical protrusion and a thin mucus membrane, classically referred to as a "sweet corn" or "molar tooth" appearance [16] (see Fig. 38.4). Granular cell tumors are generally found in patients between the ages of 10–50, with a female predominance. Endoscopic ultrasonography reveals hypoechoic, homogeneous masses with smooth margins that originate from the second or third echoic layer. Histologically, granular cell tumors are characterized by sheets of plump ovoid or polygonal cells with a small nucleus and PAS-positive, granular cytoplasm. Immunohistochemical staining is notable for positive reactivity for S100, CD68, CD57, and neuron-specific enolase, and negative reactivity for desmin, actin, CD34, and c-kit. While over 98% of granular cell tumors are benign, lesions greater than 3 cm should harbor concern for possible malignant transformation. Management consists of either endoscopic excision or surveillance with endoscopic ultrasound (Fig. 38.5).

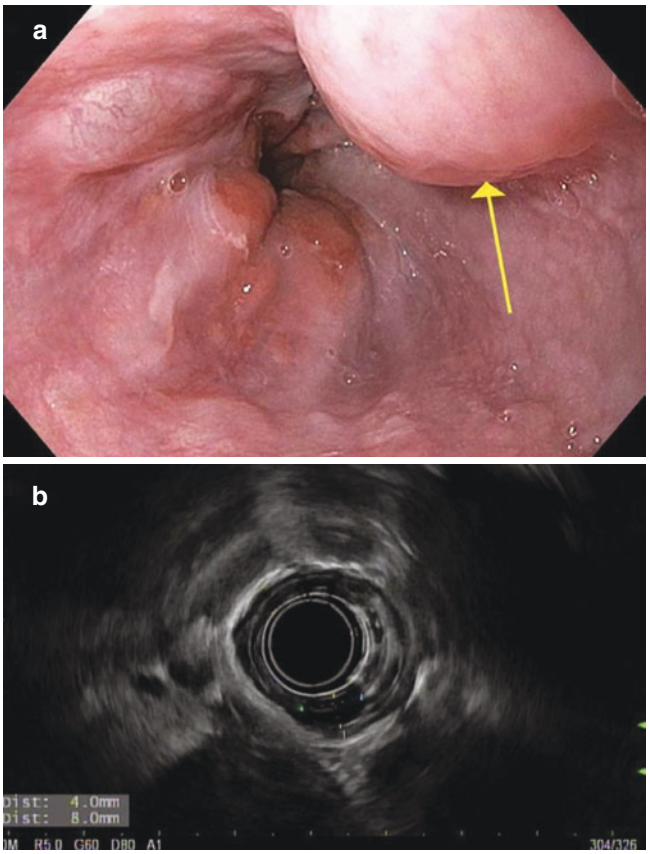

Fig. 38.4 Duplication cyst. Endoscopy (**a**) reveals extrinsic luminal compression with normal overlying esophageal mucosa. Endoscopic ultrasonography (**b**) demonstrates homogenous hypoechoic mass with a multi-layered wall and well-defined margins

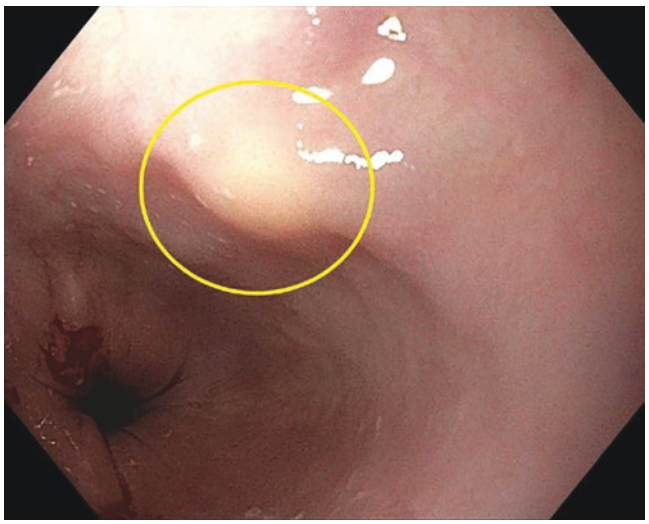

Fig. 38.5 Granular cell tumor. Endoscopic appearance is characterized by a solitary, smooth, yellow-colored lesion with hemispherical protrusion and a thin mucus membrane

Schwannoma

Schwannomas are spherical, occasionally multinodular neuroendocrine tumors that originate from the muscularis propria and account for less than 3% of mesenchymal gastrointestinal tumors. Schwannomas are primarily found in the stomach, but esophageal schwannomas have been reported, generally predominating in the upper and middle esophagus. Symptoms can include dysphagia, dyspnea, and hematemesis. Phasic CT imaging typically demonstrates a homogeneous lesion with delayed enhancement, which can be similar to gastrointestinal stromal tumors. Endoscopic evaluation generally reveals a submucosal mass with or without central ulceration. Endoscopic ultrasonography reveals a heterogeneously hypoechoic lesion arising from the fourth echogenic layer. Histologically, schwannomas consist of spindle cells with nuclear palisading and a nodular lymphatic cuff. Diagnosis is confirmed by positive immunohistochemical assay for S-100 and negative staining for CD34 and CD117. Malignant transformation is possible but uncommon, in which case endoscopic or surgical excision would be the treatment of choice, as chemotherapy and radiation are often ineffective.

Lymphangioma

Lymphangiomas are rare, benign vascular tumors that can present anywhere in the gastrointestinal tract but are most commonly seen in the stomach and small bowel. Esophageal lymphangiomas are estimated to comprise less than 1% of gastrointestinal lymphangiomas, with fewer than two dozen reported cases in the literature. Of the available reports, most esophageal lymphangiomas are discovered in the sixth decade of life and often occur in the distal esophagus, although there may be ethnic differences in presentation [17]. While small lesions are asymptomatic, larger tumors can lead to dysphagia, chest pain, or epigastric discomfort. Endoscopic evaluation reveals a round, yellow-to-white, nodular mass, with or without a stalk. While most appear to have normal overlying mucosa, there have been reports of visibly ulcerated or friable lesions. Endoscopic ultrasonography demonstrates an anechoic and septated lesion arising from the third echoic layer. Microscopically, lymphangiomas consist of dilated lymphatics lined with endothelial cells with lymphocytic infiltrate and eosinophilic lymph. The diagnosis can be confirmed by positive immunostaining for D2–40 and negative immunoreactivity for FVIII.

Glomus Tumor

Glomus tumors are well-defined submucosal tumors of mesenchymal origin, derived from glomus bodies. Generally found in adults, glomus tumors have no clear association with other disease entities. They rarely present in the gastrointestinal tract, most frequently in the stomach. There are currently fewer than a dozen case reports of esophageal involvement in the available literature. Although the majority of patients are asymptomatic, larger lesions have been associated with ulceration, reflux symptoms, and bleeding. Phasic CT imaging reveals early enhancement with possible calcification. Endoscopic ultrasonography reveals a heterogeneous solid mass arising from the fourth echogenic layer, which, depending on the report, has previously been described as hypo- or hyperechoic. Microscopic examination shows small, uniform nuclei with PAS-positive basement membranes and often demonstrates hyperplastic smooth muscle cells. Immunohistochemical staining is positive for smooth muscle actin. Vimentin, and desmin, and negative for CD34 and c-kit. While generally benign, the criteria for potential malignancy in glomus tumors are not well known due to their relative rarity.

Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumor of the stomach and small bowel, generally affecting adults in the sixth or seventh decade of life, with increasing prevalence in patients with NF1 mutations or heritable mutations in the c-kit gene. Approximately one-third of GISTs are incidentally discovered. If symptomatic, GISTs generally present with abdominal discomfort and bleeding. Benign GISTS are usually well-defined, homogenous masses with varying degrees of enhancement on CT imaging, and endoscopic ultrasound usually depicts a hypoechoic, homogeneous lesions with well-defined margins. Histologically, GISTs consist of spindle cells arranged in whorls with uniform nuclear and juxtanuclear cytoplasmic vacuoles. Immunohistochemical analysis reveals c-kit positivity in over 95% of cases, with virtually all GISTs positive for either c-kit or anotamin-1. While esophageal involvement accounts for less than 1% of cases, these GISTs have higher rates of malignant transformation and are usually more difficult to manage, often requiring esophagectomy. Endoscopic removal is possible but controversial as a primary therapeutic strategy given the risk of perforation.

Questions

1. A 2-year-old male is brought in for evaluation by his parents due to worsening dysphagia associated with emesis. Endoscopy shows luminal narrowing of the distal esophagus with normal mucosa, concerning for a subepithelial process. Endoscopic ultrasound demonstrates a hypoechoic mass with a multi-layered wall. The patient is referred for surgery. The pathogenesis of this lesion is most likely related to which of the following:
   A. Congenital predisposition or metaplastic change
   B. Congenital disorder of primitive mesenchymal tissue
   C. Incomplete vacuolization of the gastrointestinal tract in early embryonic life
   D. Exposure to human papillomavirus

Answer: C. Duplication cysts arise from incomplete vacuolization of the gastrointestinal tract in early embryonic life. They generally present in childhood, with distal esophageal lesions being associated with dysphagia, emesis, and epigastric discomfort. Ectopic sebaceous glands are thought to arise from a congenital predisposition or metaplastic change. They generally present in the sixth decade of life and appear endoscopically as yellow papules on the esophageal epithelium. Hamartomas develop from a congenital disorder of primitive mesenchymal tissue and can present in childhood. However, endoscopic ultrasonography of hamartomas usually reveals a hypoechoic septated cystic lesion. Human papillomavirus has been associated with squamous papillomas and hyperplastic polyps.

2. A 38-year-old woman presents with a history of dysphagia and retrosternal pain after a negative cardiac workup. She has no other notable medical history. Endoscopy reveals an erythematous, pedunculated, ulcerated lesion

in the distal esophagus. An endoscopic biopsy is obtained; the endoscopic report notes that the biopsy caused more bleeding than expected. Histological assessment is most likely to reveal which of the following:

A. Increased predominance of squamous cells and a fibrovascular core containing small blood vessels
B. Proliferating capillaries surrounded by inflammatory cells in connective tissue stroma
C. Vascular proliferation mixed with an inflammatory infiltrate, with clusters of bacilli identified on Warthin–Starry stain
D. Parakeratosis with a necrotic edge and basal cell hyperplasia

Answer: B. Pyogenic granulomas are lobular hemangiomas that are more common in the distal esophagus. The increased vascular proliferation in these lesions heightens the risk of bleeding with biopsy. Histologic assessment shows proliferating capillaries surrounded by inflammatory cells in connective tissue stroma. Squamous papilloma is characterized by finger-like projections lined by an increased number of squamous cells and a fibrovascular core containing small blood vessels. They have not been associated with increased bleeding after biopsy. Vascular proliferation mixed with an inflammatory infiltrate, with clusters of bacilli identified on Warthin–Starry stain is characteristic of polypoid bacillary angiomatosis, which is most often seen in immunocompromised patients. Parakeratosis with a necrotic edge and basal cell hyperplasia are suggestive of esophagitis dissecans superficialis, which is characterized by mucosal sloughing on endoscopy.

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Management of Caustic Injury and Esophageal Stricture

39

Ryan C. Broderick and Karthik Ravi

Objectives

1. Differentiate between acidic and alkali caustic ingestion
2. Identify high-risk ingestions, classify CT and endoscopy grading of injury
3. Initial, mid-term, and long-term management of caustic esophageal injury
4. Recognize the definition, etiologies, and predictors of refractory benign esophageal strictures
5. Understand the efficacy of endoscopic therapy, stent placement, and esophageal self-dilation for recurrent benign esophageal strictures

Caustic Injury

Clinical Features

Epidemiology

Caustic ingestion is defined as accidental or intentional ingestion of a corrosive substance that can cause severe injury to the esophagus and stomach. Caustic ingestion is rare, with an incidence of 7.65 out of 100,000 ER visits. Comorbid mental and substance use disorders exist in 28% of patients. Most ingestions result in mild injury, however, 16% require admission, with 0.39% resulting in death. Risk factors for admission are advanced age, male gender, and comorbid psychiatric or substance use disorders. The most commonly ingested caustic material is a strong alkali. Strong alkalis include sodium hydroxide or potassium hydroxide (pH 13–14); these are commonly contained in drain cleaners, household cleaning products, and disc batteries. The terms "lye" or "caustic soda" refers to substances containing sodium or potassium hydroxide. Strong acids are less frequently ingested and are contained in toilet bowl or swimming pool cleaners, antirust compounds, and battery fluid. Common forms of these acids are hydrochloric acid, sulfuric acid, and phosphoric acid (pH 1–2, similar to stomach acid).

Pathophysiology and Mechanism of Injury

Ingestion of strong alkali results in acute, penetrating, liquefactive necrosis. Severe injury can occur within seconds of contact with esophageal mucosa and continues until buffered by tissue fluids. The injury can be transmural, particularly with solids which tend to adhere to the esophageal mucosa. Extensive transmural necrosis can present as perforation, mediastinitis, and death. Liquefactive necrosis occurs over 3–4 days, with extensive mucosal sloughing, ulceration, and vascular thrombosis of the esophageal wall. Over the next 2 weeks, the esophageal wall becomes progressively thinner with granulation tissue, fibrosis, and re-epithelialization occurring over 1–3 months. In the stomach, partial neutralization of the alkali with gastric acid results in more limited injury, with injury typically occurring only with large-volume ingestion. Duodenal injuries are uncommon with alkali ingestion.

Acid ingestion causes a superficial coagulative necrosis which thromboses the underlying mucosal blood vessels and forms a protective eschar. Acid solutions are less viscous than alkalis and pass to the stomach quickly. Additionally, acids cause severe pain upon immediate contact with the oropharynx, usually limiting the amount ingested. As a result, severe esophageal injury is less common than with alkali ingestion. Ingested acid in the stomach causes pyloric spasm and impairs emptying into the duodenum. Stagnant acid ingested in the stomach can cause prominent antral injury.

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Classification of Injury

Identifying a high-risk ingestion is critical. Severity depends on the material's pH, concentration, volume, composition, and contact duration. Strong acids range from pH 1–2 while strong alkali pH 13–14. An average "gulp" of fluid is 70–90 mL, with large volume caustic ingestion defined as >200–300 mL. Severe esophageal injury occurs more often in liquid preparations that coat a large mucosal surface area. Solid caustic materials can adhere to the esophageal mucosa and can cause severe deep burns. While alkali typically causes greater esophageal damage, severe acidic injury portends worse outcomes, including higher likelihood of ICU admission, systemic complication, and perforation with high mortality.

Once low versus high-risk ingestion is determined, further prognosis and treatment is dictated by severity of injury. Early endoscopic grading using the Zargar classification assesses injury and predicts complications. CT with IV contrast also provides an early indicator of the extent of tissue damage and may be more helpful to determine the need for emergent surgery (Table 39.1).

Initial Management

Evaluation

Clinical features can vary widely and may not portend the extent of esophageal or gastric injury. Fever, tachycardia, and shock suggest severe and extensive injury. Symptomatic patients with oropharyngeal burns or ingestion of material with a known high risk of esophageal injury are at higher risk of complications. History and exam should focus on the type and amount of ingested material, as well as possible ingestion of other drugs. Physical exam should include inspection of oropharynx, hypopharynx, neck, chest, and abdomen. High-risk features in the oropharynx include edema, erosions, and deep necrosis with pseudo membranes. Respiratory distress or severe oropharyngeal burns should be managed with early airway control and intubation. However, the absence of oropharyngeal burns does not rule out significant esophageal injury. Signs of perforation such as persistent retrosternal chest pain or abdominal rigidity with peritonitis and hemodynamic instability should prompt immediate surgery.

Table 39.1 Grading severity of caustic injury

Endoscopic assessment (Zargar classification)		
Grade 0	Normal	Low grade
Grade 1	Mucosal edema and hyperemia	
Grade 2a	Superficial localized ulcers, bleeding exudates	
Grade 2b	Deep focal or circumferential ulcers	High grade
Grade 3a	Focal necrosis with multiple deep ulcerations and small scattered areas of necrosis	
Grade 3b	Extensive necrosis	

CT with IV contrast assessment		
Grade 1	Normal	Low grade
Grade 2	Wall edema with surrounding soft tissue inflammation and increased post-contrast wall enhancement	High grade
Grade 3	Transmural necrosis as shown by the absence of post-contrast wall enhancement	

Initial labs should include CBC, lactate, complete metabolic panel, CRP, and a drug toxin screen. Labs should be repeated following admission in high-grade injury as initial results may not reflect severity of illness. Acidosis, high CRP, leukocytosis, renal failure, abnormal LFTs, and thrombocytopenia are predictive of transmural necrosis and associated with poor outcomes. Initial imaging should include CXR in patients with respiratory symptoms to rule out other etiologies and evaluate for subdiaphragmatic air, mediastinal widening, and hydropneumothorax. CT chest/abdomen with IV contrast is essential to evaluate the extent of injury. Evidence of necrosis include esophageal wall or periesophageal fat blurring and absence of esophageal wall enhancement.

Treatment

Induced vomiting or NG tube placement is contraindicated given the risk of aspiration. Attempts to neutralize pH are also contraindicated as they may induce thermal injury. Disc batteries can release alkali, cause local electrical current discharge, and result in direct pressure necrosis. When lodged in the esophagus, battery injuries can occur within 4 h and perforation within 6 h. Concentrated forms of detergents (e.g., capsules, gel packs, or pods) when lodged in the esophagus are much more likely to cause esophageal injury than household liquid detergent or bleach due to their concentration and ability to "stick" to esophageal mucosa. In these cases, urgent endoscopy for removal is required.

Patients with high-grade injury should be admitted to the intensive care unit for airway monitoring as 10% require intubation and mechanical ventilation. Emergency surgery is needed for signs of perforation and transmural necrosis on CT. Laparotomy or MIS exploration should be pursued depending on available surgical expertise. The goal of initial surgery is to resect all obvious transmural necrotic injuries, but reoperation is often needed for ongoing necrosis. Endoscopic vacuum therapy for focal perforation has been described to attempt preservation of esophageal patency, but data is limited. In severe injury, esophagogastrectomy with esophageal spit fistula may be necessary. In 20% of such cases, concomitant necrosis

requires excision of other organs such as the spleen, colon, pancreas, and small bowel. The mortality rate of these injuries is up to 65%. If necrosis is limited to the stomach, a total gastrectomy can be performed with preservation of native esophagus. One-stage reconstruction in emergency surgery is not recommended, with a delay of at least 6 months required to stabilize the injury.

Patients who do not present in extremis are typically managed medically. Asymptomatic patients without significant volume ingestion or oral burns receive a diet trial and can be discharged without upper endoscopy. Symptomatic patients or those with large-volume ingestion should be admitted. Supportive measures with respiratory support, IV fluids, and pain control should be initiated. IV PPI are given early, while antibiotics are reserved for suspected perforation. Corticosteroids are not recommended. Endoscopy within 24 h should be performed. Upper endoscopy can accurately grade the injury and predict the risk of stricture formation. Those with low-grade injury can be started on liquid diet with advancement and potential discharge within 24–48 h (Fig. 39.1).

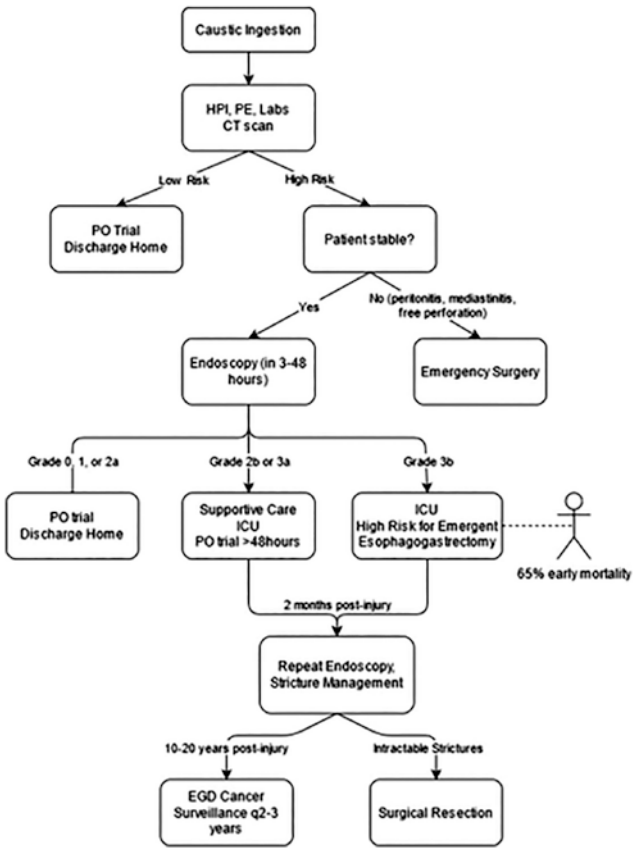

Fig. 39.1 Flow diagram for caustic ingestion management

Subsequent Management and Long-Term Sequelae

Medical Management

Patients with high-grade injury require inpatient monitoring for at least a week. Oral liquids are started after 48 h if the patient can swallow saliva. Otherwise, enteral nutrition support or even TPN should be considered early. Esophageal strictures develop in 70–100% of patients (Fig. 39.2) with Grades 2b and 3a injury on endoscopy, while Grade 3b injuries are associated with 65% mortality and often require esophageal resection in those who survive. Strictures develop within 2 months of ingestion, therefore repeat EGD is recommended at that time (Fig. 39.3). Endoscopic dilation is deferred until at least 6 weeks after initial injury. Dilation of caustic strictures have a higher perforation rate than other benign strictures and are more likely to be refractory. However, prophylactic esophageal stenting is not recommended.

Long-term complications also include bleeding, tracheobronchial or aortoenteric fistula, and esophageal cancer. Bleeding occurs within a few weeks of injury in 3% of patients. Fistula formation can occur at any time and requires a high index of suspicion. Squamous cell carcinoma of the esophagus is seen in up to 30% of patients after severe caustic ingestion, with a mean latency of 41 (range 13–71) years after injury. Surveillance endoscopy should be performed 10–20 years after initial injury and continue every 2–3 years.

Reconstructive Surgery

Surgical reconstruction is reserved for patients who survive emergency resection or fail endoscopic management. Reconstruction is highly complex and requires referral to a tertiary care center for a multidisciplinary approach. In severe cases, esophagectomy with esophagogastric anastomosis or colonic interposition may be required. If needed, colon interposition is typically in the retrosternal plane. Whether the remnant esophagus should be bypassed or resected is debated, as formation of cancer in the mucocele is weighed against morbidity in setting of severe mediastinal scarring. In the absence of significant gastric injury, gastric pull-up can potentially be achieved via Ivor-Lewis or transhiatal esophagectomy with cervical anastomosis depending on injury pattern, local resources, and expertise. Reconstruction has a high risk of complication, including leaks, strictures, and graft failure. Patient psychiatric comorbidity can also affect outcomes, making patient selection challenging. Most patients achieve nutritional autonomy with reconstruction, although functional outcomes are poor if combined pharyngeal reconstruction is needed.

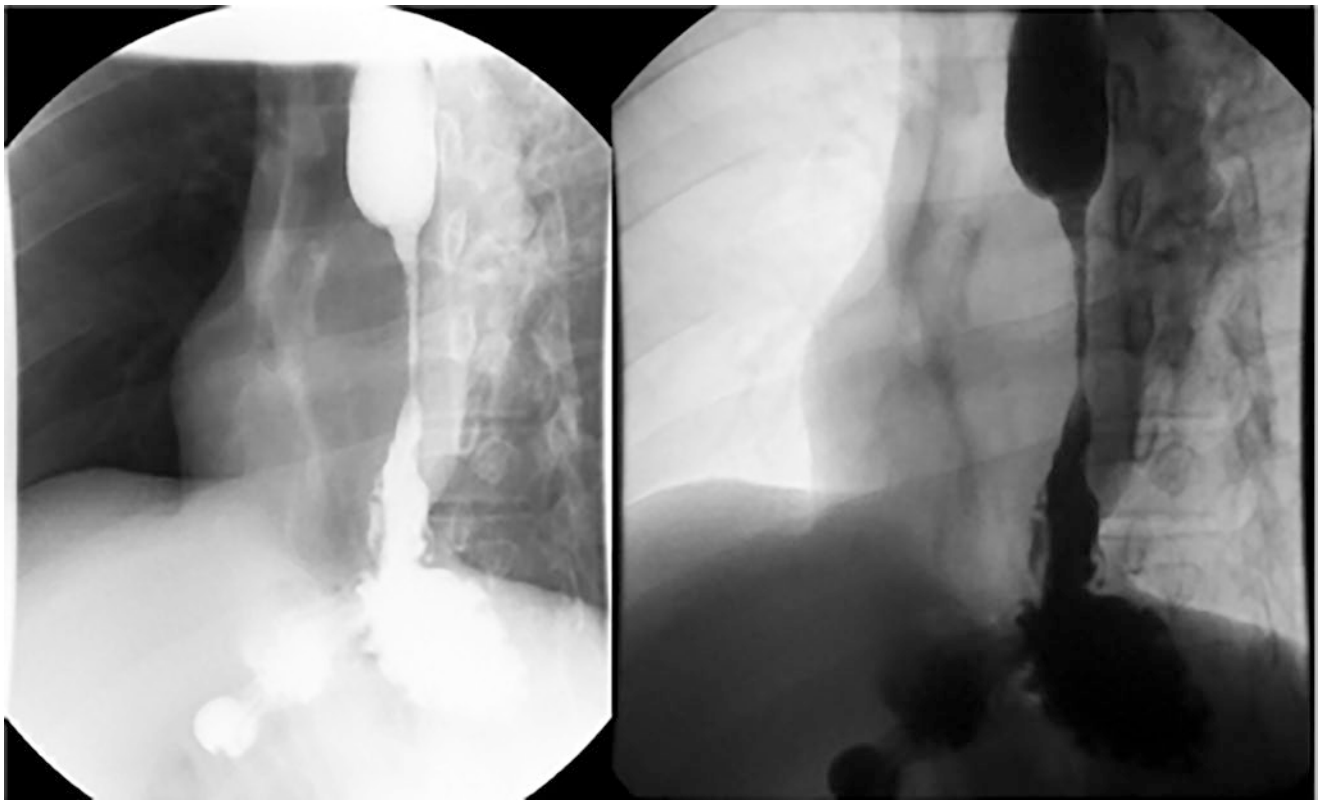

Fig. 39.2 Barium swallow of long mid-esophageal stricture

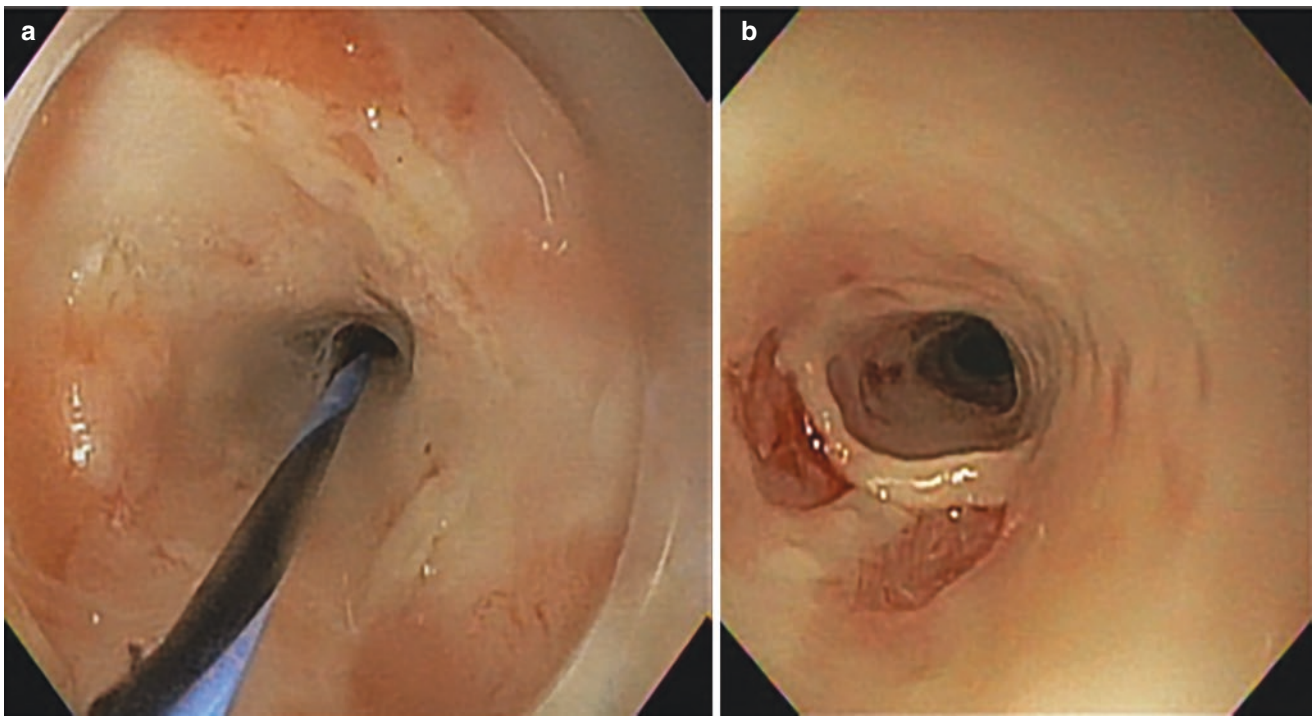

Fig. 39.3 Caustic ingestion stricture. Panel (**a**) demonstrates the stricture with wire in place; Panel (**b**) shows the stricture following endoscopic dilation

Management of Esophageal Strictures

Clinical Features

Etiology

Esophageal strictures are a common finding in patients with solid food dysphagia. Peptic strictures, Schatzki's ring, caustic ingestion, radiation, and anastomotic strictures are among the most common benign etiologies. In addition, malignant strictures related to squamous cell cancer or adenocarcinoma constitute an important consideration in patients presenting with progressive solid food dysphagia (Table 39.2). The diagnosis of an esophageal stricture is typically made during upper endoscopy. However, patients presenting with clinical features suggestive of a proximal esophageal stricture may require a barium esophagram as part of the initial evaluation prior to upper endoscopy.

Stricture Characterization

Strictures are characterized as simple or complex. Simple strictures are <2 cm in length, focal, straight, and allow passage of the standard upper endoscope. Most peptic strictures and Schatzki's rings fall are simple. In contrast, complex strictures are >2 cm, angulated, and do not allow passage of a standard upper endoscope. Radiation, anastomotic stricture, and caustic ingestion are common etiologies of complex strictures.

Table 39.2 Etiologies of esophageal strictures

Benign simple	Benign complex	Malignant
Peptic stricture	Post EMR/ESD	Adenocarcinoma
Schatzki's ring	Anastomotic	Squamous cell CA
EoE[a]	Caustic injury	
Lichen planus[a]	Radiation induced	
	NG tube trauma	

[a]Most often simple but can present as complex

Strictures are also categorized by their response to endoscopic dilation. Recurrent strictures are those in which a luminal diameter ≥14 mm is not maintained for at least 4 weeks after dilation. Refractory strictures are defined by an inability to achieve and maintain an inner diameter ≥14 mm over 5 endoscopic dilation sessions, typically occurring every 2 weeks. Complex strictures are more likely to be refractory.

Management of Benign Esophageal Strictures

Endoscopic Dilation

Endoscopic dilation is the initial therapeutic approach to benign esophageal strictures. Dilation is typically performed either with a through-the-scope (TTS) balloon dilator passed with or without a guidewire or with a wire-guided polyvinyl tapered dilater (bougie). To date, studies have not shown a difference in terms of therapeutic outcome or adverse events between TTS and bougie dilation. In clinical practice, a bougie dilation may be chosen for a proximal stricture while a TTS balloon dilation may be preferred for a tortuous mid or distal esophageal stricture. In complex strictures, fluoroscopic guidance is often utilized to ensure proper positioning of the dilator across the stricture regardless of whether a bougie or TTS balloon is used (Fig. 39.4).

In cases in which stenosis does not permit passage of a guidewire, a rendezvous approach can be employed. Typically, a pediatric upper endoscope is passed via an existing percutaneous gastrostomy tube while a standard upper endoscope is passed trans orally. Alignment of the 2 scopes is ensured by transillumination across the stricture and fluoroscopy. Recanalization is then achieved from above and below, typically with the sharp tip of a wire, following which dilation utilizing a guidewire can be accomplished. This approach is typically limited to shorter strictures given the need for transillumination to ensure alignment of both endoscopes (Fig. 39.5).

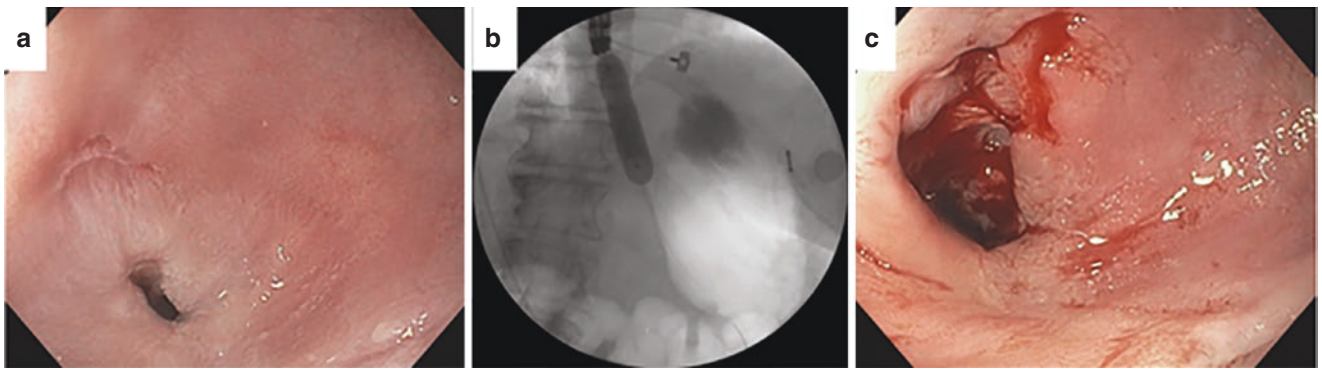

Fig. 39.4 TTS dilation of a peptic stricture with fluoroscopic guidance. Panel (**a**) depicts a 3 mm peptic stricture at the GE junction; Panel (**b**) demonstrates TTS balloon dilation to 15 mm with a guidewire under fluoroscopy; Panel (**c**) shows the stricture after the dilation

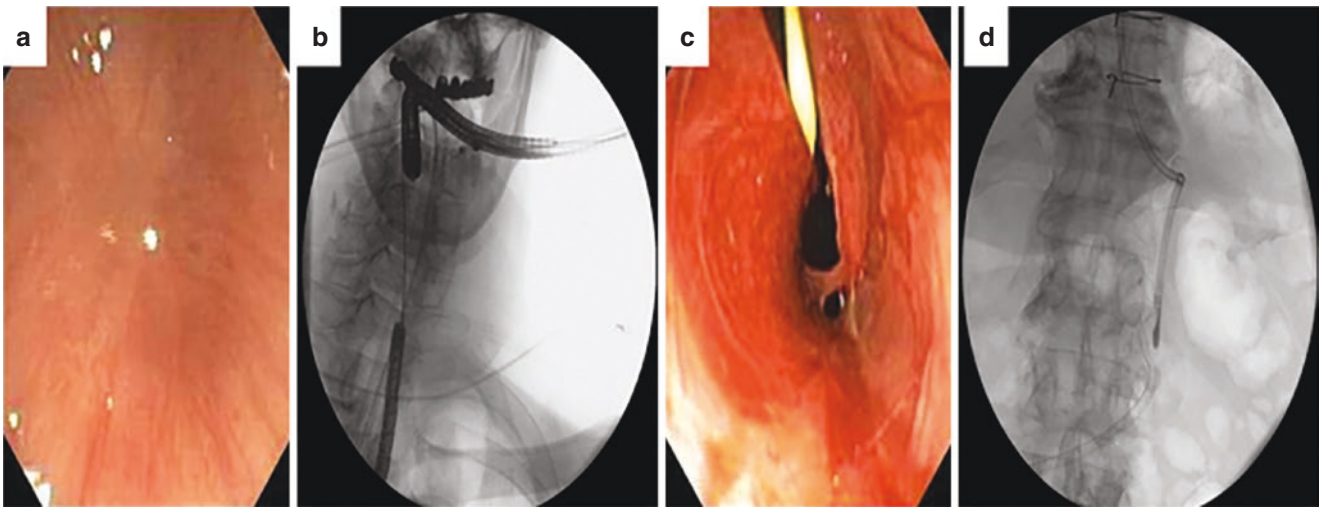

Fig. 39.5 Rendezvous dilation. Panel (**a**) depicts a completely occluded esophageal lumen; Panel (**b**) demonstrates alignment of the standard upper endoscope and the endoscope via the existing PEG tube; Panel (**c**) demonstrates recanalization using the share tip of the wire; Panel (**d**) demonstrates positioning of an NG tube across the stricture

Bleeding and perforation are the primary complications of endoscopic dilation, with a rate of roughly 0.5% or less reported in the literature. In order to minimize the risk of complications, the "rule of 3's" is generally employed, with no more than a 3 mm increase in luminal diameter during one endoscopic dilation session. However, there is no clear evidence that the rule of 3's reduces complications and studies have suggested that achieving a luminal diameter of 16 mm or greater during an endoscopic dilation session is more likely to result in a sustained therapeutic response. Ultimately, factors such as initial starting diameter, etiology, and stricture location should be considered when considering the risks and benefits of sequential dilation during an individual endoscopy session.

Endoscopic dilation has an initial therapeutic success rate of 80–90% in benign esophageal strictures, however, up to 30–40% of strictures recur within 1 year. For most simple strictures, a total of up to 3 endoscopic dilation sessions will result in sustained therapeutic success, with 5% or less failing to respond to 5 dilations or less. However complex strictures are more likely to fail endoscopic dilation and be termed refractory. In these cases, alternative therapeutic options should be considered.

Endoscopic Dilation with Steroid or Mitomycin C Injection

Steroid injection in conjunction with endoscopic dilation is thought to be an effective treatment in recurrent or refractory strictures by inhibiting the inflammatory response and thereby preventing recurrent fibrosis. In one randomized prospective study of patients with a recurrent peptic stricture, triamcinolone injection after dilation compared to sham reduced the need for repeat endoscopic dilation from 60 to 13%. Historically, therapeutic success for steroid injection has been ascribed to inflammatory strictures such as peptic strictures and esophageal lichen planus while results with more fibrotic strictures including radiation and anastomotic strictures have been mixed. However, recent studies have suggested that endoscopic technique may be important regardless of etiology. A randomized controlled trial of anastomotic strictures found greater efficacy with steroid injection with regards to number of dilations and dilation-free interval than previous studies, a result potentially related to steroid injection into areas of mucosal disruption after rather than before endoscopic dilation. While no standard protocol exists, triamcinolone 40 mg/mL is typically used with 4 quadrant injection of 0.5 mL aliquots into areas of mucosal disruption after dilation.

Mitomycin C is a chemotherapeutic agent which inhibits fibroblast proliferation and is used in clinical practice to reduce scar formation. As a result of its anti-fibroblast properties, its application following endoscopic dilation has been thought to be particularly effective in refractory fibrotic strictures such as radiation and anastomotic strictures. Further, there is evidence of its efficacy in caustic ingestion-related strictures. Mitomycin C is typically applied topically via a sponge or injection. In our practice, 4 quadrant injection of mitomycin C 0.4 mg/mL into areas of mucosal disruption in 0.5 mL aliquots following dilation is performed.

Endoscopic Incisional Therapy

Endoscopic incision therapy is accomplished utilizing an electrocautery needle knife. Typically, 4–8 radial incisions of the stricture are performed parallel to the longitudinal

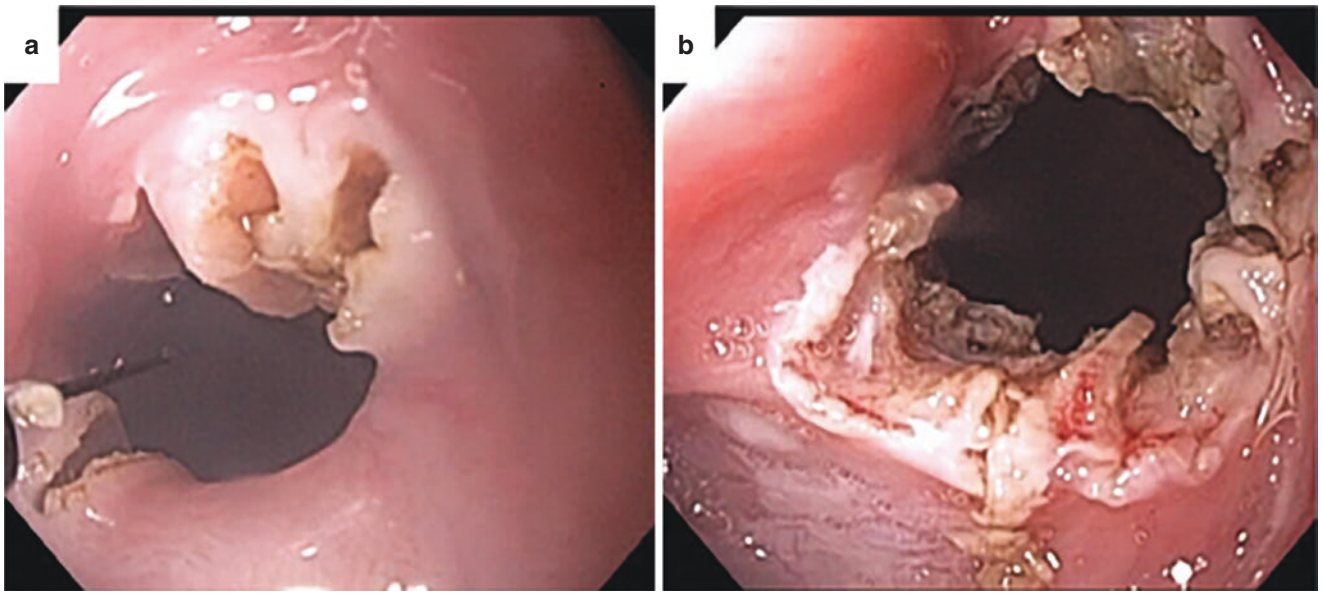

Fig. 39.6 Needle knife incisional therapy of anastomotic stricture. Panel (**a**) depicts electrocautery incision of the anastomotic stricture; Panel (**b**) demonstrates the completion of the incisional therapy following needle knife removal of intervening stricture between incisions

axis of the esophageal lumen. The intervening parts of the stricture between the incisions are then removed with the knife (Fig. 39.6). Endoscopic incisional therapy is particularly useful in short stricture with an associated ridge or shelf and often, is not technically feasible in longer complex strictures. Endoscopic incisional therapy was first described in patients with recurrent Schatzki's rings, with multiple studies showing that both initial response and durability were superior to endoscopic dilation. More recently, anastomotic strictures have become a growing therapeutic target for this approach. Some studies have suggested that patients with refractory esophagogastric anastomotic strictures treated with electrocautery needle knife have symptomatic response in over 90% of cases, with the majority demonstrating durable response for 1 year or greater. However, endoscopic incisional therapy should be reserved for patients with recurrent or refractory esophageal strictures, as no benefit over endoscopic dilation has been found in treatment of naïve patients.

Esophageal Stents

While steroid or mitomycin C injection and endoscopic incisional therapy can be effective in recurrent or refractory strictures, if these approaches fail, then esophageal stent placement is often considered. Unlike esophageal dilation, esophageal stents can be left in position for 4–12 weeks. Self-expanding plastic stents are FDA approved for benign refractory esophageal strictures. However, in clinical practice, the use of such stents is limited by the large diameter of the delivery system and high rates of migration with a relatively low rate of durable therapeutic success. Uncovered metal stents are typically not used for benign refractory esophageal strictures due to high risk of adverse events including erosion, bleeding, stent embedment, and risk of stent-associated esophagorespiratory fistula (SERF). Partially covered metal stents have been used with limited success. However, in clinical practice, placement of these stents can be complicated by tissue ingrowth or overgrowth. Further, stent embedment can make removal challenging with risk of perforation or tear. To mitigate this, a "stent in stent" technique has been described in which a fully covered stent is placed within the embedded partially covered stent for 10–14 days. This results in necrosis of the ingrown tissue and allows removal of both stents. Biodegradable stents maintain radial force for 6–8 weeks and disintegrate over 8–12 weeks, thereby eliminating risks related to stent removal. However, adverse events are still reported in 20–25% of cases and limited studies to date have yielded disappointing results overall. Biodegradable stents are not currently available in the United States.

Currently, the best evidence for esophageal stent placement for benign strictures is with fully covered metal stents. Studies have shown that compared to other stents, fully covered metal stents have the highest rate of durable success and lower complication rates, thus making them the preferred stent for benign refractory esophageal strictures. However, placement of these stents still carries risk of tracheoesophageal fistula formation and is contraindicated in cervical esophageal strictures. Further, migration rates are reported as high as 40%. To minimize the risk of migration, stent posi-

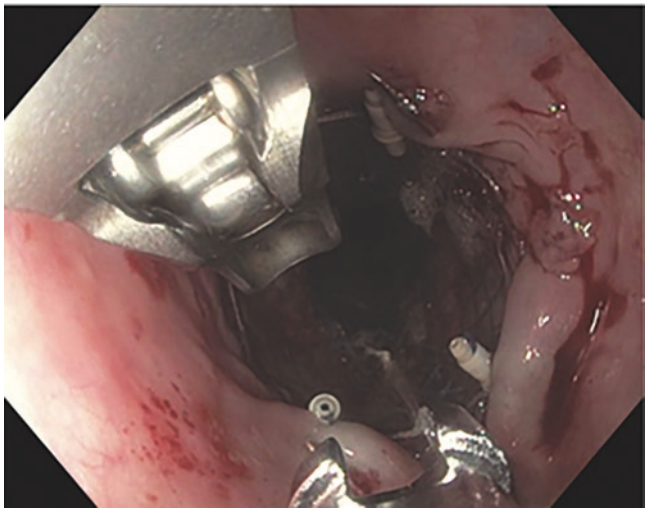

Fig. 39.7 Anastomotic stricture with self expanding metal stent positioned across and secured via endoscopic suturing

tion is often secured with clips or endoscopic sutures (Fig. 39.7). However, success rates are relatively low at 30–40%, with recurrence as high as 40%.

Self-Dilation

In patients with benign refractory strictures, esophageal self-dilation is another therapeutic option. Initially, endoscopic serial dilation is performed to achieve an esophageal luminal diameter of 10–18 mm. In our practice, this consists of dilations every 2–3 days with a goal diameter of 14 mm or greater. Immediately after achieving this, patients are educated to pass a malleable tungsten-filled polyvinyl dilator with tapered ends orally with the goal of preventing restenosis. The chosen dilator is sized 2–3 mm less than the achieved luminal diameter, and the insertion distance is measured by adding 10 cm to the distance from the incisors to the distal end of the stricture. Patients will typically pass the dilator twice daily for a week and then once daily. While most patients require daily passage of the dilator indefinitely, in some patients the interval can be extended out to up to a weekly or biweekly over time.

This technique is most effective for proximal and straight strictures, with failure more likely in distal and angulated strictures. Among patients with appropriate anatomy, patient acceptance is excellent, with less than 10% either declining or failing education in our experience. Similarly, self-dilation is safe, with bleeding being the most common reported complication and seen in approximately 5% of patients. Overall outcomes appear to be excellent, with removal of an existing percutaneous gastrostomy tube in 85% of patients, along with eliminating the need for dilation for at least 1 year for virtually all patients in our clinical experience.

Management of Malignant Esophageal Strictures

Esophageal Stents

In patients with malignant esophageal strictures, endoscopic dilation is limited by the risk of perforation and a short duration of response and consequently, is not typically employed in this setting. Esophageal stent placement results in relief of dysphagia within 24–48 h with reasonable cost and high technical success rates. However, stent placement may not be possible in proximal strictures and may bridge the gastroesophageal junction in distal strictures, resulting in nausea, pain, and uncontrolled reflux. Further, up to one-third of patients will have recurrence after stent placement. Additionally, stent placement is associated with a significant adverse event rate of 30–35%, including stent migration to esophagorespiratory fistula (SERF).

Studies have demonstrated that plastic and metal stents have similar rates of dysphagia improvement in malignant esophageal strictures. However, plastic stents are more likely to be subject to technical failure, complicated by stent migration, become occluded by tissue ingrowth or overgrowth and have an overall higher rate of associated adverse events. Consequently, partially or fully covered self-expanding metal stents are typically preferred (Fig. 39.8). Partially covered metal stents may be preferred in patients with unresectable esophageal cancer, particularly those undergoing palliative chemoradiation, with lower rates of tumor ingrowth reported. Fully covered metal stents are often considered in patients with locally advanced esophageal cancer. However, response to radiation therapy is robust and typically seen within 2 weeks in this population, explaining stent migration

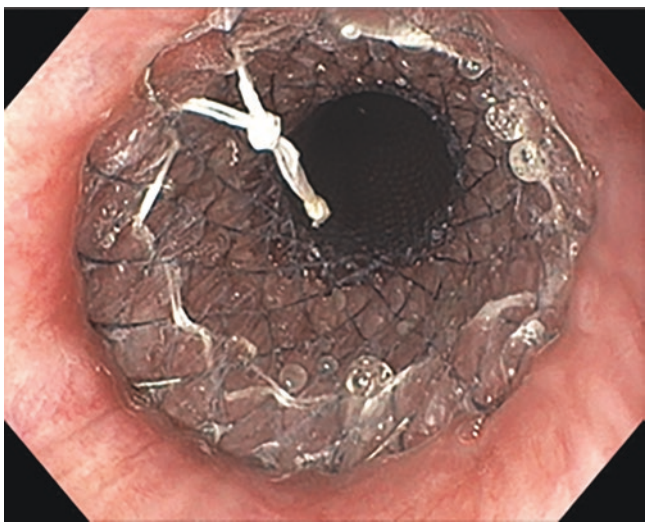

Fig. 39.8 Malignant stricture with self expanding metal stent in place

rates as high as 30% in such patients. Consequently, we reserve stent placement for patients unable to receive radiation or with near complete obstruction.

Debulking Endoscopic Therapy

Argon plasma coagulation (APC) can be used to debulk malignant esophageal tumors, thereby improving dysphagia in the majority of treated patients. Spray cryotherapy utilizes liquid nitrogen which, when applied to neoplastic tissue, results in immediate oxidate cell death and tumor debulking with thawing. The use of Nd:YAG laser or injection of absolute alcohol to debulk esophageal malignant tumors has been described as well. However, reports of efficacy with these techniques are largely limited to case series. Photodynamic therapy was previously described for palliation, but this is no longer used in clinical practice due to the risk of severe photosensitivity.

Questions

Question 1.

1. What is the long-term risk of esophageal cancer after high-grade caustic ingestion?
   A. 1%
   B. 30%
   C. 50%
   D. 90%

Answer: B. Squamous cell cancer occurs in up to 30% of patients after severe caustic ingestion and surveillance endoscopy beginning 10–20 years after injury is recommended.

Question 2.

2. A 60-year-old gentleman with prior history of Siewert Class II T3N1 gastroesophageal junction adenocarcinoma treated with neoadjuvant chemoradiation followed by Ivor Lewis esophagectomy 1 year ago presents with persistent dysphagia. A barium esophagram demonstrates a 3 cm long, angulated anastomotic stricture with an estimated inner diameter of 7 mm. Upper endoscopy with TTS balloon dilation is performed every 2 weeks over a total of 5 sessions with failure to achieve a luminal diameter greater than 10 mm. Which of the following most improve dysphagia and reduce the need for repeat endoscopic treatment?
   A. Triamcinolone 40 mg/mL in 0.5 mL aliquots injected in 4 quadrants prior to bougie dilation
   B. Triamcinolone 40 mg/mL in 0.5 mL aliquots injected in 4 quadrants prior to TTS balloon dilation
   C. Placement of an uncovered metal stent
   D. Esophageal self-dilation

Answer: D. Self-dilation for refractory benign esophageal strictures has demonstrated efficacy in improving dysphagia and reducing the number of endoscopic repeat dilations needed. Triamcinolone injection into areas of mucosal disruption following rather than prior to TTS dilation appears to have more efficacy for anastomotic strictures. Covered metal stents are preferred for benign refractory esophageal strictures.

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Management of Esophageal Perforation

40

Christy M. Dunst and Timothy Mansour

Introduction

Esophageal perforation is a condition with a broad range of causes and presentations but universally poor outcomes unless treated in an expedient and thoughtful manner. The first description of esophageal perforation came from Herman Boerhaave in the 1720s with the first successful surgical repair performed by Norman Barrett in 1947 [1]. Since then, the management options have evolved considerably. With the advent of numerous percutaneous, endoscopic, and operative techniques, now more than ever, a provider treating esophageal perforations must have an intimate understanding of the anatomy, pathophysiology, and techniques in order to select and perform the appropriate life-saving treatments. Despite the complexity of treatment choices, the primary principles of treatment apply regardless of etiology or severity. The aim of this chapter is to discuss esophageal perforation in detail and provide a framework of guiding principles of management that are applicable to any scenario.

Etiology

The most common cause of esophageal perforation is iatrogenic, with up to 60% of cases associated with endoscopy. While diagnostic flexible upper endoscopy has a very low perforation rate (<0.1%), therapeutic endoscopy is becoming increasingly common and can have perforation rates much higher (up to 15%) depending on the specific intervention and the underlying pathology. Additional causes of esophageal perforation include foreign body ingestion, caustic ingestion, trauma, and malignant perforation.

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Boerhaave's syndrome is a unique pathophysiologic phenomenon that deserves special mention. Boerhaave's syndrome refers to a specific scenario in which there is a rupture of the distal esophagus at the gastroesophageal junction in the setting of induced rapid elevation in intra-abdominal pressure such as in retching or in association with other causes of sudden and vigorous Valsalva [2]. Boerhaave's perforations are generally associated with the presence of a hiatal hernia. The theory is that a rapid increase in intra-abdominal pressure is transmitted to the hernia, which, by definition, is exposed to negative intra-thoracic pressure. This rapid and forceful transmission across a pressure gradient leads to a perforation at or near the gastroesophageal junction and on the left side of the distal thoracic esophagus.

Presentation

With an increasing percentage of esophageal perforations due to endoscopy, one may expect that the majority of these injuries present early and therefore receive prompt treatment. However, up to half of all cases still present greater than 24 h after symptom onset and 25% of cases present with sepsis at the time of presentation [3]. The presentation of esophageal perforations is variable based on the location of the perforation and extent of contamination. The key to early diagnosis is a high level of suspicion in individuals with recent history of forceful emesis, exposure to ingested foreign body, endoscopy, or other esophageal intervention. Systemic signs of sepsis may be present with perforation at any level of the esophagus and include fever, tachycardia, tachypnea, leukocytosis, and varying levels of circulatory shock. Cervical perforations may present with neck pain, difficulty swallowing (either dysphagia or odynophagia), or dysphonia. Hemoptysis or hematemesis may also be present. Crepitus due to subcutaneous emphysema may be appreciated on physical exam. Intra-thoracic perforations are present commonly with chest or back pain, dyspnea, or emesis. Mediastinitis may also cause the sensation of heart

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palpitations and may present with arrhythmia. Perforations of the abdominal esophagus present signs similar to perforation of other hollow viscous structures of the abdominal cavity: nausea, vomiting, abdominal pain, and peritonitis. In fact, the finding of pneumoperitoneum on imaging may prompt negative operative exploration if the index of suspicion for esophageal perforation is not high enough to prompt a thorough examination at the hiatus.

Diagnosis

The goal of the workup of a suspected esophageal perforation is to document the presence, location, and extent of a full-thickness defect in the esophageal wall and evaluate the degree of contamination in the surrounding tissue. No single test is sufficient to achieve these goals routinely and in almost all cases, numerous tests will be required to obtain a complete understanding of the injury.

Plain film radiography is rapid, inexpensive, and may provide some insight into the case of known or suspected esophageal perforation. It is a blunt instrument, however, and typically is able only to demonstrate large volumes of air or fluid that have distributed through a perforation into adjacent tissues or body cavities, often missing more subtle injuries. In the setting of cervical perforation, this may manifest as air tracking in the soft tissues of the neck. In thoracic perforations, pleural effusions or the presence of hydropneumothorax may be seen. Abdominal perforations may present with free air in the abdomen on an upright or lateral decubitus film. Importantly, what appears to be extraluminal air around the esophagus radiographically is insufficient alone to confirm the diagnosis of an esophageal perforation even when localized to the mediastinum.

The gold standard imaging modality for the diagnosis of esophageal perforation is oral contrast esophagram either by fluoroscopy or computed tomography (CT) scan. An esophageal contrast examination is necessary to confirm a full-thickness injury, to identify the location of the perforation, and to direct the next steps in management. Our preference is soluble contrast fluoroscopic esophagram in most cases to get the clearest view of the extent of the defect, particularly in stable patients with early presentations. Fluoroscopic contrast esophagram provides a dynamic image of the esophagus in relation to surrounding landmarks, which can be very useful for further planning for potential surgical or endoscopic approaches. When a perforation is present, the contrast can be followed to see whether it flows freely into adjacent body cavities or remains contained in a space adjacent to the esophagus and to what extent. In some contained injuries, the contrast can empty back into the esophageal lumen. Additionally, due to the lower dose of radiation, fluoroscopy is better suited for repeat evaluation to determine efficacy of interventions and ultimately evaluate healing and readiness for initiation of an oral diet. Water soluble contrast should be used initially but can be followed by thin barium contrast to increase sensitivity if necessary.

Unfortunately, the quality of the fluoroscopic esophagram images is operator-dependent and small contrast extravasations can be missed if appropriate complete images are not obtained. In the absence of a skilled fluoroscopic radiologist, CT scans provide a more reliable 360° image of the esophagus and are widely available even in more remote areas. Recent studies have shown that as an initial test for esophageal perforation, CT with oral contrast has higher sensitivity, specificity, and negative predictive value than traditional fluoroscopy [4]. Therefore, CT imaging is typically the preferred diagnostic modality due to widespread availability, rapidity of the test, and the ability to concurrently evaluate the surrounding contamination. It is not uncommon for a critical perforation to have a screening non-contrast CT scan upon presentation. It can demonstrate subcutaneous air, pneumomediastinum, pleural effusion, esophageal wall thickening, mediastinal fluid, or inflammation, however, once the perforation is suspected, contrast imaging is required to confirm the diagnosis and quantitate the injury (Fig. 40.1). For example, it is not uncommon for non-contrast CT to show extensive mediastinal air in even small, observable esophageal perforations after endoscopic manipulation or for a pulmonary bleb rupture to result in air tracking within the mediastinum, leading to initial misdiagnosis. This latter scenario is particularly misleading in the clinical setting of retching and emphasizes the importance of a contrast study.

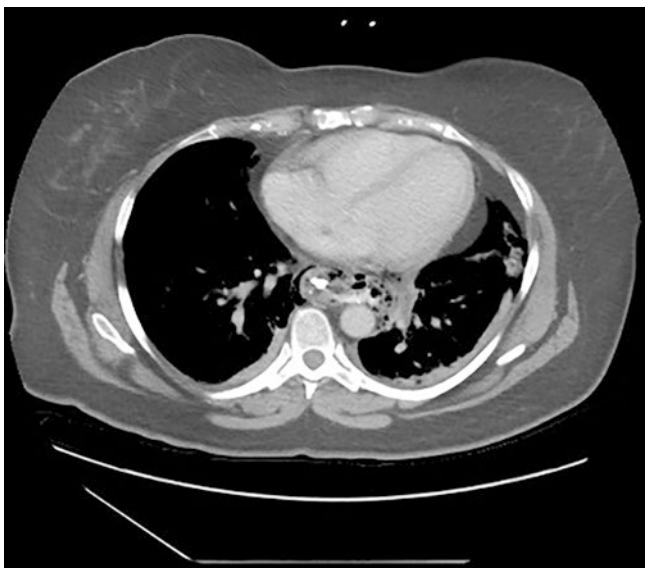

Fig. 40.1 A CT image of thoracic esophageal perforation with distribution of contrast and air into the mediastinum and left pleural space

There are some clinical scenarios where a contrast examination is contraindicated. While contrast can be administered via a carefully placed proximal nasogastric tube in the incapacitated patient, direct endoscopy may be safer and is often more useful in this scenario.

Endoscopy provides unique diagnostic information in the setting of esophageal perforation in experienced hands. Direct visualization allows for in-depth evaluation of the location and extent of an injury as well as the quality of the mucosa and surrounding tissues. Endoscopy allows for assessment of underlying pathology (such as tumor or stricture) that may influence definitive intervention. In many cases, the definitive intervention may be performed at the time of endoscopy in appropriately selected patients. Endoscopic evaluation in the setting of esophageal perforation should be performed with some caution though. Insufflation should be used sparingly to prevent unnecessary dissection of extraesophageal tissue planes and, in the setting of communication with the pleural space, chest drainage should be achieved, or at least anticipated prior to endoscopy to prevent the development of tension physiology with air insufflation. Carbon dioxide insufflation substantially decreases this risk and should be used whenever possible.

Guiding Principles for Management

The high mortality rate associated with esophageal perforation has long been recognized. For decades, early and aggressive surgery remained the cornerstone of therapy. However, in 1979, John Cameron published criteria for non-operative management of esophageal perforations. Patients who did not necessitate open debridement and drainage, with or without repair, met the following requirements: (1) The esophageal disruption should be well contained within the mediastinum or between the mediastinum and visceral lung pleura. (2) The cavity should be well drained back into the esophagus. (3) Minimal symptoms should be present. (4) There should be minimal evidence of clinical sepsis [4].

Since Cameron's original publication, innovative medical technology has developed at an incredible rate facilitating substantially expanded the criteria for "non-operative" management of esophageal perforations. The Pittsburgh Severity Score (PSS) was developed to objectify and guide these critical clinical decisions. The PSS uses a combination of 10 clinical variables to create a composite score of 0–18 (Table 40.1). In their retrospective review, they demonstrated that patients with lower scores underwent higher rates of successful non-operative management and had lower morbidity and mortality than those with higher scores. Additionally, they found that patients with low scores who were managed operatively had worse outcomes than those with similar scores who were managed non-operatively [5].

Table 40.1 Pittsburgh Severity Score (PSS) criteria

PSS variables	Score
Age >75 years	1
Tachycardia >100 beats per minute	1
Leukocytosis >10,000 WBC/mL	1
Pleural effusion on chest X-ray or CT	1
Fever >38.5 °C	2
Noncontained leak on CT or esophagram	2
Respiratory compromise (respiratory rate >30 or mechanical ventilation)	2
Time to diagnosis >24 h	2
Cancer	3
Hypotension	3
Total potential score	18

Follow-up studies have had mixed results in confirming the prognostic ability of the score, but most agree that it is a useful tool that should be employed when considering various treatment pathways [6].

Regardless of severity of injury or available resources, successful management of confirmed esophageal perforations can be simplified to addressing these three guiding principles:

1. **Resuscitation and control of sepsis.**
2. **Diversion of the salivary stream.**
3. **Nutritional support.**

Principle #1) Resuscitation and Control of Sepsis

The degree of sepsis upon presentation is often the most important factor in determining treatment and predicting outcome. The general principles of resuscitation and supportive critical care in the septic patient will not be addressed here specifically as they are not unique to esophageal perforation. However, while the patient is being stabilized, plans to achieve source control are paramount. Primary source control refers to addressing the injury itself as well as addressing the infectious repercussions in surrounding tissues. All patients with suspected esophageal perforation should receive prompt initiation of broad-spectrum antibiotic therapy with consideration for additional antifungal agents depending on clinical suspicion prior to radiologic confirmation. The spectrum should remain broad until the patient's condition improves or it can be tailored based on culture data [7]. Antibiotics alone are often sufficient for patients with minimal contamination. Besides the perforation itself, which will be addressed separately, the primary driver of persistent sepsis in patients is undrained fluid collections and associated necrotic tissue. Early, and often serial, CT scans are frequently required to diagnose, quantify, and monitor such secondary infections. Patients who are well-appearing and have minimal clinical

sepsis typically will respond well to having fluid collections managed with the least invasive approach, such as percutaneous drainage. Patients who are more severely septic or showing declining clinical status need a more aggressive approach. This may mean escalation to a more invasive treatment strategy, but not always, as long as the next strategy is effective (such as additional drains). However, at any point along the course of a minimally invasive treatment strategy, if a patient develops worsening sepsis, then alteration to a definitive surgical approach should be considered. *Overall, the tenants of controlling sepsis from an esophageal perforation are (1) identifying and treating sources of infection early and effectively, (2) frequently assessing status with clinical and radiographic surveillance, and (3) escalating care expeditiously when necessary.*

Principle #2) Diversion of the Salivary Stream

The goal here is to prevent saliva and any other esophageal contents from exiting the lumen across the injury. Successfully diversion prevents ongoing contamination and allows for the perforation to heal. The factors that will determine the way this can be accomplished include the time to diagnosis, mechanism of perforation, the extent of the injury, underlying pathology, and clinical condition. Patients with very small defects with a contained leak may not require interventional diversion as limiting oral intake is sufficient. Some practitioners choose to provide oral antimicrobial agents (chlorhexidine or other) to further minimize risk. Although rarely required, in large injuries presenting with severe sepsis, the ultimate salivary diversion is a cervical esophagostomy (spit fistula). The remainder (and majority) of perforations exist along the spectrum between these extremes and require a more thoughtful approach. Selection and considerations for various techniques will be discussed in detail later in the chapter.

Principle #3) Nutritional Support

The final critical consideration in management of patients with an esophageal perforation is establishing adequate nutritional support. The benefits of enteral nutrition in the septic patient are well documented and early enteral nutrition should be the goal. Prompt consideration of nutrition ensures that the patient will be well supported from the beginning to maximize healing. Nutritional foresight avoids additional procedures later that may be more difficult due to the status of the injury itself or from treatments already rendered limiting access such as a laparotomy or placing an endoscopic tube through a fragile repair. Some patients with small defects that are either observed or repaired primarily via a surgical or endoscopic approach may be able to resume oral intake within a matter of days and feeding tube placement can be avoided. For patients who are not anticipated to require an extended period of time without oral intake, temporary access measures such as nasoduodenal tube may be adequate to administer tube feeds. These tubes, however, are uncomfortable and prone to displacement, so if the patient is to require access for a matter of weeks, then a percutaneous access is preferred. For patients treated with covered stents, documentation confirming that the stent is well seated without migration and provides adequate diversion of the salivary stream prior to resumption of oral alimentation with a pureed diet is required. Total parenteral nutrition can be used sparingly if needed to avoid prolonged nutritional depletion in patients expected to heal within 1–2 weeks or if they are already malnourished at the time of perforation. For patients for whom prolonged nutritional support is expected, a surgically placed feeding jejunostomy is generally preferred. Gastrostomy feeding can be used in some patients but only after thoughtful consideration. If there is confidence that the patient will not require the stomach for reconstruction at some point (i.e., after an esophagectomy), then gastrostomy is an option. However, an important concept remains that gastric feeding can only be accomplished if the injury is protected from reflux with an intact gastroesophageal reflux barrier. This can occur either naturally in a patient without hiatal hernia or in the presence of a functioning antireflux surgery. Otherwise a post-pyloric jejunal extension tube can be used but only if concurrent gastric decompression not needed as well. Esophageal protection can also be accomplished by surgical diversion in extreme cases. Importantly, gastrostomy feeding tubes often do not work well when combined with a stent that has been placed across the gastroesophageal junction or fundoplication which leads to severe reflux. If the stent cannot be adjusted due to the location of the injury, these patients often require a jejunostomy tube. After there is clinical and radiographic evidence that the perforation has healed, then an oral diet can be initiated, nutritional support can be weaned, and devices removed.

Management of Esophageal Perforations

With advanced imaging technology, minimally invasive surgery, interventional radiology, and therapeutic endoscopy, many patients are successfully managed without the morbidity associated with traditional open surgery. Presently, there is not a simple "gold standard" one size fits all management strategy for the singular diagnosis of "esophageal perforation". A stable patient may benefit from a less interventional, often more thoughtful and even creative approach, while a patient in extremis needs expedient care tailored to imminently present resources. Urgency of care is guided by the

Table 40.2 Treatment modalities for consideration in the treatment of patients with esophageal perforations

	Observation/ medical	Interventional radiology (IR)	Flexible endoscopy	Minimally invasive surgery (laparoscopy/thoracoscopy)	Open surgery (laparotomy/ thoracotomy)
Diversion of salivary stream	NPO	Percutaneous drain placement	• Primary closure of defect with endoscopic clips or suturing • Placement of temporary stents • Endo-vac therapy	• Primary closure of defect • Distal division • Esophagectomy	• Primary closure of defect • Proximal diversion with cervical esophagostomy • Distal division • Perform adjunctive muscle flaps • Esophagectomy
Control of surrounding contamination	IV Antibiotics	Percutaneous drain placement	• Translumenal lavage • Endoscopic drain placement (transillumenation assisted percutaneous drains double J stents) • Endo-vac therapy	• Surgical irrigation and drainage • Placement of drains	• Surgical irrigation and drainage • Placement of drains
Nutritional support	• Monitored oral diet • TPN	Percutaneous feeding tube placement	• Well positioned covered stent • Percutaneous gastrostomy tube +/− post pyloric jejunal extension • Percutaneous proximal jejunostomy tube	• Feeding jejunostomy tube • Gastrostomy tube	• Feeding jejunostomy tube • Gastrostomy tube

patient's clinical status but the precise approach can vary widely. The decision on how to approach each of the three guiding principles depends on the skills and resources available at the presenting facility as well as patient acuity. The condition and extent of injury of the patient determine the urgency and therefore, it is perfectly reasonable to utilize a more aggressive approach if the clinical situation demands immediate action. Resources notwithstanding, the overall goal in management should be to perform the most effective treatments in the least invasive way possible to decrease long-term morbidity. Physicians must rely heavily on sound clinical judgment to create the treatment strategy best suited to each unique injury scenario with close monitoring and a willingness to escalate care in accordance with the patient's clinical status. In nearly all circumstances, patients with esophageal perforations should be transferred to an experienced tertiary center with adequate resources to address these complex patients as timing of source control is critical to patient outcomes. Most hospital systems and physicians recognize this and will transfer a patient with esophageal perforation to a tertiary center if they need intervention beyond observation after stabilization (Table 40.2).

Conservative Management

True "non-operative" management is uncommon as many of the patients who present with perforation will require a procedure of some kind. Therefore, we prefer the term "conservative/medical management" for the cohort of patients who do well without procedural interventions. These patients typically present early in the clinical course and have small injuries. If the patient is stable with minimal symptoms and the contrast study shows a contained contrast extravasation (contrast extends minimally beyond the wall of the esophagus, does not involve adjacent body cavities, and does not create a fluid collection that prohibits the contrast from freely returning to the lumen), they can be observed without formal diversion of the salivary stream. Recommended treatment includes hospital admission, nothing by mouth, broad spectrum IV antibiotics, serial infectious indicator blood work, and a follow-up contrast (or potentially endoscopic) examination to confirm healing. If there are no significant fluid collections away from the injury, IV antibiotics will generally be sufficient to control surrounding contamination. Oral diet can be resumed after serial contrast study confirms adequate healing. Soft or liquid diet for a period of time appropriate to clinical suspicion is routine (typically 3–10 days depending on scenario). TPN should be considered if more than a few days of nutritional depletion is expected. If the patient has not resumed oral alimentation by approximately 1 week but is still responding favorably to conservative management, an alternative feeding tube should be considered. Any worsening of symptoms or condition should prompt additional objective evaluations and escalation to an interventional approach.

Interventional Radiology Management

Interventional radiologists often play a key role in the care of patients with esophageal perforations. Most commonly, IR techniques are used to control surrounding infections by draining retained collections after other treatment modalities

have achieved salivary diversion. Although IR interventions most commonly supplement other procedures, there are times when these techniques provide the only necessary treatment. In some circumstances, percutaneous drains placed as close to, but typically not into, the injury are the only necessary intervention. While a more definitive direct esophageal salivary diversion is more expeditious, a well-placed drain alone can be enough to control the sepsis and divert the salivary stream in circumstances where the patient is clinically stable and external drainage is required. The esophageal mucosa will typically heal rapidly in these situations as long as they are kept nil per os. In some cases, the mucosa heals by forming a tract around the drain, creating an eventual spit fistula. These long, thin tracts will typically heal if surrounding contamination is also well drained and the volume is relatively low, either from a small injury or from an injury that also has upstream diversion (spit fistula or covered stent). Lastly, in some centers, the interventional radiologist can place percutaneous feeding tubes if necessary.

Flexible Endoscopic Management

The management of esophageal perforation with endoscopy has grown exponentially in the past few decades. As devices and proficiency in employing them have improved, so have their chances of success. These techniques can be grouped into three major categories: stenting, drainage, and defect closure.

Stenting is the most commonly used and most well-studied endoscopic intervention for esophageal perforation. Self-expanding metal stents were first introduced in the 1990s for the treatment of malignant strictures. Since fully covered versions of these stents became available, they have been applied with increasing frequency for perforations and anastomotic complications as well. Stenting can reliably divert saliva from esophageal defects of varying locations and sizes. As long as adequate external drainage is achieved, this can allow for healing and contracture of the defect. The key technical aspects of stent placement are selecting the appropriate diameter and length of stent such that it abuts the lumen of the circumference of the esophagus and covers the entirety of the defect, ensuring adequate proximal and distal landing zones to allow for an adequate seal and preventing stent migration. To allow for an adequate seal, the proximal flange of the stent should ideally be at least five centimeters proximal to the defect. Fluoroscopy can aid in positioning the stent and/or it can be visualized endoscopically throughout deployment (Fig. 40.2).

In a retrospective study, Freeman et al. found that stent failure was much more likely in the setting of one of the following situations: proximal cervical location of the leak, gastroesophageal junction location of the leak, or defect size greater than 6 cm [8]. This is likely because the most proximal and distal esophagus are the most challenging locations to get an adequate seal.

Once the stent is in place and ongoing leakage has been ruled out with a contrast study, a diet can be initiated. Full liquids and most soft foods are usually tolerated well. Stents

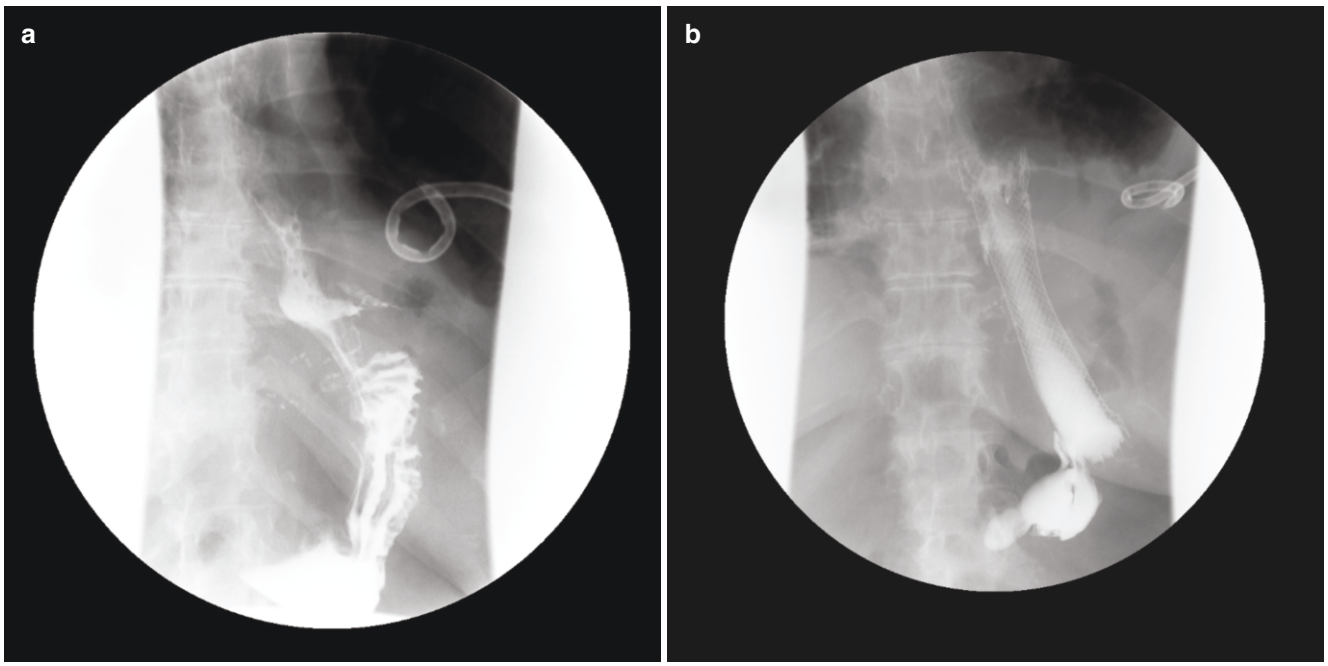

Fig. 40.2 Contrast esophagram before (**a**) and after (**b**) stenting of a distal thoracic perforation

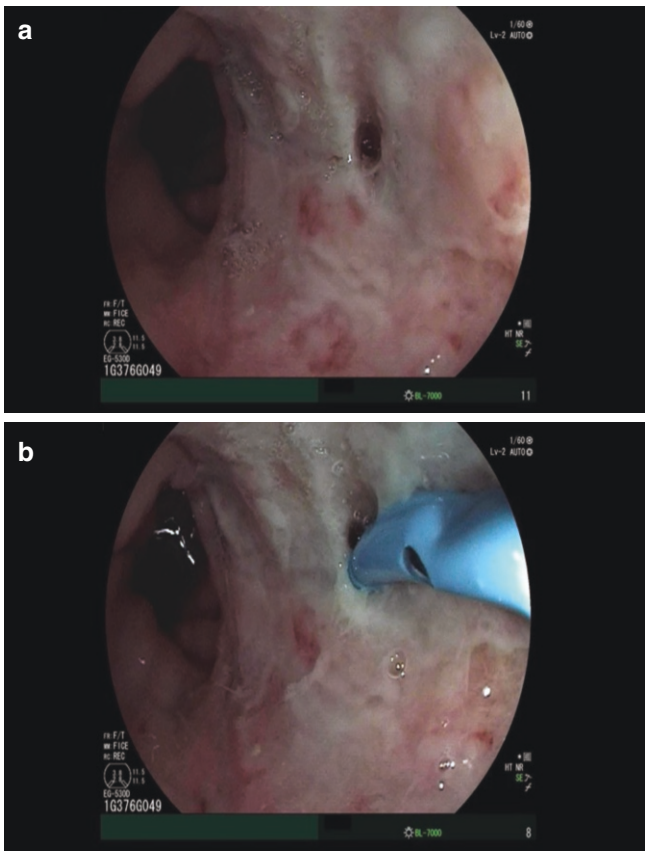

Fig. 40.3 Placement of a double pigtail drain through a persistent sinus in the setting of a healing esophageal injury (**a**) before (**b**) successfully positioned drain

are typically left in place for 3–6 weeks prior to removal. Complications related to stents are typically minor, and the most common by far is migration (10–20%). However serious complications have been reported including erosion, development of tracheoesophageal fistula, and bleeding. These are typically due to too much radial force applied from the stent on compromised esophageal tissue [9].

Endoscopic drainage procedures can allow for perforations to heal while obviating the need for external drainage. In the setting of a very small perforation or defect with an associated extramural fluid collection, a double pigtail drain can be placed to allow the adjacent cavity to drain internally and collapse on itself (Fig. 40.3).

Primary closure of an esophageal perforation can be achieved by endoscopic means. This is best performed in small or linear tears with healthy-appearing mucosa at the edges. The ideal setting is in iatrogenic perforations recognized at the time of index endoscopy. Although these techniques can also be employed in more delayed injuries, the tissues become more friable with ongoing inflammation and the techniques become more challenging and less effective. Devices available for primary endoscopic closure include over-the-scope clips, through-the-scope clips, endoscopic purse-string devices, and endoscopic suturing devices.

Through-the-scope clips were initially developed as hemostatic devices but have been found to work for tissue approximation as well (Fig. 40.4). These are best used for longitudinal tears in the esophagus that are less than 2 cm. The initial clip should be placed on the most distal aspect of

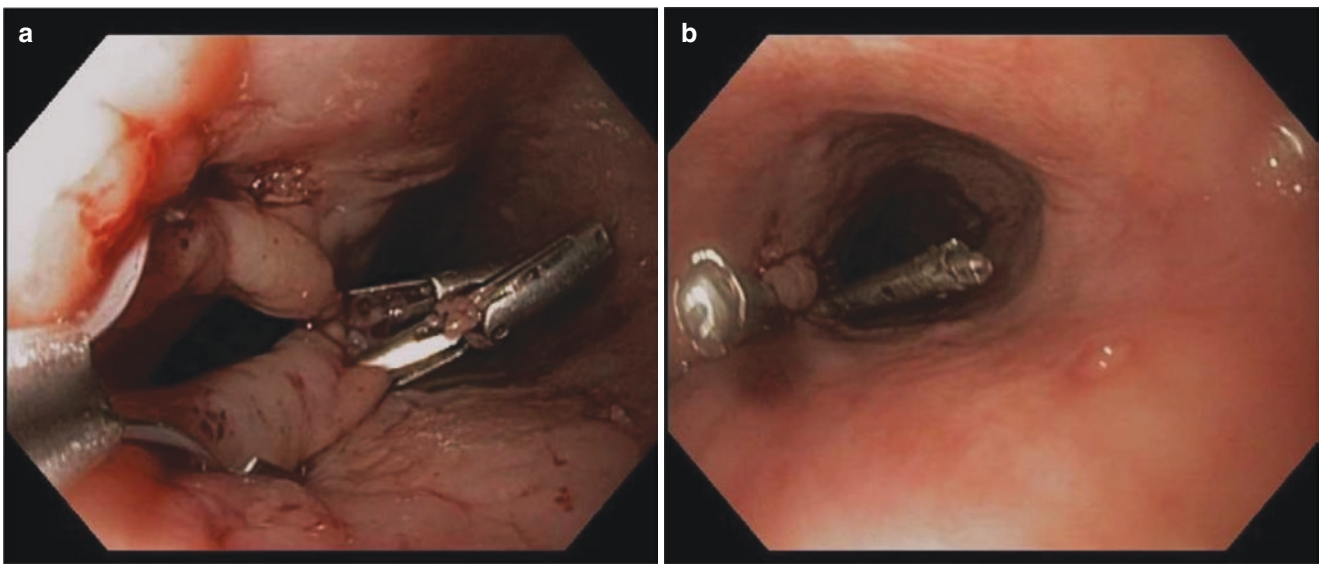

Fig. 40.4 Through the Scope Clip application for closure of a full thickness esophageal perforation from bougie dilation (**a**) beginning of closure (**b**) completion of repair

the perforation and subsequent clips placed proximally until the defect is closed. These clips do not acquire deep purchase into the tissue, however, closing defects that are wide or with inflamed edges can be very challenging.

Over-the-scope clips have a more aggressive, claw-like tooth which can be used to incorporate more tissue or tissue with higher degrees of inflammation (Fig. 40.5). The largest such clip is 14 mm so it is also limited to small-sized defects. To place the clip, it is affixed to the end of an endoscope with a clear cap, the defect is drawn into the cap using suction and the clip is deployed over it.

Endoscopic suturing techniques may be used to close larger or more irregularly shaped lacerations. There are several endoscopic suturing platforms that may be used through a dual channel or, more recently, a single channel scope to place full-thickness sutures to approximate esophageal tissues. These require a high degree of skill to place but can be quite effective. There are also systems that place a series of endoscopic clips all affixed to the same suture so that a purse-string mechanism can be then tightened to approximate the clipped tissue together.

Lastly, endolumenal vacuum therapy has been described for larger defects. A vacuum sponge on the end of a flexible nasogastric tube is advanced through the lumenal defect and into the adjacent wound cavity. Continuous negative pressure is then applied to the nasogastric tube. This simultaneously drains the cavity while also allowing it to collapse and theoretically stimulate the production of granulation tissue and neovascularization [10]. The sponge must be replaced every 3–4 days until adequate granulation has been achieved to discontinue therapy. It is worth noting that an appropriately sized sponge must be placed with great care through the site of perforation or a small defect can quickly become a large one. In some situations, leaving the sponge adjacent to the defect but in the lumen can be effective.

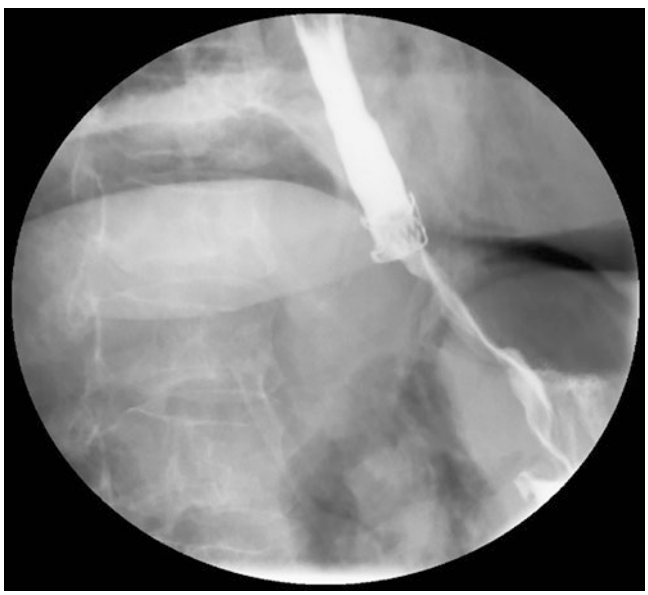

Fig. 40.5 Upper GI after over-the-scope clip placement for closure of a distal esophageal perforation

As endoscopic technology and skill evolve, there are situations where both control of surrounding contamination and diversion of salivary stream can be accomplished through endoscopic means. Such a NOTES (natural orifice translumenal endoscopic surgery) approach can be accomplished through the defect itself. Generally, this should only be attempted if the injury is already large enough to accommodate the endoscope and simultaneously divert the salivary stream without the need for additional surgery. For example, a 12 mm defect can be traversed and the contaminated cavity lavaged gently to reduce the volume of the collection prior to endoscopic salivary stream diversion, most often with a clip closure. If the cavity is large, additional drainage may be required for full source control. In rare circumstance, depending on the anatomy of the problem and the experience of the endoscopist, percutaneous drains can be placed under direct endoscopic guidance. In these cases, the cavity must extend to the body wall (thoracic or abdominal) where an unobstructed pathway can be visualized. Placement of endoscopic chest drains and trans-abscess abdominal drains have been described. These drains, or previously placed drains, can be grasped and positioned precisely within the cavity near the injury for more accurate and effective drainage in some circumstances.

Surgical Management of Esophageal Perforations

Definitive surgical options in the setting of esophageal perforation include three basic options; repair, resection, and diversion. Primary repair has long been held as the gold standard and indeed has shown to have good results over the years, especially in patients who present within 24 h of perforation before the tissues become stiff and necrotic. Laparoscopic or thoracoscopic surgery can be used to primarily close a defect with suturing and repair associated hiatal hernias if necessary, depending on scenario and location of injury. Intraoperative endoscopy can confirm adequate diversion of the salivary stream. The approach for the repair should be determined by preoperative imaging and work-up, but in general, cervical perforations can be approached via an incision along the left sternocleidomastoid, the proximal and mid thoracic esophagus can be approached through the right chest, and the distal thoracic esophagus through the left chest or transabdominally. For injuries with extensive extralumenal contamination or patients in extremis, often the most expeditious approach is surgical. The key steps to successful repair are debridement

of non-viable tissue, esophageal myotomy to expose the extent of the mucosal injury, a single or multi-layered repair, and wide drainage. Repairs can be buttressed by a flap of healthy tissue (strap muscle, pleura, intercostal muscle) if needed. In the setting of delayed presentation, repair over a T-tube to create a controlled esophagocutaneous fistula has also been described.

For patients with very extensive injuries not amenable to repair or underlying pathology that would require resection, proceeding directly to esophagectomy is the right choice. In most cases, reconstruction should be deferred to a later time and a cervical esophagostomy should be created at the time of resection. A final option that may facilitate future reconstruction is esophageal exclusion and diversion without resection. This may be accomplished by cervical esophagostomy and stapled division of the esophagus distal to the injury. Stapled diversion of the esophagus without division has also been reported but should be used with caution as the staple line could open and re-establish GI continuity prior to completion of healing.

An open approach is required if the characteristics of the injury and surrounding contamination exceed the technical skill or hospital resources for a less invasive approach. If patient transfer to a higher-level facility is not possible either due to transfer constraints of clinical severity, an open approach to stabilize a patient, control contamination, and ideally provide definitive diversion of the salivary stream is a necessary and life-saving option.

Boerhaave's Syndrome

Boerhaave's syndrome represents a unique scenario for esophageal perforation. With the perforation often extending into the peritoneal cavity, it does not meet Cameron's criteria for conservative management. With Boerhaave's perforations, the phrenoesophageal ligament, or hernia sac, typically contains the escape of gastric contents to the peritoneal space although broader contamination in the chest can occur. Because of the location of injury, these perforations are generally approached transabdominally and will involve reduction of the hernia to expose the full extent for repair. If diagnosed early in a stable patient with minimal contamination, endoscopic repair can be explored and the same tenets of management apply. Some unique considerations include difficulty positioning a covered stent across the distal injury due to the increased diameter relative to the more tubular esophagus, challenges to placing endoscopic clips within a hernia (often necessitating a retroflex approach), and challenges to placing effective percutaneous drains near the diaphragmatic hiatus. Often, a more invasive laparoscopic or sometimes open approach that can definitively address all concerns is the more efficient and effective treatment.

Conclusion

Esophageal perforation remains a challenging disease to treat, but a broad and growing spectrum of treatments exist and can be applied with success if attention is paid to the key tenants of management. After stabilization, the three principles of (1) Controlling sepsis (2) Diversion of the salivary stream, and (3) Addressing nutrition provides an overall framework to guide management. A multitude of options across specialties are available to effectively combat the potentially devastating outcomes historically associated with esophageal injuries. Frequent assessments and a readiness to escalate care when indicated are paramount to a successful conclusion.

Questions

1. All of the following are guiding principles of esophageal perforation management except:
   A. Early consideration of nutritional support
   B. Prompt stabilization with early cervical esophagostomy
   C. Aggressive resuscitation and sepsis management
   D. Diversion of the salivary stream

Answer: B. Cervical esophagostomy is a last-ditch option for salivary diversion in extreme cases of esophageal perforation.

2. Which of the following is true regarding the management of esophageal perforations?
   A. Observation of esophageal perforations is contraindicated
   B. Modern endoscopic techniques have made esophagectomy obsolete
   C. Management of esophageal perforations mandates utilizing the least invasive therapy for effective control with a low threshold for escalating therapy
   D. Thoracotomy is usually the best method for controlling the contamination of the chest after esophageal perforation

Answer: C. Management of esophageal perforations relies on multiple strategies with a variety of levels of invasion and generally, the least invasive method should be employed as long as it is effective, which is determined by frequent surveillance and examination to determine the next steps in therapy.

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Part V

Gastric Disorders

Pathophysiology of Gastric Neuromuscular Disorders

41

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Introduction

Gastric neuromuscular disorders constitute a significant healthcare burden. Gastroparesis, a well-characterized gastric neuromuscular disorder, is commonly seen in ambulatory and inpatient settings. The constellation of symptoms that patients experience can include some or all of the following: nausea, retching, vomiting, stomach fullness, inability to finish a meal, anorexia/early satiety, bloating/distension, heartburn, and abdominal pain. More severe cases can result in dehydration and malnutrition that can require supplemental nutrition. While gastroparesis is defined by delayed solid gastric emptying, there are several syndromes that do not have delayed solid gastric emptying, with similar clinical symptoms and analogous pathophysiology. This group of patients are characterized differently, more commonly as functional dyspepsia, but can be identified as other disorders such as chronic nausea and vomiting syndrome. For the purposes of this chapter, this group of disorders (without delayed gastric emptying) will be referred to as gastroparetic syndrome (GPS).

Most patients with GPS are characterized as having functional dyspepsia. Based on Rome IV criteria, functional dyspepsia is characterized by bothersome postprandial fullness, early satiation, epigastric pain, and/or epigastric burning for at least 3 months with symptom onset at least 6 months prior to diagnosis [1]. Functional dyspepsia is further phenotyped into epigastric pain syndrome and/or postprandial distress syndrome. The criterion for functional dyspepsia also includes the absence of organic disease that could explain symptoms, with the solid gastric emptying time distinguishing functional dyspepsia from gastroparesis. However, natural history literature supports functional dyspepsia and gastroparesis as existing on a spectrum rather than as distinct diagnoses. Patients classified into functional dyspepsia and gastroparesis based on solid gastric emptying were found to have similar clinical and pathologic features after 1 year, and gastric emptying times changed in both groups on later tests reclassifying patients from both groups if using adherence to disease classification based on solid emptying times [2]. Because of the similar pathophysiology, this group of disorders will be combined with gastroparesis, under the combined title of gastric neuromuscular disorders. In this chapter, we explore the epidemiology, clinical presentations, and pathophysiology for patients with gastric neuromuscular disorders.

Clinical Implication: Patients with symptoms of gastroparesis present with characteristic symptoms such as nausea, retching, vomiting, stomach fullness, inability to finish a meal, anorexia/early satiety, bloating/distension, heartburn, and abdominal pain.

Epidemiology and Clinical Presentation

Epidemiology

Disease Prevalence and Patient Characteristics

Due to multiple factors, information regarding the true epidemiology of gastric neuromuscular disorders is limited. These factors include delay in diagnosis, suboptimal gastric emptying tests, and ICD10 codes lacking specificity. However, there is information available on this population. The prevalence of gastroparesis among the general worldwide population is approximately 20–38 per 100,000 persons in women and 9–10 per 100,000 persons in men [3, 4].

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However, the real prevalence is likely higher due to ongoing under-recognition of gastroparesis around the world. In a survey of members of the Asian Neurogastroenterology and Motility Association (ANMA) across Asia, 25.2% never diagnosed gastroparesis, while 52.1% diagnosed <5 patients per year [5]. The incidence appears to be increasing, with estimates of approximately 2–6 per 100,000 person-years [3, 4]. The risk of developing gastroparesis is higher in the general diabetic population with type I or type II diabetes, with estimates at 4.59% and 1.31%, respectively [6]. Women have a higher proportion of gastroparesis regardless of etiology, generally with a ratio of 4:1 [7]. Women also appear to be more likely to have more severe symptoms of stomach fullness, early satiety, postprandial fullness, bloating, stomach visually larger, and abdominal pain [7]. Despite the high prevalence, a lower proportion of women appear hospitalized compared to men [7]. Racial differences also exist in both clinical presentation and etiology. Caucasian patients comprise the largest majority of patients with gastroparesis regardless of etiology at tertiary academic centers in the USA (77%) [7]. Non-Hispanic blacks are more likely to have diabetic gastroparesis (60% vs. 28%), more likely to have severe retching and vomiting, and more likely to have hospitalizations within the past year [7]. Natural history demonstrates generally poor long-term outcomes in patients managed at tertiary academic centers, and after following patients for a median of 2.1 years, only 28% experienced a reduction in gastroparesis-related symptoms [8].

Information is also limited regarding patients with GPS, due to the variety of clinical diagnoses applied to this population, such as functional dyspepsia and chronic nausea and vomiting syndrome; differing practices in the identification of patients; and poorly tailored diagnostic ICD codes. Of these disorders, functional dyspepsia has the most available information. While studies often use the broader term for dyspepsia, most patients have been shown to have functional dyspepsia rather than an identified organic process; therefore, the studies convey a reliable picture of the disease [9]. Estimates of annual incidence of functional dyspepsia range from 1% to 3%, and estimates of the prevalence of functional dyspepsia range from 10% to 17% [9–14].

The natural history of functional dyspepsia appears to be better than patients with gastroparesis, with a proportion of patients experiencing resolution or improvement in symptoms (17% and 38%, respectively, in one study over mean follow up of 68 months) [15]. A proportion of patients with functional dyspepsia do appear to have progression of symptoms, and some patients may develop delayed gastric emptying [2].

Clinical Implication: Gastroparesis symptoms occur not uncommonly and seem to be increasing in incidence and prevalence.

Healthcare Burden

The healthcare burden is significant for patients with gastroparesis with increased rates of emergency visits, hospitalizations, and hospital readmissions. Overall, the numbers appear to be increasing, constituting significant healthcare cost. In 2013, there were over 36,000 emergency visits with a mean cost of $4531 in the USA [16]. Inpatient hospitalizations have increased significantly, with estimates of 16,460 admissions in 2013, mean length of stay 4.8 days, and total charges over $590 million. Additionally, gastroparesis is associated with a longer length of hospitalization compared to other upper gastrointestinal conditions [17]. Readmission rates are high for patients with gastroparesis with 30- and 90-day readmission rates of 26.8% and 45.6% [18]. Opioid use has been identified as a strong predictor of healthcare utilization [19].

Clinical Implication: Patients with gastroparesis constitute significant healthcare burden with high cost of emergency and inpatient admissions.

Clinical Implication: Opioid use in gastroparesis is associated with increased health care utilization.

Patients with GPS constitute a large ambulatory burden.

Etiologies

For gastroparesis, most patients are broadly characterized as idiopathic, diabetic, and postsurgical. While a large proportion of patients with gastroparesis have an unknown cause (classified as idiopathic), several etiologies have been better described and include long-standing diabetes with associated peripheral neuropathy, connective tissue disorders, prior gastric surgery/vagal injury, ischemia, post-infection, and other inflammatory or neurologic disorders (Table 41.1). These etiologies result in

Table 41.1 Causes of gastroparesis

Causes of gastroparesis
Idiopathic
Diabetes mellitus
Postsurgical/trauma
Medications (i.e., narcotics, anticholinergics [i.e., dicyclomine, hyoscyamine, tricyclic antidepressants], dopamine agonists, calcium channel blockers, clonidine, GLP analogs)
Infection (i.e., Epstein-Barr virus, cytomegalovirus, varicella zoster virus, Norwalk, rotavirus)
Neurologic (i.e., Parkinson's, multiple sclerosis, brainstem stroke or tumor)
Infiltrative (i.e., amyloidosis, sarcoidosis)
Autoimmune disorders (i.e., autoimmune autonomic neuropathy)
Connective tissue disease (i.e., systemic lupus erythematous, Sjogren's syndrome, dermatomyositis, Ehlers-Danlos syndrome)
Ischemia
Malignancy
Genetic disorders
Environmental exposures (i.e., caustic ingestion)

disruption to normal gastric neuromuscular function and may present with different clinical features depending on the mechanism and location of the injury. Long-term prognosis is dependent on the cause, with post-infectious gastroparesis having the best resolution of symptoms.

For GPS, causative factors for functional dyspepsia are better delineated but still poorly understood. Multiple mechanisms are involved and include infections more commonly *H. pylori*, but other infections have also been described such as *Salmonella*, *Shigella*, *E. coli*; environmental exposures (e.g., diet, tobacco); medications (NSAIDS); stressful life events/coping skills; genetic predispositions; and duodenal inflammation (e.g., mast cells and eosinophils) [20–26]. GPS may also be an earlier manifestation for evolving gastroparesis (i.e., diabetes) [2].

Because gastroparesis and GPS result in significant morbidity and decreased quality of life, understanding the pathophysiology is crucial to guide therapeutic approaches for this challenging patient population.

Clinical Implication: Gastroparesis can have a diverse number of etiologies and has significant morbidity.

Pathophysiology of Delayed Gastric Emptying

Normal Gastric Motor Function

Understanding the process of normal gastric neuromuscular function is fundamental to understanding areas that lead to gastric neuromuscular disorders. Normal gastric neuromuscular function depends on complex coordination between smooth muscle contraction and relaxation of the gastric fundus, corpus/antrum, pylorus, and duodenum, which are controlled by the intrinsic (enteric) and extrinsic (autonomic) nervous systems. The enteric nervous system is made up of the submucosal and myenteric plexuses. The autonomic nervous system is comprised of the parasympathetic pathways mediated by the vagus and sympathetic pathways mediated by the spinal cord (T5–T10) via the celiac ganglia [27]. Parasympathetic activity modulates sensation, increases secretions, and stimulates motility, while sympathetic activity decreases secretions and motility.

Ingestion of a meal triggers relaxation or accommodation of the fundus, which effectively increases gastric volume without increasing gastric pressure. Tonic contractions of the proximal stomach transfers food to the gastric antrum where high amplitude contractions perform the process of trituration, breaking down food to particles <2 mm in diameter [28, 29]. Thus, postprandial gastric accommodation influences gastric emptying [30]. The coordinated propulsion of food from the stomach into the duodenum in the postprandial period is dependent on peristaltic contractions of the antrum and organized contractions of the duodenum. Particles >2 mm are cleared from the stomach during the interdigestive period, propelled by phase 3 contractions of the migrating motor complex (MMC) [31] that is coordinated with pyloric relaxation. This coordination is controlled by the interstitial cells of Cajal (ICC), which form the pacemaker and conduction system of the gut. Disruption anywhere during this complex coordinated process can lead to delayed emptying of a meal. Factors that influence stomach emptying are shown in Table 41.2.

Clinical Implication: Normal gastric motor function is a complex process involving coordination of multiple components of the stomach and regulated by the intrinsic and extrinsic nervous systems. This complex process can be disrupted at any point, and in some cases more than one factor may be involved.

Pathophysiology of Gastroparesis

Regulation of gastric accommodation is vagally mediated through activation of non-adrenergic, noncholinergic (NANC), myenteric neurons that release nitric oxide (NO)

Table 41.2 Factors that influence gastric emptying

Gastric Neuromuscular	Meal
• Gastric dysrhythmias • Altered fundic accommodation • Antral hypomotility • Pylorospasm	• Volume • Increased acidity • Increased Osmolarity • Fat content • Undigestible fibers
Small intestine/colon	**Additional factors**
• Fatty acids in the duodenum and /or ileum • Dysmotility • Constipation	• Glucose levels • Decreased mobility • Hormones • Medications • Other additional environmental factors

[32]. NO is a major inhibitory neurotransmitter produced by neuronal nitric oxide synthase (nNOS) that induces smooth muscle relaxation [33]. Additionally, inhibition of cholinergic neurons via presynaptic a2-adrenoceptors and 5-HT1A receptors can stimulate gastric accommodation [34]. Disruption of these pathways can lead to impaired gastric accommodation and postprandial symptoms. For example, diabetes is associated with impaired nNOS expression and impaired gastric accommodation [35] Although the mechanism for impaired gastric accommodation in idiopathic gastroparesis has not been elucidated, it can be present in up to 43% of patients with idiopathic gastroparesis [36]. Mechanisms of gastroparesis are highlighted in Fig. 41.1.

Clinical Implication: Delayed gastric emptying can be caused by any of several mechanisms. It is likely that more than one factor may be active for delayed gastric emptying in each patient.

Antral Hypomotility

The pattern of antral contractions differs based on the fasting vs. fed state. The postprandial period is comprised of the lag phase (trituration) and active gastric emptying (propulsion) [28]. Antral hypomotility is defined as decreased frequency (<3 cpm) or amplitude (<30 mmHg) of antral contractions [37]. Postprandial antral hypomotility is present in 46% of patients with delayed gastric emptying [38], while antral hypomotility during fasting can lead to bezoar formation [39]. Acute hyperglycemia (>275 mg/dL) can cause antral hypomotility and delay gastric emptying, while acute hypoglycemia accelerates gastric emptying [40]. Conversely, chronic hyperglycemia can lead to either rapid or delayed gastric emptying [41].

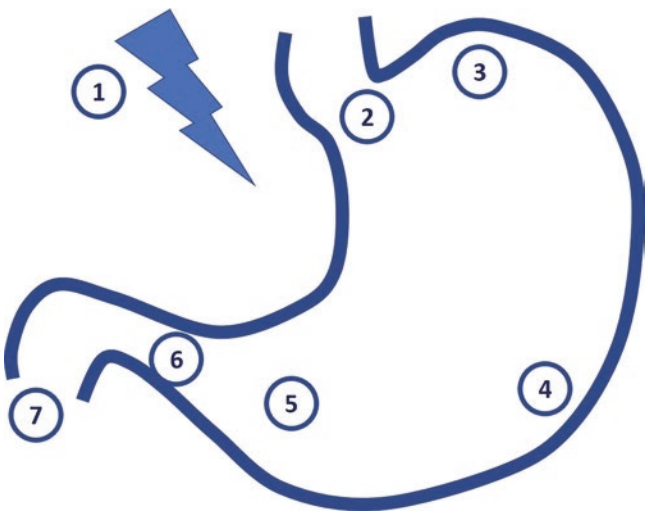

Fig. 41.1 Mechanisms of gastric neuromuscular disorders that can also be targets for treatment: (1) Enteric nervous system; (2) esophagogastric junction; (3) fundus-impaired relaxation and/or emptying; (4) gastric dysrhythmias; (5) antral dysmotility; (6) pyloric dysfunction; (7) small intestinal/colonic dysmotility

Clinical Implication: Disordered antral motor function may be a factor in delayed gastric emptying.

Pyloric Dysfunction

The pyloric pressure is made up of both tonic and phasic contractions, which can be measured using a water-perfused sleeve. Pylorospasm, which is defined as basal pyloric pressures >10 mmHg, has been found to be present in 42–58% of patients with delayed gastric emptying [42, 43]. However, in a study comparing basal pyloric pressures with pyloric distensibility using the EndoFLIP system (Medtronic, Minneapolis, MN), basal pyloric pressure did not correlate with severity of delayed gastric emptying, while pyloric distensibility <10 mm^2/mmHg was associated with severely delayed gastric emptying (4-h gastric retention >20%) [42]. Pyloric intervention including intrapyloric botulinum toxin injection and pyloromyotomy (surgical or endoscopic) are currently utilized to treat patients with medically refractory gastroparesis. However, two RCTs of intrapyloric botulinum toxin therapy were negative [44, 45], while no controlled trials of surgical or endoscopic pyloric intervention exist.

Clinical Implication: Pyloric dysfunction may add to gastric factors as part of the pathophysiology of delayed gastric emptying.

Duodenal Dysmotility

Similar to antral contractions, patterns of duodenal contractility differ based on the fasting or fed state, which is vagally mediated [46]. During fasting, there is a distinct pattern called the migrating motor complex (MMC) that is abolished with oral intake. Duodenal dysmotility can manifest as hypomotility (contraction frequency <11 cpm and/or amplitude <15 mmHg) and/or alteration in the normal MMC pattern and propagation. Patients with gastroparesis were found to have decreased duodenal contractility and antropyloroduodenal coordination that can be stimulated with cisapride [47].

Clinical Implication: Like pyloric function, small bowel motor abnormalities are commonly seen in patients with delayed gastric emptying.

Autonomic Dysfunction

The autonomic nervous system is responsible for maintaining homeostasis. The parasympathetic nervous system is innervated by the vagus nerve, which is comprised of sensory (60–80%) and motor fibers [27]. Vagal afferents convey sensory signals from the GI tract to the central nervous system (CNS), while vagal efferents mediate smooth muscle contraction and motility. Dysfunction of either the sympathetic or parasympathetic system is associated with upper GI symptoms and altered gastric emptying [48]. In a study examining heart rate variability, gastric emptying scintigraphy, and gastroparesis symptoms (gastroparesis cardinal

symptom index), patients with sympathetic hypofunction had milder symptoms of gastroparesis (GCSI <4), while parasympathetic hypofunction was associated with more severe symptoms (GCSI >4). Conversely, presence of parasympathetic excess in response to Valsalva or standing was associated with delayed gastric emptying. Hypersensitivity to balloon distention is present in patients with diabetic (55%) and idiopathic (29%) gastroparesis [36, 49].

Clinical Implication: Autonomic dysfunction is commonly seen in patients with gastroparesis and delayed gastric emptying.

Visceral Hypersensitivity

Gastric sensation is mediated by mechano- and chemoreceptors that sense volume transmitting signals to the CNS [50]. Visceral hypersensitivity is defined as a lower threshold for sensing a mechanical or chemical stimulus. Hyperalgesia is sensing pain at a lower threshold, while allodynia is sensing a non-painful stimulus as painful. The mechanism for visceral hypersensitivity is still poorly understood; however, the transient receptor potential (TRP) channels may be contributing to the altered sensation. TRP channels are involved in sensory transduction throughout the body including chemo-, thermo- and/or mechanosensation. The capsaicin-sensitive vanilloid (TRPV1) receptors are expressed in visceral afferents as well as the dorsal root and nodose ganglia. Upregulation of TRPV1 has been associated with IBS [51] and functional dyspepsia [52]. Given the overlap between idiopathic gastroparesis and functional dyspepsia, TRPV1-mediated hypersensitivity may be playing a role in dyspeptic symptoms in patients with gastroparesis.

Clinical Implication: Visceral hypersensitivity may also play a role in symptoms and disordered physiology in gastroparesis.

Immune Dysregulation in Delayed Gastric Emptying

Inflammation or immune dysregulation has been implicated in gastroparesis. Systemic inflammation or autoimmunity has been described with presence of elevated autoantibodies in patients who respond to immunotherapy such as intravenous immunoglobulin (IVIG) [53, 54]. Peripheral immune dysregulation has been described in the muscularis of the antrum with presence of increased CD45+ leukocytes and loss of CD206+ (anti-inflammatory) macrophages that was associated with loss of ICC [55, 56]. Recently, immune profiling of the gastric mucosa found increased macrophages, mast cells, CD4+ T cells, and proinflammatory cytokines [57]. Additionally, presence of gastric CD45+CD68+ macrophages and CD8+ T cells correlated with severity of delay gastric emptying but not gastroparesis symptoms.

Clinical Implication: Immune abnormalities are increasingly recognized in patients with gastroparesis.

Pathophysiology of Gastroparesis Syndromes with Non-delayed Gastric Emptying

Introduction

Symptoms of gastroparesis are also seen in patients without delayed gastric emptying, referred to as GPS in this chapter, and include Rome IV disorders such as functional dyspepsia and chronic nausea and vomiting syndrome. The pathophysiology of this is complex and has some overlap with gastroparesis; some patients later exhibit delayed gastric emptying [2]. Full-thickness biopsies showed loss of interstitial cells of Cajal and CD206+ macrophages in both groups compared to controls. Additionally, gastric emptying times were labile in both groups where at 48 weeks, 42% of gastroparesis patients had a normal emptying time and 37% functional dyspepsia patients were reclassified as having gastroparesis [2].

While some of the discordance of gastric emptying with symptoms relates to suboptimal diagnostic testing, many patients with gastroparesis-like symptoms have normal or rapid emptying rates under optimal methodology [58]. The constellation of potential symptoms is identical including nausea, vomiting, anorexia/early satiety/postprandial fullness, bloating/distension, and/or abdominal pain. The pathophysiology can be viewed as one general concept characterized by at least five specific areas. The general concept is that GPS may be part of a systemic or localized illness with both GI and non-GI manifestations. The specific areas are (1) enteric, (2) neurologic, (3) inflammatory, (4) immune/genetic, and (5) serosal/hormonal. These will be discussed separately, with an emphasis on recent research that may have practical applications to patient care.

Clinical Implication: A constellation of commonly seen upper gut symptoms can be viewed as gastroparetic syndromes.

Further Descriptions of the Concept of GPS

Other Aspects of Gastroparetic Syndromes

Systemic factors of GPS can include a more expansive GI illness involving other areas of the gastrointestinal tract, including esophageal, small bowel, and colonic/anorectal manifestations [59]. GPS are frequently associated with several overlap syndromes, such as migraine headaches, fibromyalgia, interstitial cystitis, endometriosis, and localized neuropathies, and learning disabilities may co-exist [60] These additional GI disorders and overlap syndromes may share common pathophysiology, including autonomic, autoimmune, and/or genetic basis, inflammation, and in some cases serologic markers of neuromuscular diseases [42, 61].

Some aspects of these additional manifestations of GPS are discussed below.

Clinical Implication: Many patients with gastroparetic syndromes (GPS) have overlap with other disorders, several of which are classically defined as autoimmune or neuroinflammatory (e.g., fibromyalgia). These other diagnoses may relate to a similar underlying cause but can also complicate management of GPS.

Specific Areas of Gastroparetic Syndromes (GPS)

Enteric Aspects of GPS

Enteric factors play a major role in GPS and are subcategorized as anatomic, physiologic, and luminal. Each will be discussed separately.

Anatomic abnormalities may be localized or generalized and in either case have microscopic changes that demonstrate pathology in GPS [62]. While gross anatomic abnormalities in GPS have been demonstrated for many years, microscopic abnormalities have taken longer to be recognized [63]. The recognition that the interstitial cells of Cajal (ICCs) can be detected by CD-117/C-Kit stains has been a major factor in the recognition of enteric abnormalities in GPS regardless of solid gastric emptying rates.

Cajal cell stains are important for GIST tumors, which arise from ICC cells, and any laboratory that can detect GIST can measure Cajal cells. Additional anatomic abnormalities have been measured with several other stains including S-100, which measure neural fibers and tryptase that identify mast cells. Other stains include CD 3, 4, and 8 (particularly of the myenteric plexus) and CD-68, as a measure of inflammation [64]. Figure 41.2 shows stains reveals in healthy con-

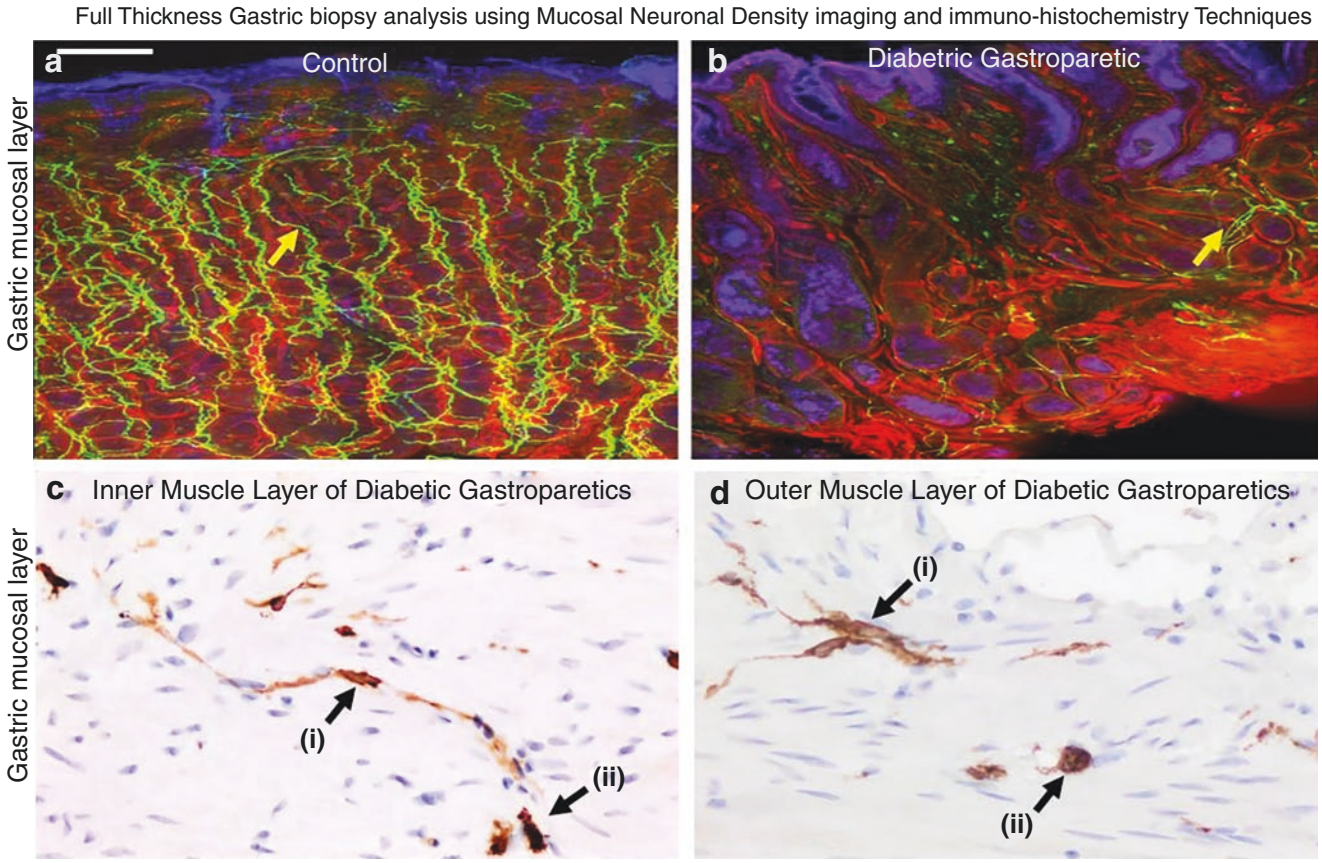

Fig. 41.2 (**a**) Immunofluorescence stain image of gastric mucosal layer where the nerve fibers are observed as bright-green stained filaments in the healthy control biopsy sample. (**b**) Immunofluorescence stain reveals a significant reduction in the nerve fibers of the gastric mucosa of patients with diabetic gastroparesis. (**c**) Immunohistochemistry imaging of c-KIT stained interstitial cells of Cajal (ICC) cell bodies (seen as fusiform bodies) labeled (i) in the gastric inner (circular) muscular layer from full-thickness biopsy of diabetic gastroparesis patients. c-KIT stained mast cells (globular bodies) labeled (ii). (**d**) Outer (longitudinal) muscle layer imaging of gastric full-thickness biopsy using c-KIT stains to identify ICC cell bodies labeled (i). c-KIT stained mast cells (globular bodies) labeled (ii) show observable morphological differences between the two cell types. (Reproduced with permission from Abell TL, Kedar A, Stocker A, Beatty K, McElmurray L, Hughes M, Rashed H, Kennedy W, Wendelschafer-Crabb G, Yang X, Fraig M, Gobejishvili L, Omer E, Miller E, Griswold M, Pinkston C. Pathophysiology of Gastroparesis Syndromes Includes Anatomic and Physiologic Abnormalities. Dig Dis Sci. 2021 Apr;66(4):1127–1141. doi: 10.1007/s10620-020-06259-6. Epub 2020 Apr 23)

trols compared to diabetic gastroparesis, where a significant reduction in the nerve fibers of the gastric mucosa is seen in patients with diabetic gastroparesis as well as lower numbers of ICC cells than in normal controls.

Other identified cells, such as CD-206, appear to be markers of cells involved with both the maintenance and destruction of ICCs [65]. The role of anatomic changes in GPS is evolving and rapidly changing and can only be mentioned in the most general terms here. However, GI tract biopsies, both mucosal and full thickness, are now demonstrated to reveal pathophysiology. New and less invasive ways to obtain full-thickness GI biopsies are now available and approved for endoscopic use [66].

Physiologic abnormalities can include both gastric emptying and electrophysiologic [64]. Gastric emptying is still the gold standard for GPS but is variable and has several limitations. Figure 41.3 demonstrates significant variability in symptomatic patients when summing up gastric emptying times in patients with normal and delayed gastric emptying. Newer ways of measuring gastric emptying include the ability to detect fundic relaxation, as well as gastric antral contractions, and, although available, are not yet widely used [67]. Gastric electrical measurements, mentioned above, have been demonstrated for literally 100 years [68], are rapidly evolving, and may play increasing roles in the diagnosis of GPS soon [69, 70] Fig. 41.4a, b demonstrate gastric slow-wave propagation in healthy controls and patients with gastroparesis.

Luminal factors can include both the direct GI biome and stool biome [22]. The emerging area of luminal biology has the potential to revolutionize much of GI and medicine. However, more published work has become available on the role of the GI biome in GPS. With the advent of direct biome/enteric measurements as well as number of current investigations, more descriptions of the role of the GI microbiome in GPS are anticipated [71, 72].

Clinical Implication: Enteric factors play crucial roles in the pathophysiology of GPS, and the advent of microscopic analysis of GI tract anatomy biopsies has opened new understanding. Evolving enteric physiology allows for better demonstrations of abnormalities, and new GI microbiome measures may allow for better understanding of the pathophysiology of GPS.

Neuropathic Factors in GPS

Neurologic factors as part of GPS can include central, peripheral, and autonomic aspects. Central factors include the fact that central causes can influence GPS [73]. These central causes of GPS can be primary, as is thought to be the case with cyclic vomiting syndrome, which is most often a migraine variant [74]. Likewise, peripheral neuropathies may play a role in GPS [75]. Recent data has shown that sensory testing in GPS is often abnormal, which is one indication of peripheral neuropathies .Other studies looking at EMGs in GPS patients show frequent abnormalities [76]. Lastly, autonomic nervous system

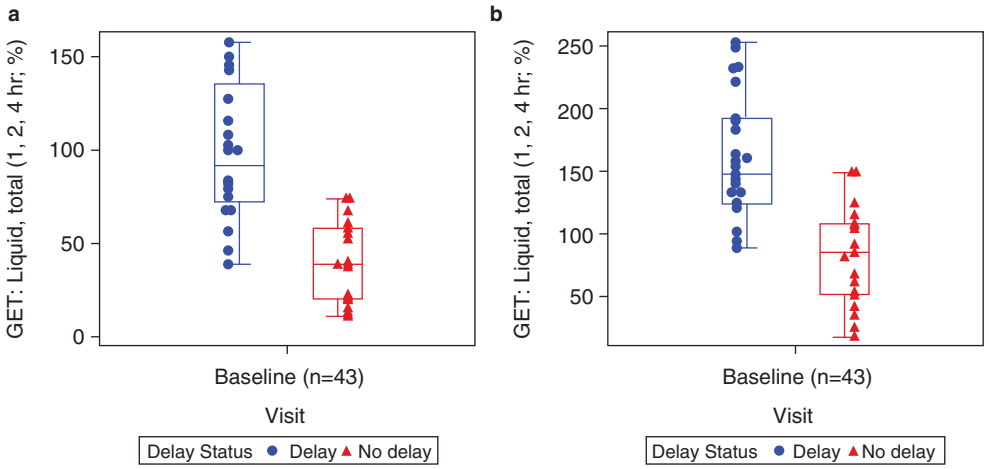

Fig. 41.3 Values for 43 consecutive patients with symptoms of gastroparesis and their total gastric emptying percentages (defined as the sum of % retention at 1, 2, and 4 h) for liquids (**a**) and solids (**b**). Initial categorization as delayed for non-delayed gastric emptying was defined at baseline based on either 1-h liquid retention (>50% at 1 h) or 2-h solid retention (>60% at 2 h) and/or 4-h solid retention (>10% at 4 h). Note the overlap in emptying between classically defined liquid or solid emptying categories as delayed or not delayed when using percentage totals. (Reproduced with permission from Abell TL, Kedar A, Stocker A, Beatty K, McElmurray L, Hughes M, Rashed H, Kennedy W, Wendelschafer-Crabb G, Yang X, Fraig M, Gobejishvili L, Omer E, Miller E, Griswold M, Pinkston C. Pathophysiology of Gastroparesis Syndromes Includes Anatomic and Physiologic Abnormalities. Dig Dis Sci. 2021 Apr;66(4):1127–1141. doi: 10.1007/s10620-020-06259-6. Epub 2020 Apr 23)

(ANS) abnormalities are widespread in GPS, and many patients have autonomic nervous system symptom dysfunction and ANS abnormalities on testing [48]. Some patients with GPS meet autonomic criteria for specific neurologic syndromes such as the postural orthostatic tachycardia syndrome (POTS), but other patients with similar symptoms are not as easy to categorize [77]. Other neurologic factors include involvement of the enteric nervous system, discussed above, and serologic neuropathic findings, discussed below.

Clinical Implication: Neuropathic involvement in GPS is widespread and may present with central, peripheral, or autonomic symptoms and findings.

Inflammatory Aspects in GPS

Inflammatory aspects of GPS can be both systemic and local. As with many illnesses, disorders, and syndromes, inflammation may be a common pathway for pathology to manifest. Systemic inflammation in GPS is common in patients regardless of gastric emptying time [64]. Figure 41.5 demon-

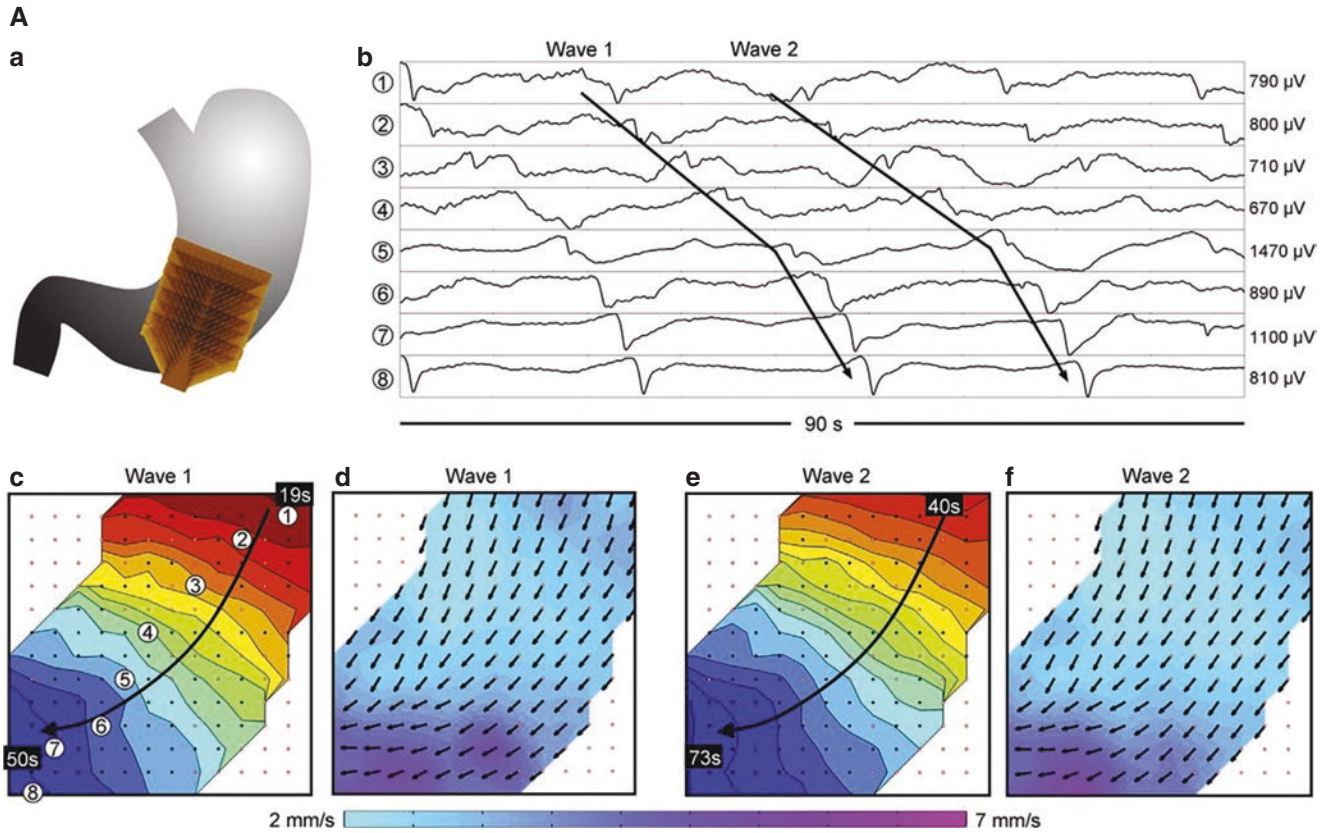

Fig. 41.4 (**A**) Normal gastric slow-wave propagation in a control patient. (a) Position of the array. (b) Electrograms from positions indicated in panel c (mean frequency ± SD, 2.8 ± 0.1 cycles/min). (c) Isochronal activation map of wave 1 indicated in panel B, showing normal antegrade propagation. Black dots represent electrodes, with white dots outlined in red representing electrodes where activity was interpolated. Each color band shows the area of slow-wave propagation per 2 s. (d) Velocity map of wave 1, showing the speed (color spectrum) and direction (arrows) of the wavefront at each electrode. (e, f) Isochronal activation and velocity field maps of wave 2 in panel B, showing consistency of the antegrade propagation. (Reproduced with permission from Angeli TR, Cheng LK, Du P, Wang TH, Bernard CE, Vannucchi MG, Faussone-Pellegrini MS, Lahr C, Vather R, Windsor JA, Farrugia G, Abell TL, O'Grady G. Loss of Interstitial Cells of Cajal and Patterns of Gastric Dysrhythmia in Patients With Chronic Unexplained Nausea and Vomiting. Gastroenterology. 2015 Jul;149(1):56–66.e5. doi: 10.1053/j.gastro.2015.04.003. Epub 2015 Apr 8). (**B**) Abnormal slow-wave initiation and conduction (isochronal intervals, 1.5 s). (a) Position of the array. (b) Representative electrograms from positions indicated in panel c; propagation sequences are labeled based on their corresponding waves 1–4, shown in panels c–f. (c) Isochronal activation map. Slow-wave activity propagated onto the array from the greater curvature, colliding with an unstable focal activity on the distal portion of the array. (d) The unstable focal activity was consistent over a second cycle. (e) A new stable ectopic pacemaker emerged in the distal portion of the array (star), initiating retrograde propagation that collided with the uncoupled antegrade wavefront. Circumferential propagation was out of phase with distal activity that was propagating in the opposite direction circumferentially, resulting in a complete functional conduction block (thick black line). (f) Propagation repeated as described in panel e, with stability of the ectopic pacemaker and distal block that remained consistent through the end of the recording period. A frequency increase occurred between the unstable focal activity shown in panels c and d (bradygastric, 2.0 ± 0.1 cycles/min) and the stable ectopic activity shown in panels e and f (normal frequency, 3.2 ± 0.2 cycles/min). (Reproduced with permission from Angeli TR, Cheng LK, Du P, Wang TH, Bernard CE, Vannucchi MG, Faussone-Pellegrini MS, Lahr C, Vather R, Windsor JA, Farrugia G, Abell TL, O'Grady G. Loss of Interstitial Cells of Cajal and Patterns of Gastric Dysrhythmia in Patients With Chronic Unexplained Nausea and Vomiting. Gastroenterology. 2015 Jul;149(1):56–66.e5. doi: 10.1053/j.gastro.2015.04.003. Epub 2015 Apr 8)

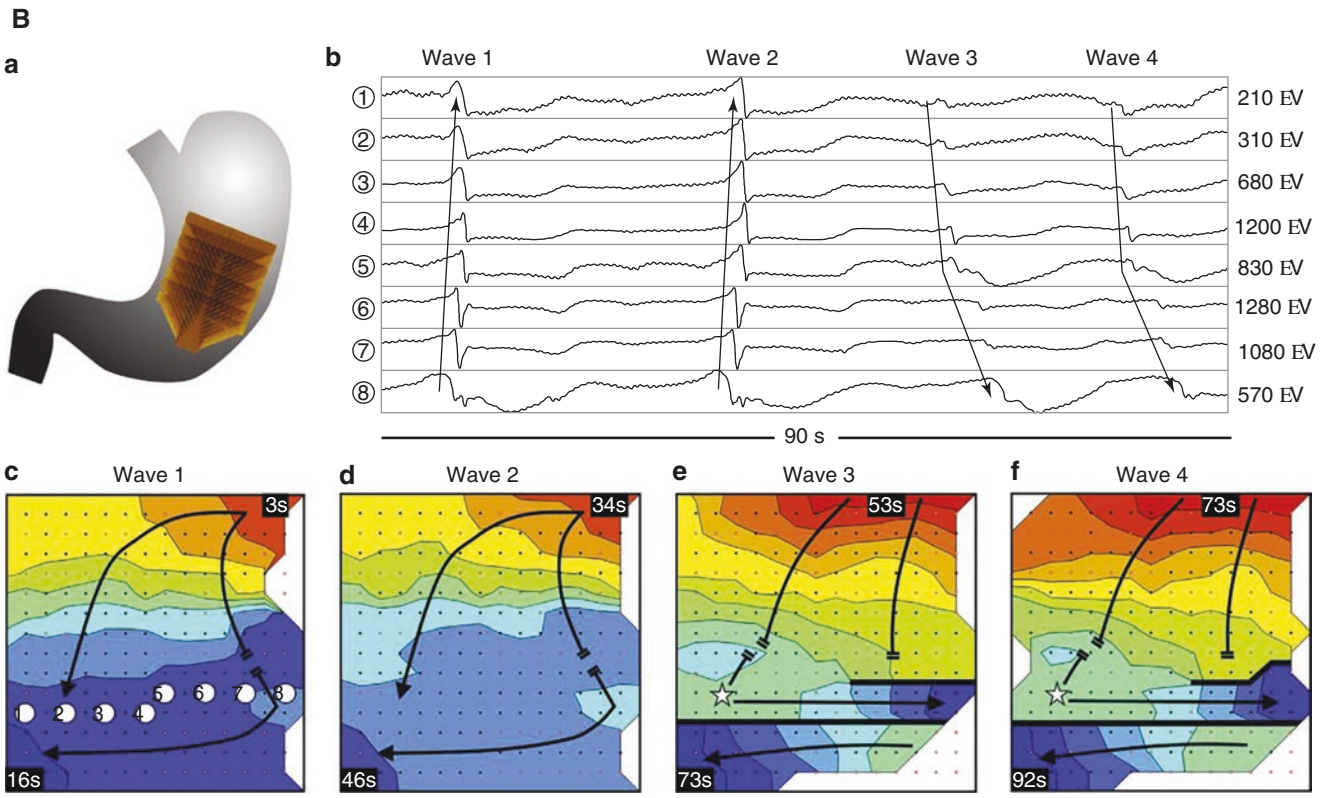

Fig. 41.4 (continued)

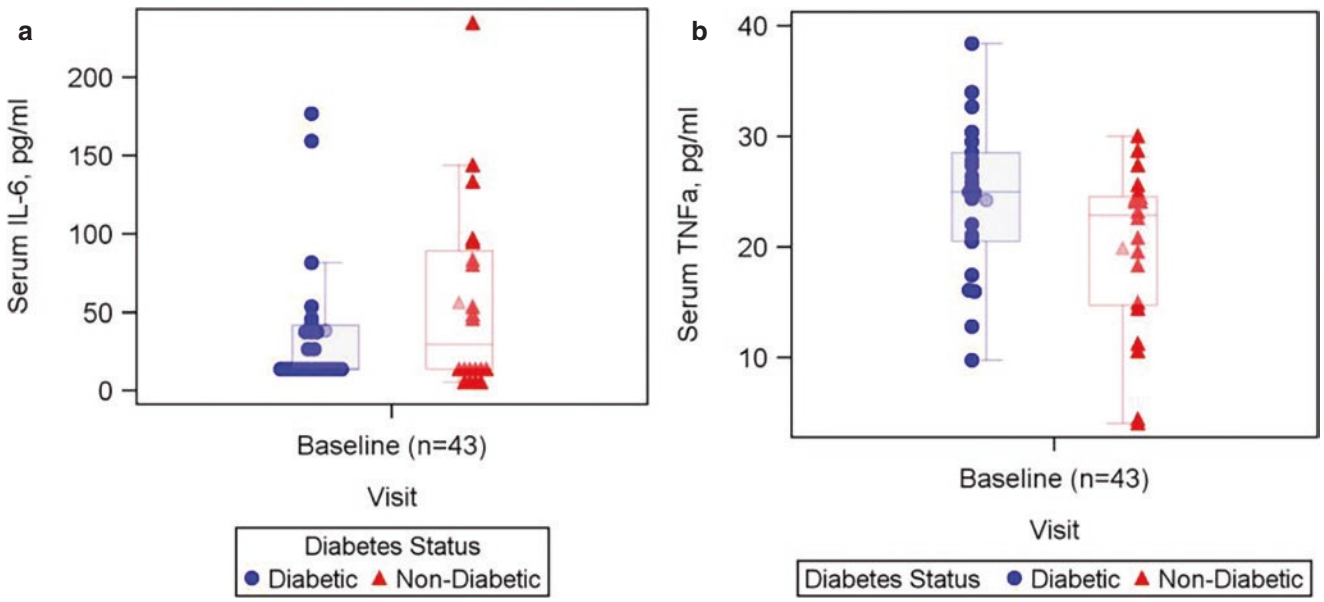

Fig. 41.5 Inflammation stratified by diabetes status measured by IL-6, pg/mL (**a**) and TNFα (**b**). (Reproduced with permission from Abell TL, Kedar A, Stocker A, Beatty K, McElmurray L, Hughes M, Rashed H, Kennedy W, Wendelschafer-Crabb G, Yang X, Fraig M, Gobejishvili L, Omer E, Miller E, Griswold M, Pinkston C. Pathophysiology of Gastroparesis Syndromes Includes Anatomic and Physiologic Abnormalities. Dig Dis Sci. 2021 Apr;66(4):1127–1141. doi: 10.1007/s10620-020-06259-6. Epub 2020 Apr 23)

strates inflammatory markers in patients with diabetic and non-diabetic gastroparesis. Localized inflammation can be harder to categorize but may be related to many of the "non-specific" symptoms seen in GPS, including some of the overlap syndromes described above [60, 61]. Inflammation in GPS may relate to items such as mortality; recent work has shown that mortality is associated with specific systemic inflammatory markers [78]. Other aspects of GPS, such as

hypercoagulability, could also relate to inflammation (as well as autoimmunity, discussed below) [64, 79]. While inflammation in GPS may be common and widespread, why certain organs are affected more than others is currently unknown. There is evidence that inflammation is one possible mechanism of injury for GPS patients [64].

Clinical Implication: Inflammation is a common occurrence in GPS, can be detected with commonly available laboratory markers, and may contribute to both morbidity and mortality.

Immune/Genetic Aspects of GPS

Immune/genetic aspects of GPS can be both congenital and acquired. While it may be difficult to establish, emerging evidence shows that GPS, much like delayed gastric emptying, may have immune abnormalities [63]. These immune abnormalities have been demonstrated by several methods [57]. Immunologic abnormalities can be seen in younger individuals with GI motility disorders, many of which may be genetic [62]. Similarly, the concurrence of GI symptoms in individuals with documented immune abnormalities suggests that other GPS patients may have immune dysfunction as part of the pathophysiology of their illness [64]. Perhaps related to immune and/or genetic abnormalities in GPS are the neurologic manifestations of antibodies against nerve and/or muscle that can be detected in peripheral blood [80]. These antibodies, which can target acetylcholine as well as sodium and potassium and other channels, appear be present in a small but well-defined number of patients with GPS [80]. The response of some of these patients to immunotherapy suggests a role of these factors in the pathophysiology of GPS.

Clinical Implication: The emerging work on immunologic abnormalities in GPS patients suggest that the immune system may be part of the pathophysiology of GPS, whether delayed gastric emptying or not, and offers a future role for immunotherapy in selected patients.

Serosal/Hormonal Aspects of GPS

Serosal/hormonal aspects of GPS can include both diabetes and non-diabetic patients [64]. The impact of hormonal and metabolic abnormalities in several illnesses can contribute to pathophysiology by numerous pathways, most of which are beyond the scope of this review. While the hormonal changes in diabetes mellitus, which classically involve insulin, amylin, and glucagon, among others, is the best documented part of pathophysiology of GPS, increasing evidence finds hormonal changes as part of non-diabetic patients as well [60]. The reason for hormonal abnormalities in non-diabetes mellitus patients is not clear and can be due to interactions with inflammation as well as pancreatic function, both of which have been described in GPS [81]. Pancreatic function has been associated with GPS in patients with and without diabetes mellitus. New ways to deliver peripheral hormones have the potential to impact GPS, but these are only beginning investigations [82].

Clinical Implication: Hormonal abnormalities, including pancreatic hormones, are also described in patients with and without diabetes mellitus. Modifications of hormonal function have potential clinical use in the future.

Additional Factors Involving GPS

The stomach has classically been defined as two sub-organs, proximal and distal stomach, with and upper and lower sphincters. Factors regulating gastric emptying call involved any or all these anatomic and physiologic areas. The relation of GI symptoms can often, although not always, be correlated with gastric function in patients presenting for care.

A discussion of gastric physiology is also beyond the scope of this discussion, but two specific areas are worthy of comment: gastro-pyloric dysfunction and gastroesophageal dysfunction.

Gastro-Pyloric Dysfunction

Recent work with gastroparetic patients has focused on pyloric dysfunction. The fact that patients with Gp Sx have pyloric dysfunction is not new, but specific interventions, especially endoscopic myotomies, are increasingly being used to treat symptomatic patients [83]. Many patients improve with disruption of the pyloric sphincter, but not all do, and a subset may have a worsening of symptoms, including new-onset diarrhea. The basis for rational use of pyloric therapies may rest with the pathophysiology of the gastric-pyloric area. Full descriptions of which pyloric sphincter therapies work best are not the focus of this chapter. Studies of pyloric FLIP in Gp patients often demonstrate abnormal compliance of the pyloric sphincter, an abnormality that may be amenable to therapies such as intra-pyloric botulinum toxin. Recent work has shown that patients with abnormal pyloric function, by pyloric FLIP, may have concomitant gastric pathology, both anatomic and physiologic [84, 85]. The interest in pyloric pathology has led to the term gastro-pyloric dysfunction or GPD, the full exploration of which is yet to be undertaken.

Gastroesophageal Dysfunction

A related aspect of sphincter function in GPS is that of the gastroesophageal sphincter. While the lower esophageal sphincter (LES) is well studied, its function in GPS has not been studied in detail. The correlation of LES function in patients with GPS offers an area for potentially useful clinical work. An understanding of gastroesophageal dysfunction (or GED) in GPS may provide further insights into the pathophysiology of gastroparesis and related disorders [86].

Clinical Implication: The upper and lower gastric sphincters may play a role in the symptoms seen in gastroparetic patients. Physiologic measures of these sphincters may help define subsets of patients who may respond to newer therapies, such as esophageal and/or pyloric myotomies by any of several available methods.

Many patients additionally have small bowel and/or colonic motility disorders with more than half of patients reporting moderate or severe constipation and a third of patients having delayed colonic transit [87].

The Role of Diet

Most patients with gastric neuromuscular disorders report exacerbation of symptoms with meals. The specific composition of food can exacerbate delayed emptying. Undigestible fiber, poorly chewed food, high fat, and large volume meals can all result in delayed gastric emptying.

Dietary factors play an important role in symptoms of gastroparesis.

Pathophysiology Based on Symptoms

Nausea is the most common symptom for patients with gastroparesis, occurring in up to 95% of patients, and it is the predominant symptom in approximately a third of patients [6]. The pathophysiology is generally multifactorial and involves a complex neural pathway related to a collection of nuclei in the dorsal lateral reticular formation of the medulla with afferent signals from the throat, gastrointestinal tract, vestibular system, and chemoreceptor trigger zone (CTZ). This neural pathway responds to noxious stimuli, related to gastric distension or other signals. Intractable nausea can also be an atypical symptom that can occur in a subset of patients with reflux disease [88].

Vomiting is triggered by noxious stimulation of the vomiting center directly or indirectly at one or more sites of the vomiting center, which includes the gastrointestinal tract, the vestibular system, the chemoreceptor trigger zone, and higher centers in the cortex and thalamus. Once the CTZ is triggered, vomiting is elicited via coordinated actions of the motor system, parasympathetic nervous system, and sympathetic nervous system. Vomiting appears related to peripheral and central abnormalities, psychological disorders, gastric dysmotility, and/or visceral hypersensitivity [89].

Bloating is a complex symptom that is also multifactorial and includes a variety of mechanisms including visceral hypersensitivity, gut microflora alterations, changes in gas productions or transit, and decreased gastric elasticity and can be heightened with psychological distress. Small intestinal bacterial overgrowth may play a role in symptoms with estimates of 39–60% in patients with gastroparesis [90, 91].

Early satiety is attributed to impaired gastric accommodation and/or hypersensitivity to gastric distension [92, 93]. Abnormal sensory processing is also attributed to this symptom [94].

Symptoms of heartburn and regurgitation can relate to delayed proximal gastric emptying, provoking transient lower esophageal sphincter relaxations. Regurgitation could also be provoked by rumination syndrome.

Abdominal pain, previously not thought to be related to gastroparesis, is commonly seen in patients with gastroparesis, with as many as 90% of patients reporting abdominal pain [7, 95]. The cause of pain is likely multifactorial, and the pathogenesis is poorly understood but likely includes one or multiple areas of somatic, visceral, and neuropathic physiology. Possible contributors to pain include abnormalities with gastric accommodation, gastric distension, and/or visceral hypersensitivity. Gastric emptying does not appear related to abdominal pain [95]. Chronic abdominal wall pain is another potential cause, and a positive Carnett's sign is diagnostic [96]. Pain is thought to be further heightened by opiate use and increased attention/stress heightening effects [96].

Specific gastrointestinal symptoms are manifestations of the pathophysiology of gastroparetic syndromes.

Conclusion

Gastric neuromuscular disorders, described here as gastroparesis and gastroparetic syndromes, are increasing in prevalence and constitute a significant healthcare burden. Patients can have symptoms that include nausea, vomiting, early satiety/postprandial fullness, bloating, and/or abdominal pain. Gastric neuromuscular disorders appear most prevalent in women. Other disorders such as constipation, autonomic dysfunction, and overlap syndromes (migraines, fibromyalgia) are commonly found. Multiple mechanisms can result in symptoms, which is one major factor making this patient population difficult to effectively treat. Because gastric emptying is a complex coordinated process, the pathophysiology of gastroparesis includes several factors, including antral hypomotility, gastric dysrhythmias, pyloric dysfunction, and duodenal dysmotility as shown in Fig. 41.1. Extra-gastric factors may play an additional role in gastroparesis such as visceral hypersensitivity and immune dysregulation.

The wide number of abnormalities seen in patients with GPS, with non-delayed and occasionally rapid gastric emptying, offers additional challenges as well as opportunities for therapeutic interventions within enteric, neurologic, inflammatory, immune/genetic, and serosal/hormonal pathways. Several complex pathophysiologic factors can result in symptoms regardless of solid gastric emptying findings.

Current tests used to measure gastric emptying vary and include radionuclides, breath tests, or transit measures such as wireless capsules. Most of these tests measure solid

emptying but can include liquid emptying. New radionuclide gastric techniques measure proximal gastric emptying/gastric accommodation and antral contractions, allowing better identification of patients that may benefit from therapies guided toward those processes, particularly in patients where gastric emptying does not reflect symptom severity. Additional ancillary tests such as gastric electrical measures of gastric electrophysiology further identify factors resulting in symptoms. These tests can use electrodes in the serosa or the mucosa (these two technically called electrograms) or, more commonly, with cutaneous electrodes (called electrogastrogram or EGG) and are performed as single-point, low-resolution, or now high-resolution recordings. Accurate identification of the underlying factors resulting in symptoms can lead to improved patient selection for different therapies for improved patient outcomes. A full discussion of techniques to measure gastric function is discussed in the next chapter.

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Diagnostic Testing and Pharmacotherapy in Gastroparesis

42

Brian Surjanhata and Braden Kuo

Introduction

The clinical signs of gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating, and abdominal discomfort, which can present in varying degrees [1]. Symptomatology alone, however, is a poor predictor of underlying pathophysiology since presenting complaints often overlap with other gastrointestinal (GI) disorders. In patients with symptoms suggestive of gastroparesis, between 25% and 33% have documented gastric emptying delay [2]. Once patients have mechanical obstruction ruled out by upper endoscopy, further testing is required to elucidate the presence or absence of delayed gastric emptying. Both the cardinal signs of gastroparesis and established gastric emptying delay are required to diagnose gastroparesis [1], and therefore guide targeted management as other GI motility disorders can present similarly but may have different treatment paradigms.

Diagnostic Testing

Several different tests that provide distinct information on gastric motility exist for the evaluation of suspected gastroparesis and can be categorized as transit or contractility testing, with some able to offer information on both (Fig. 42.1). Gastric motility testing can be challenging for patients with severe symptoms or who may not tolerate the often-required test meal. The ideal scenario would be to perform the examination without medications that can affect motility to provide an accurate picture of underlying dysmotility. However, considerations should be made whether to test while on medications for symptom control, with a partial test meal, or with a substitute test meal in order to be able to obtain some information on gastric function rather than none at all. Under these conditions, care should be taken while interpreting results as medications for symptom management can often affect motility and alternate test meals may not be fully validated [3]. Imperfect test conditions can still be clinically useful if results particularly are extremely abnormal or normal.

Both abnormal and normal motility testing can be helpful. Abnormal contractile function implies a therapeutic focus on promotility agents. Normal or even mildly abnormal test results suggest a prominent sensory disorder where pharmacologic neuromodulation or therapies for symptom control is most likely helpful. In some cases, a combination of sensorimotor abnormalities may be at play, which will require more complex management.

In suspected or established gastroparesis, evaluation of alternative dysmotility disorders may be clinically warranted. In a study with 154 patients with symptoms suggestive of gastroparesis, 21.1% of patients had generalized transit delay (≥2 regions), and 5.4% had global delay (in all three regions: gastric, small bowel, and colon) [2]. Constipation symptom severity as measured by validated questionnaires has correlated well with the severity of gastroparesis symptoms and was irrespective of gastric delay [4]. Therefore, it is important to consider other dysmotility that may mimic gastroparesis or contribute to symptoms not explained by gastric delay alone.

Gastric Emptying Evaluation

Gastric emptying scintigraphy (GES) measures gastric emptying of a solid meal and is considered the standard diagnostic modality for gastroparesis. Liquid emptying is not routinely assessed because emptying of liquids is often preserved [1, 3]. Patients are instructed to hold medications that affect motility such as promotility agents, opiates, or anticholiner-

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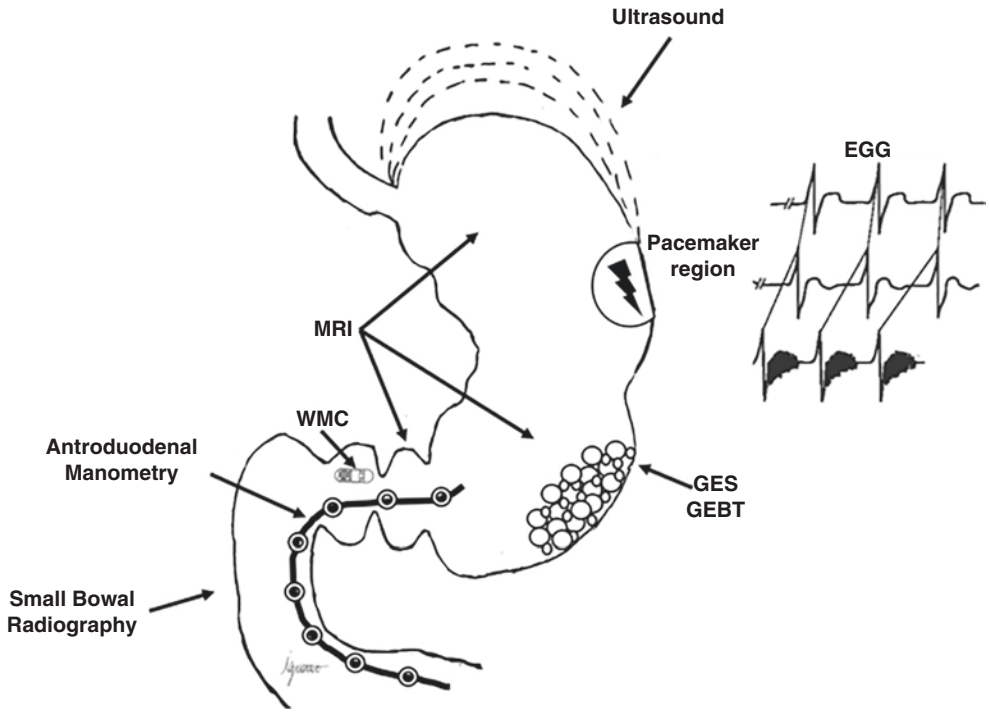

Fig. 42.1 Several diagnostic modalities are available for the evaluation of suspected gastroparesis and measure unique aspects of upper gastrointestinal motility

gics 48–72 h prior to the study. Due to the effects of hyperglycemia on gastric emptying, the test should be performed when the fasting blood glucose is <280 mg/dL [5]. After an overnight fast, patients consume a standardized meal consisting of egg whites, two slices of white bread, and strawberry jam (total caloric value of 255 kcal, 72% carbohydrate, 24% protein, 2% fat, and 2% fiber) radiolabeled with 99mTc and 120 cc of water within 10 min. Images are obtained at 0, 1, 2, and 4 h [3]. Delayed gastric emptying is defined as greater than 60% retention at 2 h and/or 10% retention at 4 h [6]. Alternatively, results can be reported as percentage emptying. Figure 42.2 shows a normal GES. Mild, moderate, and severe gastroparesis can be defined as 10–15%, 15–35%, and >35% retention at 4 h, respectively [3, 7]. Figure 42.3 shows a severely delayed GES. Importantly, extending GES to 4 h identifies more symptomatic patients with delayed gastric emptying despite a normal 2-h study [8], which is not standard at all centers (Fig. 42.4). Adjustments can be made to accommodate those with food intolerances to gluten or eggs by using the high-caloric liquid nutrient meal Ensure Plus or oatmeal [9, 10]; however, these alternative meals have not been fully validated. New scintigraphic techniques are under development to measure gastric accommodation and antral contractility [11]. GES is a noninvasive measure of gastric emptying that has been validated with well-established standard normal values, however is limited by need for radiation exposure and currently only provides a general assessment of gastric function.

Gastric emptying breath testing (GEBT) is an alternative noninvasive method to assess gastric transit without the need for radiation and can be used in an office setting [7, 12]. The test uses ^{13}C, a non-radioactive stable isotope, bound to a medium-chain triglyceride (octanoic acid) or a proteinaceous algae (*Spirulina platensis*) incorporated into a 238 kcal test meal consisting of scrambled eggs, saltines, and the isotope substrate [12, 13]. After emptying the stomach (rate-limiting step), the substrate is absorbed by the small intestine and undergoes hepatic metabolism with the isotope exhaled as ^{13}CO and detected by using mass spectrometry at a centralized lab (Cairn Diagnostics, Brentwood, TN). In comparison to GES, GEBT has comparable performance with a sensitivity of 89% and specificity of 80% with an AUC of 0.893 [12]. GEBT should not be performed in patients with intestinal inflammation nor significant hepatic or pulmonary disease that can affect CO_2 metabolism and test accuracy. Furthermore, patients with moderately and severely delayed gastric emptying requires careful interpretation with extrapolation of emptying curves (Fig. 42.5).

Wireless motility capsule (WMC) (Medtronic, Minneapolis, MN) measures pH, pressure, and temperature throughout the GI tract for up to 5 days and is able to assess gastric emptying time (GET), small bowel transit time (SBTT), and colonic transit time (CTT) [14] (Fig. 42.6). Patients are instructed to withhold the same medications as in GES but also H2 antagonists and proton pump inhibitors prior to and during the WMC testing as the pH tracing is used to delineate regional gut transit times. The test meal provided following an overnight fast can be the same egg-based meal as GES or alternatively the included SmartBar with similar calorie, fat, carbohydrate, protein, and fiber composition [14]. GET is defined as the time from ingestion of the WMC to the abrupt and sustained pH rise as the capsule passes from acidic antrum to the alkaline duodenum [14]. Due to the indigestible nature of the capsule, GET is associated with

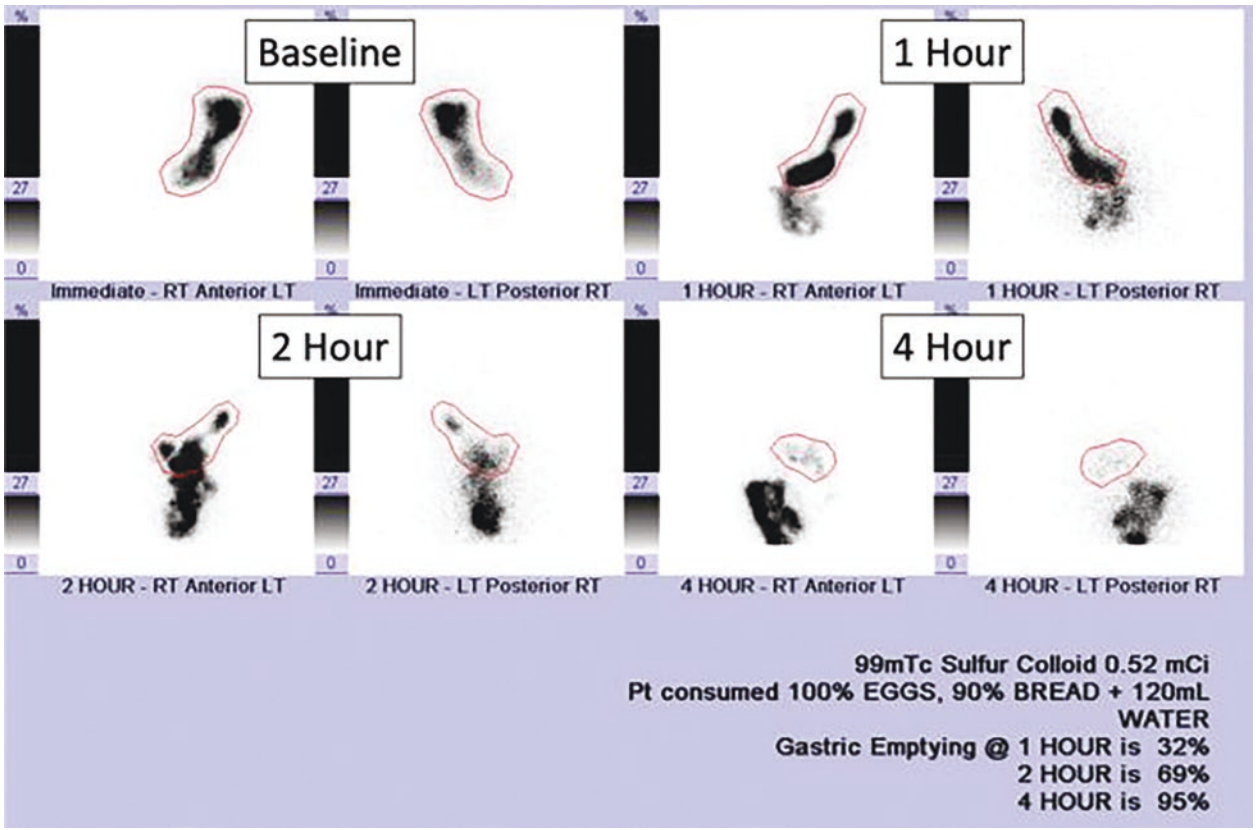

Fig. 42.2 Normal gastric emptying scintigraphy with 31% retention (69% emptying) at 2 h and 5% retention (95% emptying) at 4 h. Gastroparesis is defined as >60% retention (<40% emptying) at 2 h and/or >10% retention (<90% emptying) at 4 h

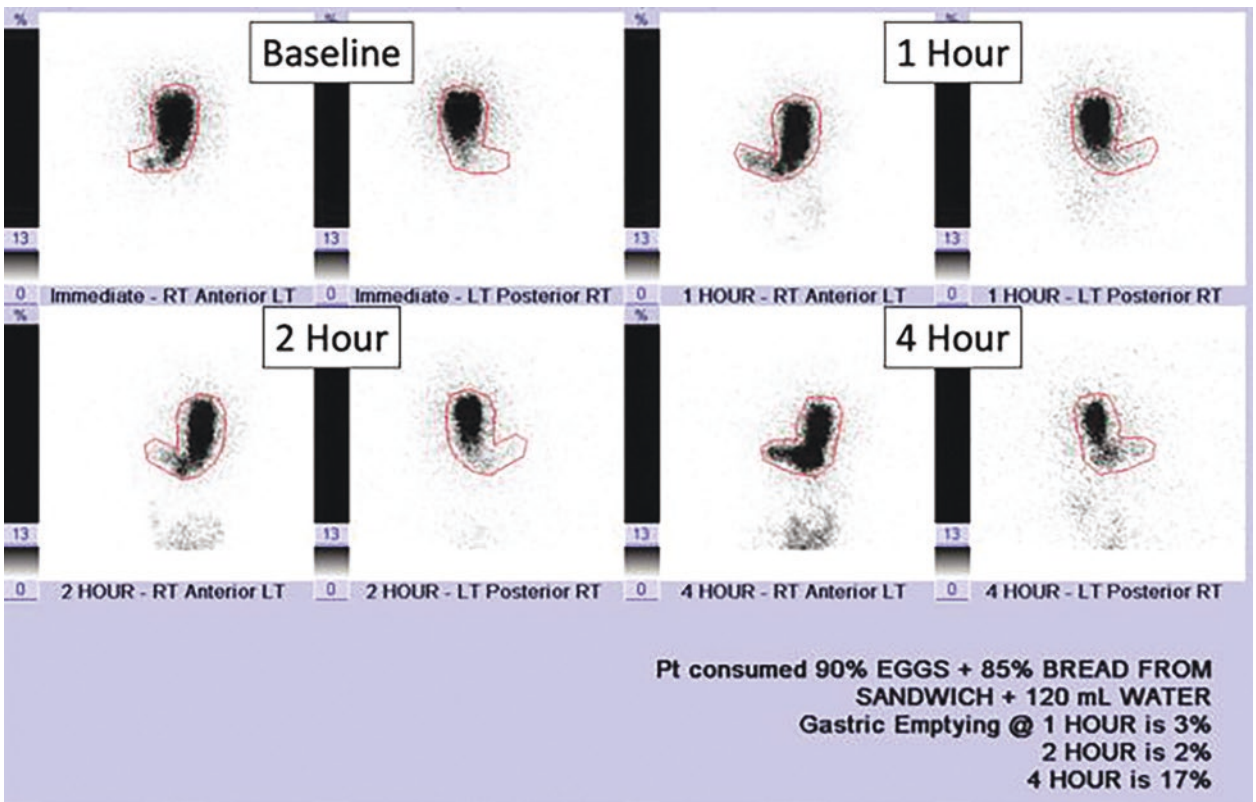

Fig. 42.3 Severely delayed gastric emptying scintigraphy with 98% retention (2% emptying) at 2 h and 83% retention (17% emptying) at 4 h. Severe gastroparesis is defined as >35% retention (<65% emptying) at 4 h

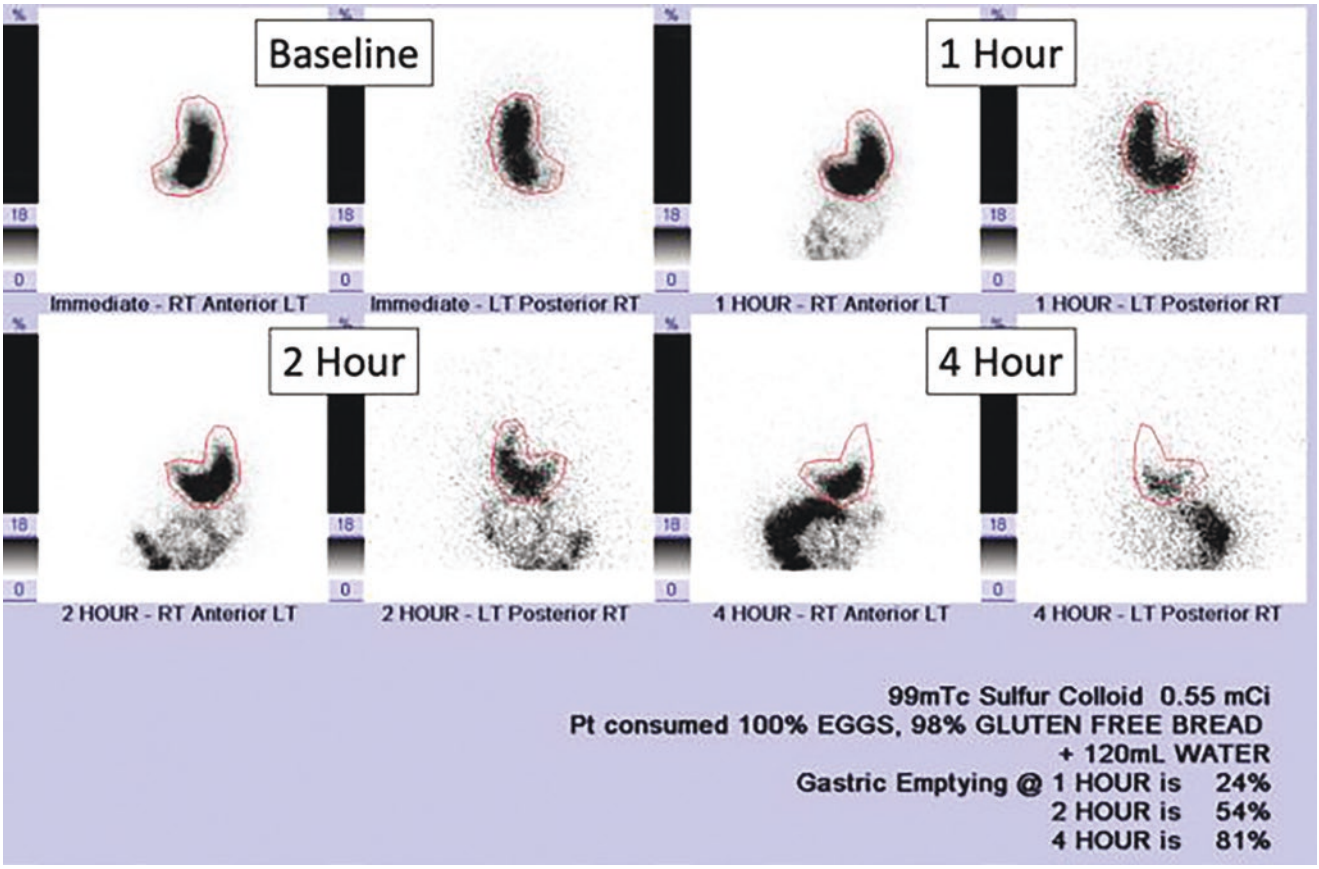

Fig. 42.4 Gastric retention is normal with 46% retention (54% emptying) at 2 h, however is abnormal with 19% retention (81% emptying) at 4 h, diagnostic for gastroparesis. Extending gastric emptying scintigraphy studies to the full 4 h evaluation is important to identify symptomatic patients with delayed gastric emptying as 2-h gastric emptying may be normal

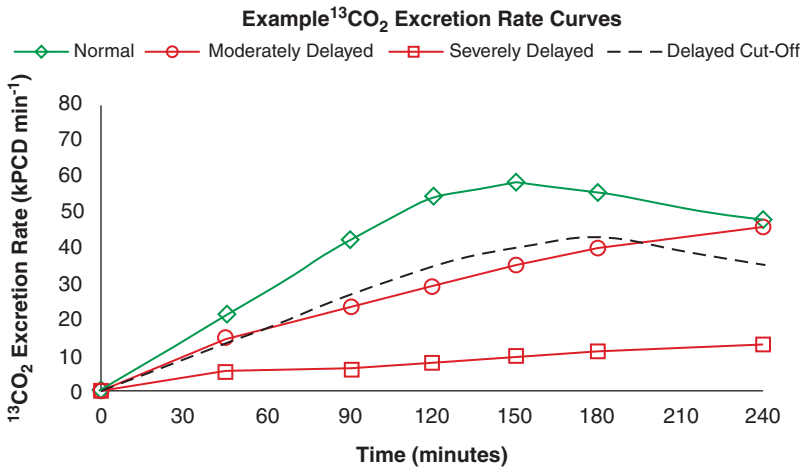

Fig. 42.5 Gastric emptying breath testing curves of normal, moderately delayed, and severely delayed emptying. Note moderately delayed curves can look normal in up to the first 2–3 h but can become abnormal in the last hour. (Figure courtesy of Cairn Diagnostics (Brentwood, TN))

the fasting phase III migrating motor complex (MMC) after >90% of the test meal has emptied [15], thereby providing an indirect measure of meal emptying. There is strong correlation in gastric emptying between WMC and 4-h GES (r = 0.73) with ROC curves for the two measures being equivalent (AUC of WMC = 0.83 vs. AUC of GES = 0.82) [16]. The cutoff point for classifying delayed GET is 5 h with a sensitivity of 0.65 and specificity of 0.87 [16]. WMC was found to have a higher diagnostic yield for delayed gastric emptying and additionally identified SBTT and CTT delays that would have otherwise been missed when compared to GES alone [2]. This led to more medication changes and fewer additional testing recommendations [17]. Prior studies have demonstrated that the WMC is able to indirectly infer

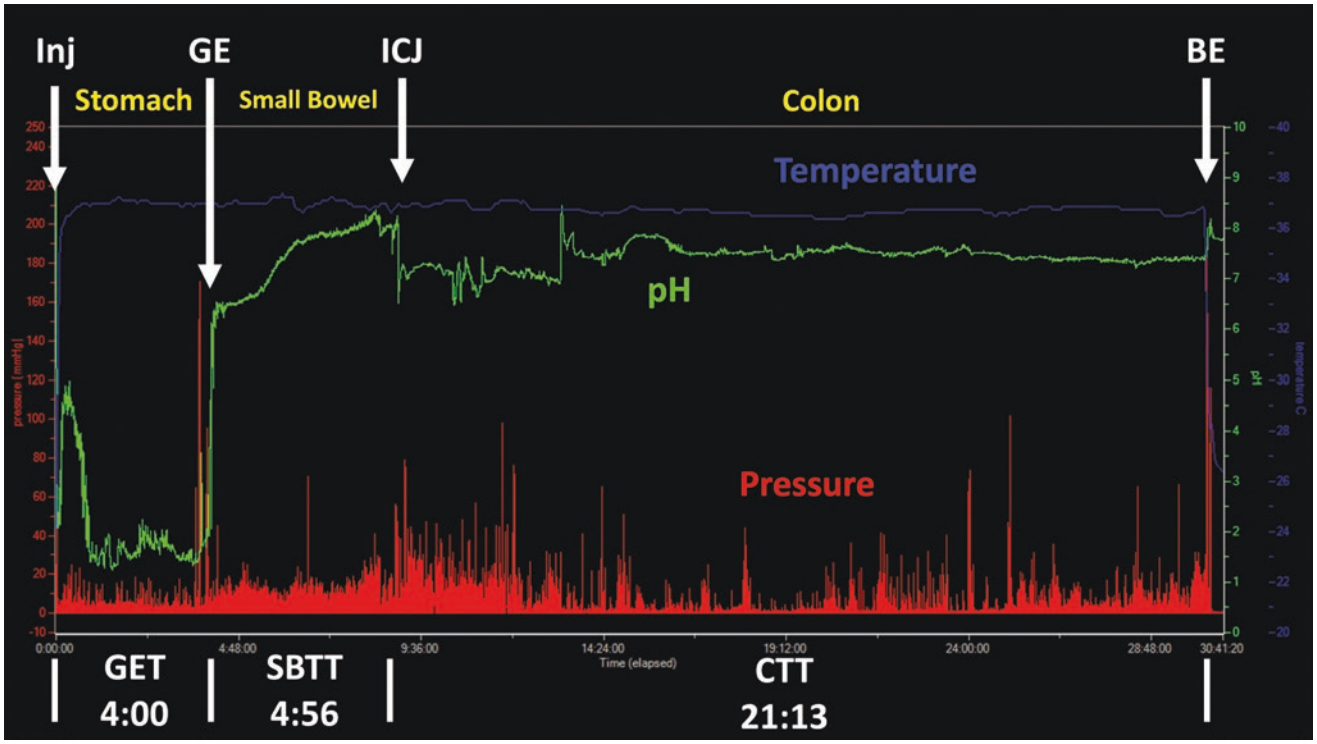

Fig. 42.6 Wireless motility capsule (WMC) measures whole-gut regional transit and intraluminal contractility. pH (green line) landmarks identify ingestion (Inj), gastric emptying (GE), the transition from ileum to cecum (ICJ), and body exit (BE). Normal gastric emptying time (GET) is <5 h, small bowel transit time (SBTT) is <6 h, and colonic transit time is <59 h

the absence of the phase III migrating motor complex [18] and measure a small bowel post-prandial response [19]. WMC is able to noninvasively measure whole gut transit and provide contractility information without the need for radiation or complex equipment, however is unable to measure propagating contractions due to the free-floating nature of the capsule and is contraindicated in patients at risk for capsule retention.

Discordance between different gastric emptying modalities can be observed and reflect a number of factors that should be recognized. WMC recently was shown to detect more patients with delayed gastric emptying despite a normal GES [2], which is likely a reflection of the inherent and separate physiology being measured. GES solely evaluates meal emptying, while gastric emptying by WMC requires both meal emptying and coordination of the MMC [15], thus evaluating different motility parameters. Gastric emptying can also have daily variation as shown in healthy volunteers by GES [20]. A study of gastroparetic and functional dyspeptic patients that had baseline GES demonstrated that 41% had changes in GES results at a 48-week follow-up that recategorized patients into the opposite diagnosis without the influence of medical management changes between tests [21]. If one of the modalities detect abnormalities with gastric emptying, symptomatic patients should still be considered as clinically having gastroparesis.

Small Bowel Radiography

Small bowel assessment with the readily available barium contrast study can be complementary as symptoms of chronic intestinal pseudo-obstruction and gastroparesis overlap. A contrast study can assess SBTT, although there is a lack of validity. Prior studies that have attempted to set normal values utilized a varied amount of barium contrast, with a resultant wide range of SBTT [22]. Given the lack of standardization, the use of small bowel scintigraphy is perhaps most useful to rule out mechanical obstruction and obtain a qualitative understanding of SBTT, with less than 2 h being reassuring. Those with severely delayed small bowel transit may poorly tolerate enteral nutrition support [23].

Antroduodenal Manometry

Further assessment in gastroparesis may include antroduodenal manometry (ADM) to assess contractility in fasting and postprandial states within the antrum and duodenum. The study consists of six to eight solid-state pressure transducers on a catheter guided into the antroduodenal region either intranasally or endoscopically, with placement confirmed by fluoroscopy [24]. Manometric evaluation is particularly considered for patients who are unresponsive to medical therapy,

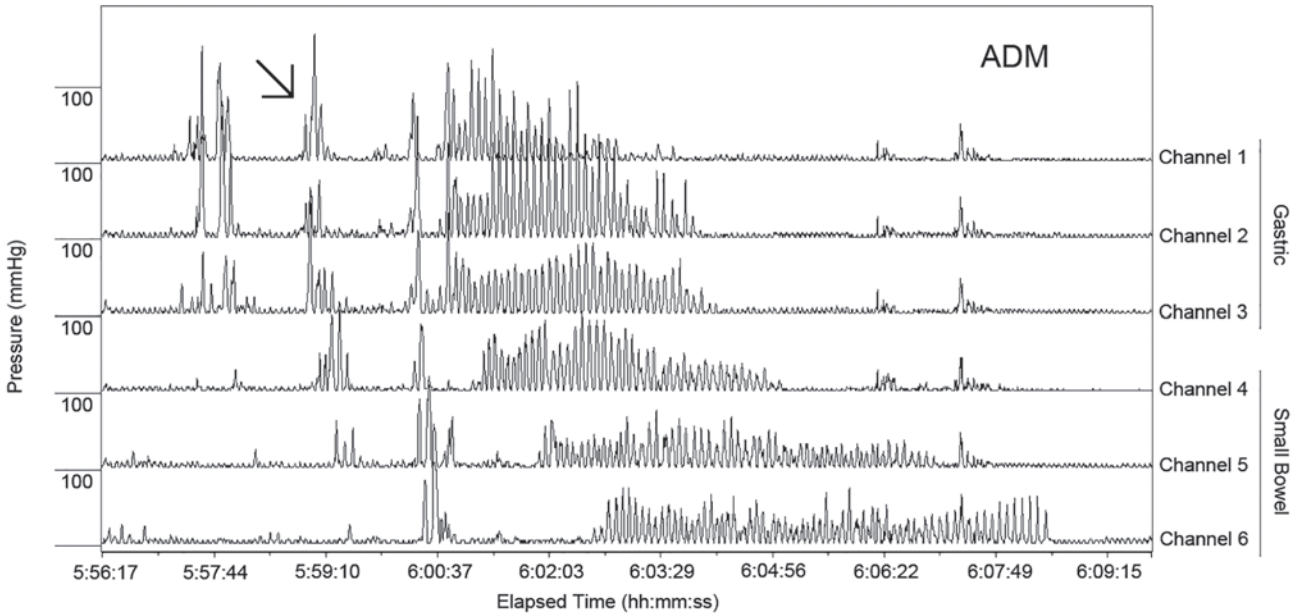

Fig. 42.7 Antroduodenal manometry (ADM) measures antral and proximal duodenum contractility. The start of a peristaltic phase III migrating motor complex (MMC) is demonstrated by the arrow. (Adapted and permission obtained from John Wiley & Sons, Inc. Brun, R. et al. *Neurogastroenterol Motil*. 24(4), 332-e165 (2012). PMID 22292793)

under consideration for intestinal transplant, or being considered for supplemental enteral jejunal feeding [24, 25]. ADM can clarify if there are myopathic (low-amplitude contractions yet intact normal peristaltic patterns such as MMC) or neuropathic (disorganized contractions with normal amplitude contractions) disorders in situations where diagnosis of dysmotility is uncertain [24]. Figure 42.7 shows a fasting phase III MMC detected by ADM. Detailed assessment of gastric, duodenal, or gastroduodenal dysmotility can guide in selecting optimal nutritional support either via gastric, enteric, or parenteral feeding [23, 26]. Identifying a neuropathic component to gastric dysmotility can help focus management on prokinetics where myopathic gastroparesis may not preferentially respond. The advantage of ADM is the ability to assess both gastric and small bowel contractility and propagating contractile patterns due to its multiple sensors. However, ADM is not widely available, relatively invasive, uncomfortable for patients, and therefore not often clinically used except at specialized GI motility centers.

Electrogastrography

Electrogastrography (EGG) records gastric myoelectrical activity using cutaneous electrodes on the anterior abdominal wall to measure gastric slow waves and spike potentials in fasted and fed states. Slow waves (pacesetter potentials) occur at approximately 3 cycles per minute (cpm) and determine the maximum frequency and propagation of gastric contractions. Spike potentials (action potentials) are considered electrical representations of contractions; however, it should be noted that not all spike potentials correlate with gastric contractions as seen in comparison studies with manometry [27]. A normal frequency for gastric slow waves is established at 2–4 cpm. Abnormal slow wave findings include gastric dysrhythmias (bradygastria, tachygastria, and bradytachyarrhythmia), abnormal slow wave propagation, and electromechanical uncoupling (normal slow waves with the absence of contractility) [24, 27]. EGG tracings do not have diagnostic waveforms that can be visually interpreted. Visual analysis serves mainly to discern artifacts and provide preliminary impression prior to fast Fourier transformation. Data from several studies show a wide positive predictive value ranging from 50% to 81% of an abnormal EGG for diagnosing gastroparesis [28]. While the study has been available for decades, the clinical role of EGG remains unclear.

Gastric Magnetic Resonance Imaging (MRI)

Gastric MRI evaluation is still under development and mainly used in research settings; however, this modality allows for assessment of gastric emptying, peristaltic activity, and volume distribution [29]. Most studies evaluate gastric motility with liquid meals labeled with gadolinium for evaluation [29], although some studies have utilized food-based enhancement without the use of contrast agents [30].

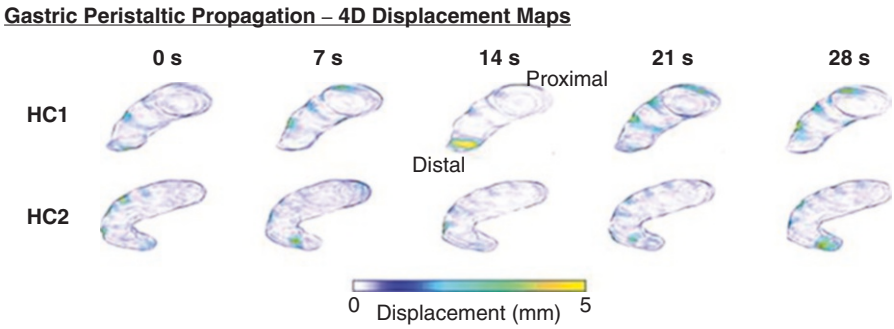

Fig. 42.8 Gastric MRI demonstrating consecutive frames of four-dimensional displacement maps for two healthy controls. Gastric wall is color-coded according to displacement magnitude and allowing for visualization and analysis of individual peristaltic propagation patterns. (Adapted and permission obtained from John Wiley & Sons, Inc. Sclocco, R. et al. *Neurogastroenterol Motil*. E-print, e14146 (2021). PMID: 33797166)

Quantifying gastric emptying with MRI has previously been shown to have high agreement with solid (R = 0.988) and liquid (R = 0.917) meal scintigraphy [29]. Recent four-dimensional techniques demonstrate ability to asses emptying, motility, and patterns of gastric wall displacement to visualize peristalsis [30] (Fig. 42.8). While MRI provides a noninvasive method to assess gastric motility and contractility, the technique requires extensive manual data processing [30] and remains a costly diagnostic technique being a current barrier to routine clinical use. Currently, gastric MRI has been suggested to be a useful comprehensive gastric physiology research tool, with ongoing work showing promise for clinical applications.

Ultrasound

Ultrasound has been shown to noninvasively measure gastric emptying of liquids by 2D ultrasound measuring changes in antral area over time [31]. 3D techniques can measure gastric volume [5]. More recent studies have been interested in measuring gastric accommodation, which is perhaps more relevant in functional dyspepsia. While the advantage of ultrasound includes easy equipment access and no radiation exposure, this modality is currently limited to research settings and assessment of liquid emptying and has inter-operator variability and suboptimal imaging in obese individuals [31].

Pharmacotherapy

When conservative approaches with lifestyle changes such as focusing on small and frequent low-calorie, low-fat, and low-residue meals alone are not effective, pharmacotherapy represents the next step. Available medication classes include prokinetics to improve gastric emptying and contractility as well as antiemetics and neuromodulators to improve symptoms not addressed by pure prokinetics (Table 42.1). It is important to note that some of these latter agents may reduce gastric motility.

Results of gastric motility testing can help guide pharmacologic management where impaired motility may suggest benefit from prokinetics, although data on the association of improvement of gastric emptying and symptoms is limited. Furthermore, evidence suggests that functional dyspepsia and gastroparesis may be two entities on the same continuum [21]. In this respect, mild gastric emptying delay could be treated similarly as functional dyspepsia with neuromodulation. Therefore, multiple medication classes may be needed to achieve symptom improvement while focusing on the predominant symptom (nausea, early satiety, bloating, abdominal pain) most distressing to the patient. A patient with nausea predominance could benefit from agents with dual-action prokinetic and antiemetic effects, whereas early satiety may benefit from pure prokinetics to improve gastric emptying and/or neuromodulator to address sensory abnormalities. Patients mainly presenting with pain may benefit more from neuromodulating antidepressants. Consideration of using dissolving or liquid formulations, when available, should be made in patients who have severely delayed gastric emptying for more reliable systemic absorption [23].

Prokinetic Agents

Metoclopramide is a dopamine D2-receptor antagonist and 5-HT_4 receptor agonist that provides dual-action prokinetic and additional antiemetic benefit through central processes. This is the only US FDA-approved treatment for gastroparesis, and its use is limited to a recommended 12 weeks unless benefits outweigh risks, owing to a black box warning for

Table 42.1 Summary of available pharmacologic treatment options

Drug	MOA	Therapeutic target	Comments
Class: prokinetics			
Metoclopramide	D2 antagonist and 5-HT4 agonist	Gastric emptying nausea	Only US FDA-approved treatment for gastroparesis limited to 12 weeks due to tardive dyskinesia concerns
Domperidone	D2 antagonist	Gastric emptying nausea	Not readily available in the USA
Cisapride	5-HT4 agonist	Gastric emptying	Off the market in the USA due to cardiac arrythmias
Prucalopride	5-HT4 agonist		Approved for constipation Ongoing studies in gastroparesis, showing improvement in cardinal symptoms with favorable side effect profile
Velusetrag	5-HT4 agonist		Studies showing improved gastric emptying Undergoing investigation
Erythromycin	Motilin agonist		Macrolide antibiotic that requires optimal dosing to avoid side effects and drug holidays for tachyphylaxis
Camicinal	Motilin agonist		Selective motilin agonist that remains under investigation
Relamorelin	Ghrelin agonist		Improvement in vomiting in diabetic gastroparesis Clinical trials ongoing
Class: antiemetics			
Promethazine	H1 antagonist	Nausea	
Prochlorperazine	D2 antagonist		
Ondansetron	5-HT3 antagonist		
Aprepitant	NK-1 antagonist		APRON trial was a negative trial for primary VAS-based nausea outcome but showed improvement using other symptom grading measures
Tradipitant	NK-1 antagonist		Phase 2 trials showed improvement in nausea
Class: neuromodulators			
Amitriptyline	Tricyclic antidepressant	Sensory	Improved symptoms of functional dyspepsia in the absence of delayed gastric emptying
Nortriptyline	Tricyclic antidepressant		NORIG trial—negative trial in primary outcomes of gastroparesis symptoms but improved secondary outcomes in abdominal pain
Mirtazapine	Adrenergic and serotonergic	Nausea, appetite loss	Studied in case series in gastroparesis
Buspirone	5-HT1a agonist	Fundic relaxation, early satiety	Studies primarily in functional dyspepsia

tardive dyskinesia (risk 1%), which may be reversible if stopped early enough at first sign [23]. Other side effects include acute dystonic reactions, depression, anxiety, insomnia, and QTc prolongation, and careful monitoring is required. Several formulations are available including oral tablet, sublingual dissolvable tablet, parenteral, and recently FDA-approved intranasal spray [23, 32]. Domperidone is another D2-receptor antagonist with similar efficacy to metoclopramide but has less CNS side effects because it does not cross the blood-brain barrier to the same degree [23, 33]. In the USA, domperidone can only be prescribed through an FDA Investigational New Drug application since it has been associated with fatal arrhythmias from QTc prolongation. Domperidone can also cause hyperprolactinemia and interact with drugs that alter CYP2D6 function [23]. Ongoing clinical trials on CIN-102, a deuterated domperidone with aim to treat gastroparesis symptoms while minimizing cardiotoxicity, are underway [34].

Cisapride is the first drug in the low-selective 5-HT_4 receptor agonist class and one of the earliest prokinetic agents for gastroparesis but has been off the market in the USA since 2000 due to significant concerns with cardiac arrhythmias. Prucalopride is a highly selective 5-HT_4 agonist that is approved for use in constipation with a favorable safety profile, and it does not affect the QTc interval nor has been shown to interact with other drugs [35]. A recent single-center crossover study showed beneficial improvement in three subscales of the Gastroparesis Cardinal Symptom Index of nausea/vomiting, fullness/satiety, and bloating/distension in patients with idiopathic gastroparesis [36]. Velusetrag is another 5-HT_4 agonist that is still being under investigation but has shown to improve gastric emptying in idiopathic and diabetic gastroparesis and is generally well tolerated [37].

Erythromycin is a macrolide antibiotic that is also a motilin receptor agonist, which increases gastric emptying by inducing the phase III MMC [23]. Side effects include nausea, vomiting, abdominal cramps, and diarrhea that are more common at high doses within an antibiotic range or used in emergent upper GI bleeding settings to clear the stomach. Erythromycin should be administered in low doses (e.g., 50–100 mg, 1 mg/kg). Benefit is seen for almost 4 weeks until tachyphylaxis occurs which can be mitigated by drug holidays [23]. Periodic EKGs are recommended to monitor for QTc prolongation with long-term use. The novel small-

molecule selective motilin agonist camicinal has been shown to preferentially enhance antral activity and remains under development for treatment in gastroparesis [38, 39].

Relamorelin is a subcutaneous injection that is a pentapeptide ghrelin receptor agonist with prokinetic effects without decreasing fundic accommodation [40]. Evidence shows accelerated gastric emptying and improvement in symptoms, particularly vomiting in diabetic gastroparesis [41]. Clinical trials on relamorelin are still underway.

While identification of delayed emptying is an objective marker that allows for targeted treatment, evidence is mixed whether pure prokinetic agents by themselves are fully beneficial. A meta-analysis of 34 trials on prokinetics, out of which 23 trials that had data on symptom and gastric emptying improvement could be included, could not confirm a statistically significant correlation between symptom improvement and gastric emptying on prokinetics [42]. However, a recent systemic review and meta-analysis demonstrated an association of cisapride, relamorelin, metoclopramide, and domperidone with improved gastric emptying and upper GI symptoms only when studies with optimal gastric emptying examinations were included [43]. Furthermore, studies have shown that there is poor correlation with gastric emptying and symptoms [44], adding to the body of evidence that gastric emptying may not necessarily be the sole driving factor to explain symptoms and other agents may be needed to complement prokinetics to achieve symptom control.

Anti-nausea

In general, use of commonly prescribed antiemetic drugs has not been thoroughly studied in gastroparesis and remains empirical [23]. Promethazine and prochlorperazine have been suggested for use in mild-to-moderate gastroparesis and ondansetron for moderate-to-severe gastroparesis [7]. Aprepitant is a neurokinin-1 receptor (NK1R) antagonist that is used for postoperative and chemotherapy-related nausea and is being studied in gastroparesis. A recent randomized controlled study failed to demonstrate improvement of the pre-specified primary outcome of nausea graded on a visual analog scale but demonstrated improvement in secondary outcomes in nausea, vomiting, and retching using alternative validated measures for symptoms [45]. Tradipitant is another NK1R antagonist that has undergone phase 2 trials, and early data suggests improvement in nausea and nausea-free days compared to placebo [46]. Synthetic cannabinoids such as dronabinol are approved for chemotherapy-induced nausea; however, optimum use in gastroparesis remains unclear, and there may be risk of hyperemesis on discontinuation [23, 47].

Neuromodulation

Tricyclic antidepressants in low doses are commonly used pharmacologic neuromodulators to reduce pain, nausea, and vomiting in other functional GI disorders [47]. Amitriptyline, compared to placebo and escitalopram, improved symptoms of functional dyspepsia in the absence of delayed gastric emptying [48], which highlights the importance of gastric emptying evaluation to guide targeted management. Nortriptyline, compared to amitriptyline, has lower anticholinergic effects on gastric motility; however, the NORIG trial was a negative study and failed to show improvement in overall symptoms of nausea, fullness or early satiety, and bloating measured by the Gastroparesis Cardinal Symptom Index [49]. Secondary outcome of abdominal pain by the Gastrointestinal Symptom Rating Scale, however, showed sustained improvement [49]. Mirtazapine, with adrenergic and serotonergic effects, has been shown to improve nausea, vomiting, and appetite loss in several case reports [47]. Buspirone has been used in gastroparesis to reduce postprandial fullness and early satiety by inducing fundic relaxation, although studies have primarily been conducted in functional dyspepsia [47].

Conclusion

Advances in diagnostic technology and standardization of examinations have pushed forward our ability to diagnose gastroparesis as well as characterize neuropathic or myopathic subtypes with clinical implications on treatment. Pharmacologic management has previously focused on prokinetics to improve gastric clearance. However, data suggests poor correlation between gastric emptying and symptoms, and therefore further management with antiemetics or pharmacologic neuromodulation can be beneficial. Personalized treatment can be designed based on diagnostic characterization of gastric dysmotility, expanding dysmotility evaluation beyond the stomach and focusing on predominant distressing symptom.

Questions

1. Which of the following gastric emptying scintigraphy results is considered diagnostic of gastroparesis?
   A. 40% retained at 2 h and 5% retained at 4 h
   B. 55% emptied at 2 h and 91% emptied at 4 h
   C. 50% retained at 2 h and 15% retained at 4 h
   D. 60% emptied at 2 h and 95% emptied at 4 h

Answer: C. Although at 2 h the percentage meal retained is normal, the percentage retained at 4 h is >10% and therefore diagnostic of gastroparesis.

2. A patient with 11% retention at 4 h on gastric emptying scintigraphy presents with the primary complaint of epigastric pain. What is the best pharmacologic management option for this patient?
   A. Prokinetics
   B. Neuromodulator
   C. Antiemetics
   D. Narcotic analgesia

Answer: B. While the gastric emptying study is diagnostic of gastroparesis, the percent of retention at 4 h is minimally abnormal, and this patient can be considered as having mild gastric emptying delay, which clinically may be similar to functional dyspepsia, and benefit from neuromodulation such as a tricyclic antidepressant to address primary complaint of epigastric pain.

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Endoscopic Pyloric Therapies for Gastroparesis

43

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Objectives

1. Describe the regional gastric motility events involved in gastric emptying with emphasis on pyloric function.
2. Highlight the role of pyloric dysfunction in patients with gastroparesis.
3. Discuss the different endoscopic therapies directed at the pylorus for treatment of gastroparesis.

Introduction

Gastric emptying is a highly regulated process reflecting the integration of the propulsive forces of proximal fundic tone and distal antral contractions with the functional resistance provided by the pyloric sphincter. Gastroparesis is a complex syndrome with a variety of potential underlying mechanisms, among which are abnormalities in fundic accommodation, gastric arrhythmia, impaired antral contractility, abnormalities of the small bowel with resultant abnormal gastric feedback, vagal injury/neuropathy, and pyloric dysfunction. Importantly, patients can be affected by more than one mechanism, perhaps explaining why data on the treatment of gastroparesis has been mixed. Patients with gastroparesis (delayed gastric emptying) have symptoms of nausea, vomiting, early satiety, postprandial fullness, and abdominal discomfort. Treatment begins with dietary modifications, prokinetic medications, and/or antiemetic medications. For patients remaining to be symptomatic, other treatments may involve surgical treatments such as gastric electric stimulator placement, pyloroplasty/pyloromyotomy, as well as endoscopic pyloric treatments such as botulinum injection, balloon dilation, and pyloromyotomy.

This chapter will discuss the therapies directed at the pylorus for the treatment of gastroparesis. There has been increased interest in the use of pyloric therapies for the treatment of refractory gastroparesis, especially with endoscopic pyloromyotomy.

Pyloric dysfunction, with pyloric restriction or "pylorospasm," defined as prolonged periods of increased pyloric tone and phasic contractions, is responsible for delayed gastric emptying in a subset of patients and has been the target of different therapies over the years, especially in those patients with refractory symptoms. Unfortunately, to date, there is no single best test that can identify which patients may benefit from treatment to the pylorus. Antroduodenal manometry recordings with closely placed pressure sensors can record pyloric sphincter pressure, showing a baseline tone to the pyloric sphincter with intermittent contractions. Endoluminal impedance planimetry (EndoFLIP; Medtronic, Minneapolis, Minnesota) with placement of a balloon catheter across the pylorus can be used to measure pressure and cross-sectional area (CSA) to calculate pyloric distensibility index (DI). Overall, a low DI suggests a stiff pylorus, whereas a high distensibility suggests an open pylorus. Data on EndoFLIP has shown that early satiety and postprandial fullness are inversely correlated with the diameter and CSA of the balloon at 40 mL. Moreover, a link between decreased pyloric DI and gastric emptying has been described.

Botulinum Toxin Injection into the Pylorus

Botulinum toxin is a potent inhibitor of acetylcholine neuromuscular transmission and has been used to treat spastic gastrointestinal muscle disorders such as achalasia and gastroparesis. Botulinum toxin injected into the pylorus may reduce pyloric pressure, reducing gastric outlet resistance to gastric emptying so that there is an acceleration of gastric emptying with reduction of symptoms (Fig. 43.1).

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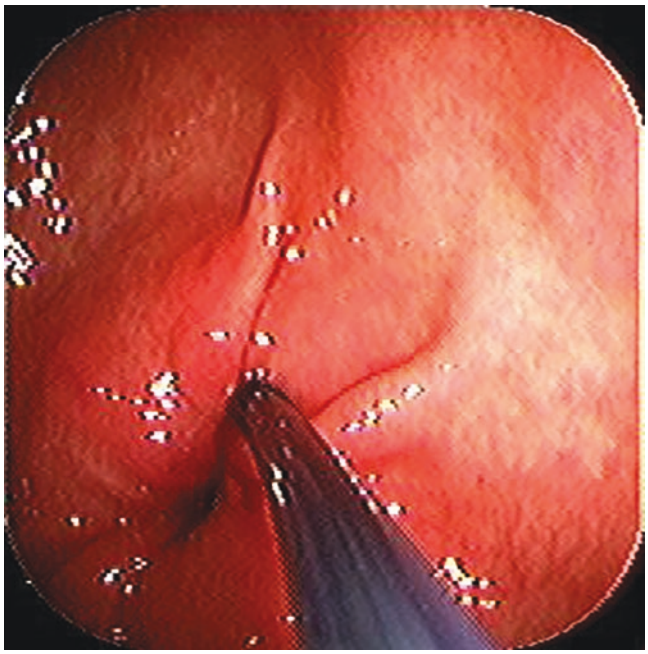

Fig. 43.1 Endoscopic injection of the pyloric sphincter with botulinum toxin

Numerous studies have tested the effects of endoscopic injection of the pyloric sphincter with botulinum toxin in patients with diabetic and idiopathic gastroparesis. Initial studies were open-label studies that observed improvements in gastric emptying and reductions in symptoms for several months. In a large series, 43% had a positive response to botulinum toxin treatment that lasted a mean of approximately 5 months. Improvements are seen with higher doses of Botox (200 units rather than 100 units) into the pyloric muscle.

Two double-blind studies have been reported in a small number of patients; these studies show an improvement in gastric emptying, but with a similar decrease in symptoms as saline injections. The botulinum toxins used clinically (Botox, Dysport, Myobloc, and Xeomin) have been reported by the Hayes Reviews and MCG™ Care Guidelines as unproven and not medically necessary for the treatment of gastroparesis. Insurance coverage for botulinum toxin has become harder to obtain for gastroparesis, although it is often covered for achalasia and lower esophageal sphincter injection.

One concern about use of botulinum toxin injection is if the patient will need repeated injections of botox into the pylorus since the response generally lasts 3 months. Scheduled botulinum toxin injections every 3 months are performed in some centers. As with botox injection into the GEJ in achalasia, repeated botulinum toxin injections could lead to scarring of the pylorus and decreased efficacy. Interestingly, a recent open-label experience showed that Botox injection into the pylorus helped 64% of patients at 1 month, and in the patients responding, it can last up to 6 months in some patients. More practically, we generally allow the patient to become symptomatic again before considering further treatment. In select patients, botulinum pyloric injections may temporize a patient for several months, as further treatments are investigated. Botulinum toxin injection into the pylorus may also be used to as a predictor to pyloromyotomy: a positive clinical response to pyloric Botox injection may suggest better response to pyloromyotomy, either surgical (laparoscopic) or endoscopic (G-POEM).

EndoFLIP, which measures pyloric distensibility and diameter, has been reported to help with selection of patients for treatments for gastroparesis that target the pylorus. Pyloric distensibility measurement predicted symptomatic improvement to pyloric botulinum toxin injection in patients with gastroparesis. Nineteen of 35 patients had impaired pyloric distensibility. In those patients, total gastroparesis symptom score decreased at 3 months, whereas it remained unchanged in patients with normal pyloric distensibility.

Endoscopic Dilation of the Pylorus

Endoscopic pyloric dilation has been used for the treatment of gastroparesis. Most prior studies with endoscopic pyloric dilation have been reported in children. A recent retrospective analysis reported on 47 adult patients referred for refractory gastroparesis, treated with endoscopic pyloric through-the-scope (TTS) balloon dilation. A clinical response, defined by a 1.0-point decrease in the Gastric Cardinal Symptom Index (GCSI), was observed in 25 patients at 2 months (53%) and in 19 patients at 6 months (40%). The GCSI score decreased significantly at 2 and 6 months compared to the pretreatment score. A second dilation was performed for eight patients, and it was effective in five of them (63%). At 2 years, 15 patients still experienced improvement following this treatment (32%).

More aggressive dilation of the pylorus might give better symptomatic response. The clinical outcomes to pyloric dilation with the esophageal FLIP (EsoFLIP), a form of pneumatic dilation, were reported. Forty-six patients with gastroparesis underwent EsoFLIP distention of the pylorus. With pneumatic dilation of the pylorus, pyloric distensibility, gastric emptying, and Gastroparesis Cardinal Symptom Index values improved significantly. After a median follow-up of 3.9 months, 57% of treated patients reported improved symptoms. Long-term follow-up to assess efficacy and comparative trials is needed.

TTS pyloric dilation for gastroparesis patients who have persistent or recurrent symptoms after undergoing pyloromyotomy/pyloroplasty for chronic refractory symptoms has been studied. This treatment has been reported in 13 patients.

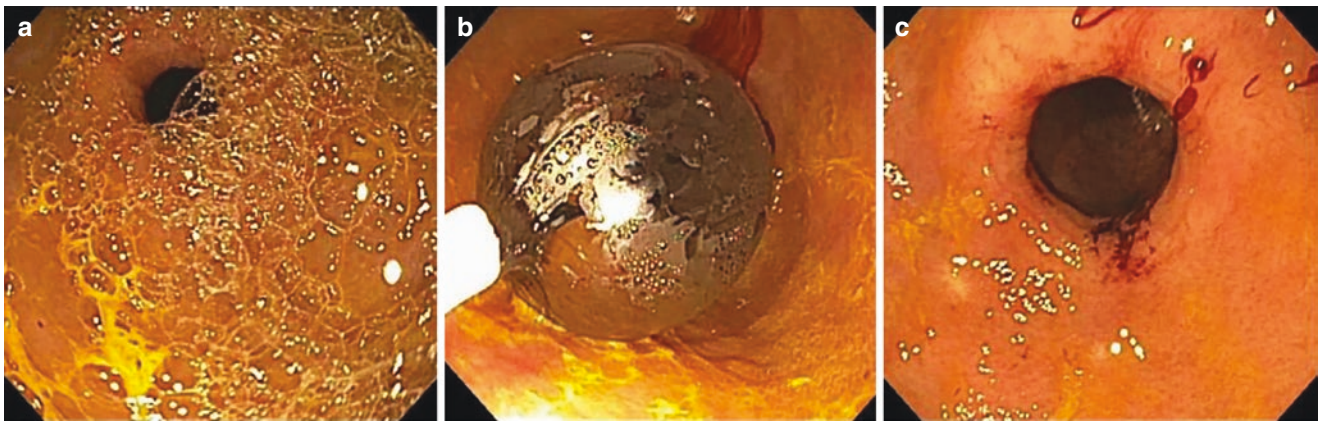

Fig. 43.2 Pylorus of a gastroparesis patient with symptoms refractory to pyloromyotomy before balloon dilation (**a**); during through-the-scope pyloric balloon dilation to 18, 19, and 20 mm (**b**); and post-dilation (**c**). (Jehangir A, Malik Z, Petrov RV, Parkman HP. EndoFLIP and Pyloric Dilation for Gastroparesis Symptoms Refractory to Pyloromyotomy/Pyloroplasty. Dig Dis Sci. 2021 Aug;66(8):2682–2690)

Overall, there was improvement in symptoms at 1-month follow-up, with five (38%) patients reporting symptoms somewhat/moderately better. Patients with symptom improvement had lower pre-dilation pyloric distensibility on EndoFLIP, suggesting incomplete myotomy, pyloric muscle regeneration, or pyloric stricture (Fig. 43.2).

Transpyloric Stenting for the Management of Gastroparesis

Indications and Patient Selection

There are no definite indications for the use of transpyloric stenting (TPS). TPS is often reserved for hospitalized patients with severe gastroparesis flares, refractory to medical therapy, or as a triage to select those patients who might respond to longer-term therapies such as surgical pyloroplasty vs. gastric peroral endoscopic myotomy (G-POEM). This technique should not be pursued in patients on high dose of narcotics or those with concomitant uncontrolled psychiatric conditions. It is contraindicated in patients with suspected obstruction distal to the pylorus.

Technical Aspects

The procedure is performed under general anesthesia, on the left lateral position and using a therapeutic gastroscope (GIF-IT140 or GIF-2TH180; Olympus, Central Valley, Pa). The gastroscope is advanced deep into the descending duodenum. Once a mechanical obstruction is ruled out, a 0.035-in. guidewire is advanced through the scope (TTS) into the distal duodenum, under endoscopic guidance, followed by an 18 mm × 8 cm in length TTS, double-layered fully covered Niti-S self-expandable metallic stent (TaeWoong Medical, Seoul, South Korea) delivery system over the guidewire. The stent is exchanged with the gastroscope and positioned 2–3 cm proximal to the pylorus. The stent is then deployed under endoscopic visualization without the use of fluoroscopy. The proximal flange is left in the antrum and the distal flange in the duodenum, proximal to the ampulla of Vater. The stent is then anchored to the gastric wall to prevent migration, preferably avoiding the greater curvature of the antrum to prevent scaring in case further therapy is pursued with gastric peroral endoscopic myotomy (GPOEM) (Fig. 43.3a, b). Anchoring methods include standard TTS clips, over-the-scope clip (OTSC) vs. the new dedicated stentfix OTSC clip (Ovesco Endoscopy AG, Tübingen, Germany), or endoscopic suturing using the over-the-scope suturing system OverStitch vs. the new TTS suturing system X-Tack (Apollo Endosurgery, Austin, Texas).

Post-procedure Care

After the procedure, patients should be started on liquid diet and progress to a low-residue gastroparesis diet next day, if tolerated. In case of post-procedure abdominal pain, acetaminophen should be used. It is important to avoid narcotics which can worsen gastroparesis symptoms. Patients are then monitored, and if no improvement, the stent can be removed after 2–3 weeks. If significant improvement, then endoscopic/surgical pyloromyotomy should be considered as a long-term therapy.

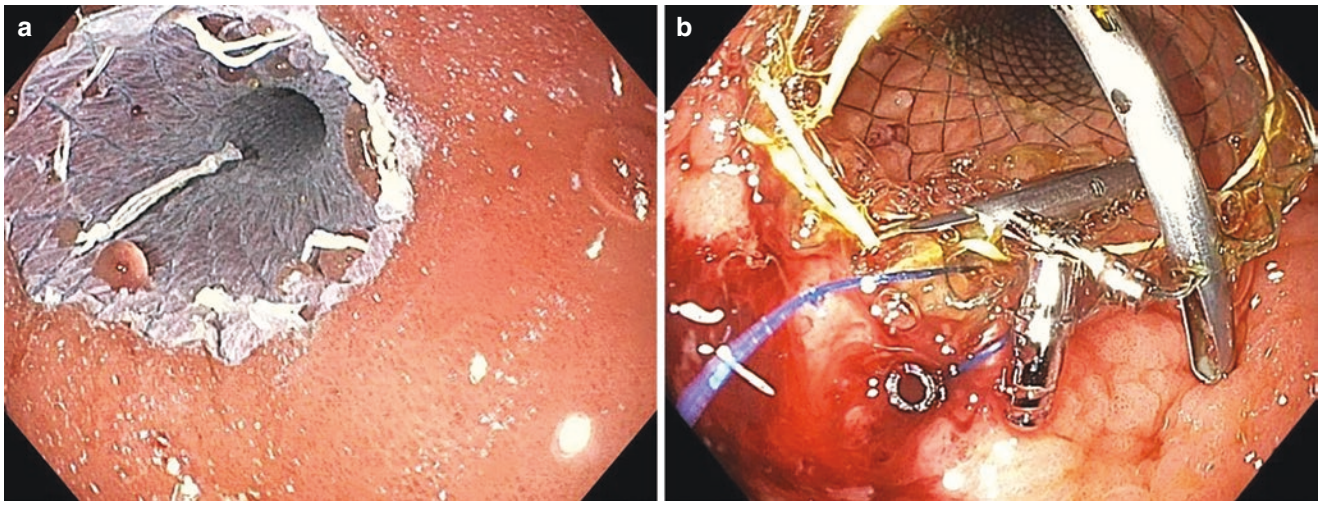

Fig. 43.3 (**a**) Endoscopic view of a deployed TPS with the proximal flange in the prepyloric area. (**b**) The stent is anchored to the gastric wall using TTS clips and the X-Tack suturing system

Outcomes

Few data regarding the use of TPS has been published to date. In 2013, the Johns Hopkins group published the first case series of three patients with confirmed idiopathic gastroparesis, by a 4-h solid gastric emptying study, refractory to multiple medical therapies. These patients underwent an upper endoscopy with placement of a TPS across the pylorus with impressive improvement in symptoms and gastric emptying, after more than 3 months of follow-up in all cases. The stent migrated in one of the patients.

In 2015, the same group published a retrospective case series of 30 patients with refractory gastroparesis, idiopathic in nature in more than half of the cases, who underwent TPS. A total of 48 TPS were deployed. Technical success, defined as the ability to place the stent, was achieved in 98% of the patients. Given concerns of stent migration, the stents were fixated to the gastric wall either by TTS clips, OTSC, or endoscopic suturing. Clinical response was achieved in 21 of 28 patients (75%), with 2 patients lost to follow-up. Response was superior in patients whose predominant symptoms were nausea and vomiting. There was also improvement in the gastric emptying test. Despite stent anchorage, there was an overall high rate of stent migration of 59%, after a mean follow-up time of 146 days.

Gastric Peroral Endoscopic Myotomy (G-POEM)

Gastric peroral endoscopic myotomy (G-POEM) is a minimally invasive technique that entails the combination of flexible endoscopy and third space endoscopy to create a submucosal tunnel at the greater curvature of the gastric antrum in order to expose the muscle layer of the pylorus followed by a myotomy. The technique was first performed in a swine model in 2012 by Kawai et al., followed by the first human case in 2013 by Khashab et al. in the care of a 27-year-old type I diabetic who failed medical therapy and had a positive response to a TPS.

Indications and Patient Selection

GPOEM is indicated in patents with refractory gastroparesis. Overall, patients with gastroparesis and poorly controlled diabetes, major psychiatric comorbidities, and a significant abdominal pain component and those on opioids respond poorly to G-POEM. Moreover, available data suggest that EndoFLIP, showing pyloric DI >8–10 mm^2/mmHg, can be helpful in identifying patients who are unlikely to respond to G-POEM. On the other hand, a lower DI does not predict adequate response. Communication between motility and endoscopy specialists is paramount for proper patient selection. The Gastroparesis Cardinal Symptom Index (GCSI) is calculated at baseline and then used as a validated tool during follow-up. A recent editorial by Khashab et al. suggested that the optimal candidate for G-POEM should meet the following criteria:

1. Clinical criteria
   (a) No major abdominal pain component
   (b) No major psychiatric comorbidities
   (c) No uncontrolled diabetes
   (d) No/minimal narcotics
   (e) Prior clinical improvement to pylorus-directed therapies (e.g. Botox, TPS)
2. EndoFLIP showing a pylorus DI <8–10 mm^2/mmHg
3. Absence of antral hypomotility

Technical Aspects

The principles of G-POEM are similar to those of POEM, consisting of submucosal injection, mucosal incision, submucosal tunneling, myotomy, and closure of the mucosal entry. The procedure is performed either in the endoscopy unit or the operating room with the patient under general anesthesia or conscious sedation. Patient can be on a supine or left lateral position. A high-definition gastroscope (GIF-H190; Olympus, Central Valley, Pa) fitted with a transparent cap and carbon dioxide insufflation (CO_2) is used to minimize the risk of tension pneumoperitoneum. A dose of intravenous broad-spectrum antibiotic is given during the procedure. Before starting the mucosal injection, food residue in the stomach should be cleaned by irrigation, suction, or lavage. Some endoscopy units will routinely perform EndoFLIP pre- and post-myotomy using the 8 cm (E-325) catheter obtaining measurements at 30, 40, and 50 mL (Fig. 43.4a). A submuco-

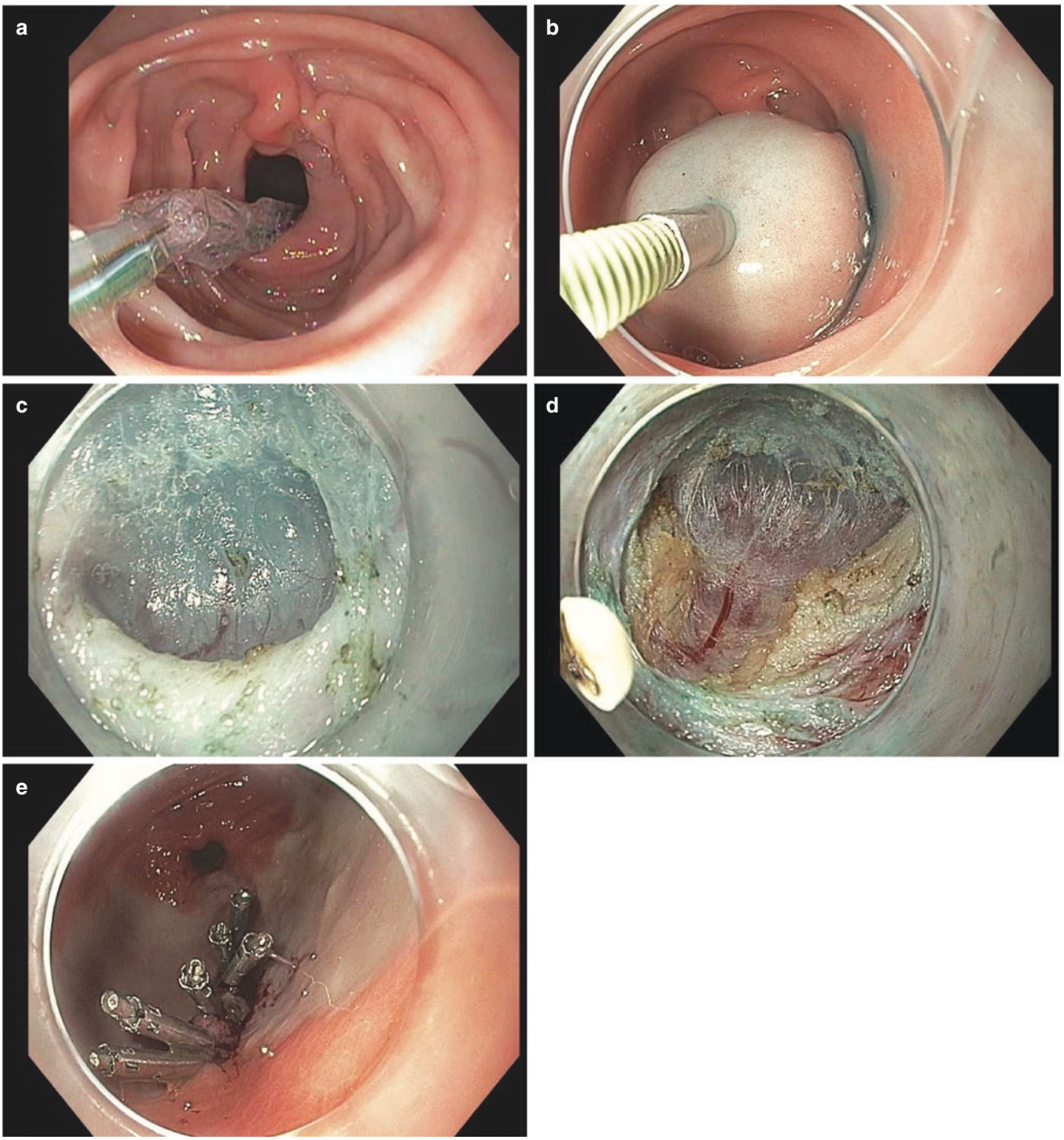

Fig. 43.4 (**a**) Endoscopic view of the EndoFLIP balloon through the pyloric channel pre-myotomy. (**b**) Submucosal bleb using saline solution and 0.25% indigo carmine in the greater curvature of the gastric antrum 5 cm proximal to the pylorus. (**c**) Pyloric ring identified after completion of submucosal tunneling. (**d**) Myotomy using the insulated tip knife. (**e**) Mucosal entry closure using TTS endoscopic clips

sal bleb is created 5 cm proximal to the pylorus at the greater curvature or anterior wall of the gastric antrum using saline solution and 0.25% indigo carmine or methylene blue solution; a total of 3–5 mL is injected (Fig. 43.4b). A 1.5–2 cm longitudinal mucosal incision is then made with a triangular tip knife (KD-640L, Olympus, Tokyo, Japan) using blended electrosurgical current (Spray coagulation 50 W, effect 3, endoCUT I 2:3:3 or 2:3:2, or endoCUT Q 3:1:1; ERBE, Tübingen, Germany). The endoscope is then introduced into the submucosal space, and tunneling is started using the same knife and spray coagulation (50 W, effect 2) to dissect the submucosal fibers. Repeated injection or direct instillation via the water pump of saline solution mixed with indigo carmine or methylene blue is used to enhance the demarcation between the submucosal layer and muscularis propria. It is of upmost important to pay attention to the orientation of the dissection to ensure that the mucosal layer is not injured during dissection while the submucosal tunnel is extended toward the pylorus. Once the pyloric ring is identified (Fig. 43.4c), the myotomy is performed proximal to distal or vice versa starting at the pyloric ring and then extended proximally. Antral myotomy involves cutting of the inner circular and oblique muscle bundles 2–3 cm proximal to the pylorus, or full-thickness myotomy, at the discretion of the endoscopist. The triangular tip knife or an insulated tip knife (KD-611L, Olympus, Tokyo, Japan) is used to catch circular/oblique muscle bundles and lift them toward the tunnel and then cutting using spray coagulation current at 50 W, effect 2 (Fig. 43.4d). Larger vessels in the submucosa are treated using hemostatic forceps (Coagrasper, Olympus Tokyo, Japan) and soft coagulation current at 80 W, effect 5. Following the myotomy, the mucosal entry is closed using endoscopic clips (Fig. 43.4e). Additional devices that can be used to close the entry include endoscopic suturing using the over-the-scope OverStitch or the X-Tack TTS suturing systems (Apollo Endosurgery, Austin, Texas).

Post-procedure Care

After the procedure, patients are admitted for a 23-h observation and kept *nil per os*. An upper GI series is performed the next day to ensure no extra gastric leak of contrast. Once the upper GI series confirms no leak, the patient is discharged on soft diet for 2 weeks. In case of post-procedure abdominal pain, acetaminophen should be used. It is important to avoid narcotics, which can worsen gastroparesis symptoms. In case of severe pain, tramadol could be considered. All patients are prescribed twice-daily oral proton pump inhibitors for a minimum of 2 weeks to prevent gastric and duodenal ulceration. Also, patients are discharged on broad-spectrum antibiotics such as amoxicillin/clavulanic acid for 3 days. Patients are seen in follow-up, 2 weeks after discharge. The GCSI is used during follow-up at 3 and 6 months post-procedure and compared to the baseline score.

Outcomes

There are multiple retrospective studies reporting short- and mid-term efficacy of G-POEM. Studies have demonstrated that it is a safe and minimally invasive technique. Khashab et al. conducted a multicenter retrospective study including 5 centers around the world and 30 patients (36.7% diabetic gastroparesis, 40% post-surgical, 23.3% idiopathic) who failed medical therapy. Moreover, 53% had undergo other endoscopic therapies with botulinum toxin injection, TPS, and PEG with jejunal extension. Aims of the study were to report safety and clinical response, defined as improvement in gastroparesis symptoms with absence of recurrent hospitalizations. G-POEM was successfully completed in all patients, with a mean procedure time of 72 min (range, 35–223 min). Only two adverse events (AEs) were reported (6.7%), including one capnoperitoneum and one prepyloric ulcer. Clinical response was observed in 86% of patients during a median follow-up of 5.5 months. Moreover, repeat gastric emptying study was obtained in 17 patients with normalization noted in 47% and improvement in 35% of the patients. Until 2018, all data regarding safety and efficacy of G-POEM was from retrospective studies. In 2018, Jacques et al. reported a single-center prospective trial including 20 patients with refractory gastroparesis (10 diabetic gastroparesis and 10 nondiabetic gastroparesis). The primary endpoint of the study was technical success, defined as the total number of successful procedures relative to the number initiated. Other endpoints included safety and clinical success, defined as a decrease of at least 0.75 on the GCSI. Technical success was 100% with a median duration time of 56.5 min (IQR 48.5–67.0). Authors reported a significant improvement in the GCSI, with 90% of patients showing a decrease of at least 0.75 points, with a median improvement of 65%. In addition, there was significant improvement in all parameters of the gastric emptying study. A total of 28 AEs occurred in 16 patients, being the most common post-procedure abdominal pain (8), bleeding (7), and perforation (3). Only one patient required an exploratory laparoscopy with no specified findings. The other AEs were managed conservatively. All cases of bleeding occurred during the procedure with no post-procedure bleeding or required transfusion. Rodriguez et al. performed a prospective cohort study including 100 consecutive patients with medically refractory gastroparesis, the majority of which had idiopathic gastroparesis (56%). Sixty-seven percent of the patients had undergone prior interventions being the most common botulinum toxin injection (46%). This group used the lesser curvature for their approach in 95% of cases. The mean procedure time was 33.8 ± 21.6 min. AEs were noted in

10% of the patients, post-procedure. There were four GI bleedings (two with no source confirmed and two with mucosal ulcers), and one patient underwent diagnostic laparoscopy and enterolysis for retained capnoperitoneum and subcutaneous emphysema on postoperative day 1. Two patients developed severe dehydration, needing prolonged intravenous rehydration. There was one mortality within 30 days from the procedure, with the autopsy determining to be related to an underlying cardiac disease. The mean GCSI prior to myotomy was 3.8 ± 0.86, which improved to 2.4 ± 1.2, or an absolute difference of 1.4 points ($P < 0.001$). At a median follow-up time of 90 days, there was an absolute reduction in the percent of retention at 4 h in the gastric emptying study of 23.6% ($P < 0.001$). Of note, 14 patients underwent a reoperation on a median time to 6.5 months (IQR 4.1–10.9 months). Our group recently published an international, multicenter (5 centers), prospective study to evaluate the safety and efficacy of G-POEM in 80 patients (41.3% idiopathic gastroparesis). The primary endpoint was clinical success at 12 months after G-POEM, defined as at least one score decrease in the total GCSI scoring, with more than a 25% decrease in at least two of the subscales. Seventy percent of patients had previously been treated with botulinum toxin injection and/or TPS placement. G-POEM was technically successful in all cases, with a median procedure time of 43 min (34–56.5 min). Clinical success at 12 months was 59.3% (95% CI, 40.7–75.5) in the postsurgical group, 52.9% (95% CI, 31–73.8) in the diabetic group, and 54.8% (95% CI, 37.7–70.8) in the idiopathic gastroparesis group ($P = 0.913$). Overall, the GCSI Score (including subscales) improved moderately after G-POEM ($P < 0.05$). In a regression model, a baseline GCSI score >2.6 (OR = 3.23, $P = 0.04$) and baseline gastric retention >20% at 4 h (OR = 3.65, $P = 0.03$) were independent predictors of clinical success at 12 months, as was early response to G-POEM at 1 month after therapy (OR 8.75, $P < 0.001$). Five AEs (6.2%) were reported (symptomatic capnoperitoneum in three, mucosotomy in one, and thermal injury in one), all of them recognized and treated successfully during the procedure. Despite all the available data on this technique, we believe G-POEM should be performed as part of prospective IRB-approved studies to help further identify optimal candidates for this procedure.

Conclusion

Endoscopic therapies directed at the pylorus are available for the treatment of refractory gastroparesis. There has been increased interest in the use of these pyloric therapies for the treatment of refractory gastroparesis, especially with endoscopic pyloromyotomy. Most studies have been open-label studies. Similar to pharmacologic therapies for gastroparesis, rigorous comparative studies and even placebo-controlled studies are needed for these pyloric interventions to better understand true efficacy and durability of these endoscopic treatments.

Questions

1. All these are *not* considered optimal candidates for G-POEM except:
   A. Patients with concomitant psychiatric conditions
   B. Patients whose main symptom is abdominal pain
   C. Patients whose main symptoms are nausea and vomiting
   D. Patients on narcotics

Answer: C.

2. In patients with gastroparesis, pyloric dysfunction is best detected with:
   A. Antroduodenal manometry
   B. EndoFLIP
   C. Gastric emptying scintigraphy
   D. Electrogastrography

Answer: B.

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Surgical Treatment of Gastroparesis

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Objectives

1. To outline use of gastric electrical stimulation (GES) as a therapeutic intervention for drug-refractory gastroparesis.
2. To introduce indications and an overview of the procedure for GES surgical implantation, as well as postoperative considerations and potential adverse effects.
3. To demonstrate the efficacy and utility of GES as a powerful antiemetic treatment for GP.
4. Delineate indications suitable for pyloroplasty as primary treatment for gastroparesis.
5. Describe outcomes for pyloroplasty as a treatment modality for gastroparesis.
6. Demonstrate the technique for effective surgical pyloroplasty.

Introduction, Definition, Incidence/ Prevalence: Gastroparesis (GP)

Gastroparesis (GP) is a clinical condition of chronic upper gastrointestinal symptoms diagnosed after elimination of any gastric outlet obstruction and confirmed with scintigraphy showing delayed gastric emptying. There are multiple causes of gastroparesis including viral disease systemic illness diabetes neurological disorders connective tissue disease postsurgical vagotomy and idiopathic. The gold standard of diagnosis is a radionucleotide colloid gastric emptying study, which is administered as an isotope labeled scrambled egg meal. If more than 60% of the meal at 2 h is still present in the stomach or 10% of the meal is present in the stomach at 4 h, then the diagnosis of gastroparesis can be made.

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Symptoms can include nausea, vomiting, early satiety, bloating, and abdominal pain, which may result in a poor quality of life and create a financial burden to the healthcare system. Options for GP treatment are very limited, and existing drugs or investigational agents fail to address symptom reduction in 30% or more of patients diagnosed with gastroparesis. Prokinetic and antiemetic agents are available, but they may cause severe side effects including extrapyramidal signs and tachyphylaxis. Since GP causes vomiting, oral medications can be difficult to implement; therefore, nutritional support modalities, optimization of diabetic control, and improving lifestyle modifications are all essential to maximize therapy. Other treatment options include surgical treatments including pyloroplasty and implantable gastric electrical stimulation (GES) system.

Surgical management of intractable gastroparesis includes a number of different modalities. Causes of this motility disorder can guide a specific surgical option. In certain patients, we routinely perform a sleeve gastrectomy as a first-line therapy for gastroparesis. This is particularly effective in our hands when gastroparesis is due to morbid obesity and diabetes related causes. The procedure can be done either laparoscopically or with robotic assistance and is performed by using a surgical stapler beginning 5 cm proximal to the pylorus and ending near the gastroesophageal junction; the staplers are typically applied alongside a calibrating gastric tube roughly around 34–40 French. This removes approximately 80% of the stomach and results in a 100–150 mL gastric pouch. Sleeve gastrectomy may relieve symptoms of gastroparesis via several mechanisms that are not completely understood. With a gastric pacemaker excision, there is greater intraluminal pressure and less distensibility in the gastric tube. Excision of most part of the body and fundus results in decreased parietal cell mass and decreased level of hormones such as grehlin.

In a study performed by Meyer et al., nine morbidly obese patients (eight female, one male) diagnosed with gastroparesis were prospectively followed after undergoing sleeve gastrectomy. All patients were preoperatively evaluated by

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radionuclide gastric emptying studies. All nine patients reported improved symptoms following longitudinal gastrectomy (mean follow-up of 8 months). Average preoperative BMI was 39.2. Postoperatively, BMI decreased to 36.2 with an average weight loss of 12.3 kg. All patients reported resolution of their preoperative abdominal pain and distension. The most common postoperative symptom noted was vomiting (3/9). One patient remains on prokinetics (metoclopramide). Four patients had postoperative radionuclide gastric emptying studies, of which three now show normal gastric emptying.

Lee and colleagues from Frankfurt, Germany, conducted a 13-year study evaluating patients with delayed gastric emptying and undergoing a laparoscopic sleeve gastrectomy. The study aimed to assess if the procedure would provide symptom relief along with improvement in quality of life. From 122 patients with gastroparesis, 19 were selected for sleeve gastrectomy. Within the group (nine women, ten men), gastroparesis was attributed to postsurgical gastric motility (nine patients, 47%), idiopathic (nine patients, 47%), and diabetes (one patient, 5%). The most common complaint associated with gastroparesis was nausea and vomiting (42%). Quality of life was evaluated by GIQLI (Gastrointestinal Quality of Life Index), with an overall score of 0 indicating the worst quality of life and a score of 144 being the best quality of life. From the patients selected, mean GIQLI was 78. BMI was 24. All patients were medically managed for gastroparesis from a minimum of 1 year with an insufficient response. Selection was performed on the following criteria. Patients with massive gastric dilation were treated with either a subtotal gastric resection or Roux-en-Y reconstruction. Gastric stimulators were used in treating patients with diabetes with only mild gastric dilation. Patients were selected for a sleeve gastrectomy who had moderately dilated stomachs with insufficient emptying and a severe reduction in GIQLI. Sleeve gastrectomy was similar to our described procedure above. Lee and colleagues' results showed that they were able to obtain postoperative information from 15/19 patients. There was an overall GIQLI improvement from a mean of 78 to a mean of 114 in the postoperative group. BMI did not change significantly as preoperatively it was 24 and postoperatively it was 23. Of the 15 patients, 3 had persistent delayed gastric emptying, suggesting a 20% failure rate, from which 2 underwent an additional partial gastrectomy and 1 underwent total gastrectomy.

Following Lee, Alicuben at USC performed retrospective review from all patients who underwent LSG for refractory gastroparesis from September 2016 to December 2017. Selection was based on the surgeon's discretion. Ten patients were included in the study that had refractory disease to medical management as well as gastric electrical stimulators (GES). Preoperative symptoms were assessed using Patient Assessment of Upper Gastrointestinal Disorders-Symptoms Severity Index (PAGI-SYM) or Gastroparesis Cardinal Symptom Index (GCSI) questionnaires. From ten patients (eight women, two men), eight had GES placed, four had diabetes, five were idiopathic, and six had previous abdominal surgeries excluding GES. Nine patients underwent LSG, and one patient had an open partial gastrectomy in conjunction with a Whipple procedure. From eight patients who had GES placed, six were removed at the time of surgery, and two were removed prior to surgery. Postoperatively, the mean follow-up was 13.3 months, and the GCSI scores improved from 3.36 to 1.49 ($p = 0.01$). All but one patient reported improvement in symptoms, suggesting an 11% failure rate. This group was noted to have a normal BMI as well. Alicuben suggests that antral dysfunction may play a critical role in refractory gastroparesis that responds to significant symptom improvement when resected.

Roux-en-Y gastric bypass has also been proposed as a means to manage gastroparesis, especially in association with morbid obesity. A number of studies have suggested that the effect of the bypass and the weight loss anecdotally has decreased patient's sensation of nausea, vomiting, and discomfort. In a study by Sun and Matthew Kroh, patients with gastroparesis were either treated with gastric pacer or Roux-en-Y gastric bypass, with or without resection of remnant stomach. Of the seven patients who underwent Roux-en-Y, five patients had improvement in their symptoms, a 71% rate of effectiveness. Unfortunately, two of the five required subsequent remnant gastrectomy, suggesting that even with a bypass, the remnant continues in some patients to cause complications.

In a later study with Landreneau and Kroh retrospectively reviewed from September 2010 to March 2018, 53 patients who underwent Roux-en-Y for refractory gastroparesis and assessed gastrectomy vs. leaving the stomach in situ would show an effect. These patients, all undergoing RYGB, were divided into two groups, 26 with the stomach left in situ (RY-SIS) and 27 with gastrectomy with RnY reconstruction. A circular gastrojejunal anastomosis was done using a 25 mm stapler. Roux and BP limbs were 75 and 50 cm. The jejunal-jejunal anastomosis was stapled linearly. Of the 26 patients in the RY-SIS group, 25 were female, compared to 18 in the subtotal gastrectomy with reconstruction group. The most common causes of refractory gastroparesis were noted to be idiopathic, followed by postsurgical and then diabetic gastroparesis. All the RY-SIS were successfully managed laparoscopically; however, three of the gastrectomy cases were converted to open due to intrabdominal adhesions. Twelve patients had complications in the postoperative period from the gastrectomy group, with only two in the RY-SIS group within 30 days. Complications include SSI, reoperation, GI hemorrhage requiring transfusion, and DVTs. There was one mortality in each group within 30 days

of discharge due to cardiopulmonary arrest. Based on their results, they noted that symptomatic improvement with a Roux-en-Y gastric bypass with the stomach left in situ vs. near total gastrectomy with reconstruction was equivalent; however, complications were higher in the gastrectomy group, along with operative times. In the gastrectomy group, it was noted that they were less likely to require further intervention as the RY-SIS group was notable for subsequent surgical enteral access for remnant drainage or for nutrition with surgical jejunostomy. The study concludes that gastrectomy may be a more definitive approach for patients who fail previous interventions.

Moszkowicz looked at nine patients with refractory gastroparesis who underwent laparoscopic RYGB as a surgical treatment at a single institution retrospectively. The majority of the patients were noted to be malnourished (seven), while a few (two) had obesity. Technical aspects included a 20–30 cc gastric pouch, a circular gastrojejunal anastomosis using a 25 mm stapler. Roux and BP limbs were 150 and 40 cm in obese patients and 70 and 20 cm in malnourished patients. The jejunal-jejunal anastomosis was stapled linearly. Patient symptoms were monitored before and 12 months after surgery using GCSI. Seven patients were women; two were men. Five patients had diabetes, and two patients had gastroparesis related to prior surgery. The mean weight for malnourished patients was 54 kg and 129 kg for obese patients. GCSI scores decreased significantly after RYGB from 3.6 to 2.1. From these patients, one required another operation for an internal hernia 6 months after the RYGB. The mean weight increased in malnourished patients from 54 to 56 kg at 1 year (BMI improved from 19.9 to 20.79). In the two obese patients, BMI improved from 45.6 to 31.9 at 1 year. The highlight of this study was that although one patient had a complication of an internal hernia, in the malnourished group, there was not a significant weight loss. This suggests that RYGB may be utilized in the malnourished population without further compromising their nutritional status. In the obese population, there was obvious advantage in BMI reduction. Special consideration between these two groups needs to be paid to the alimentary limb, which needs to be adapted to the preoperative nutritional status and preoperative BMI.

Kichler reports a case in RYGB of a 54-year-old male with a BMI of 23, insulin-dependent diabetes, severe gastroparesis symptoms, and a 40-pound weight loss who has failed improvement with medical management. The patient, prior to the bypass, underwent an endoscopic balloon pyloric dilation and GES with no lasting symptom relief. After the procedure, at 6 months, the patient was able to maintain his weight and had resolution of symptoms. In this case, the author concludes that symptoms may have improved due to the known benefit of blood glucose control that is often improved after RYGB surgery.

Gastric Electrical Stimulation (GES) System

Of about five million gastroparetics in the country, more than 30% would benefit from the neurostimulation therapy provided by the implantable gastric electrical stimulation (GES) system with two electrodes implanted in the lamina propria of the gastric smooth muscle.

Indications for GES

GES is marketed as the Enterra Therapy System (Medtronic, Inc., Minneapolis, MN), a Class III medical device under the FDA Humanitarian Device Exemption™ (HDE) application (H990014) for treatment of chronic drug-refractory nausea and vomiting symptoms of diabetic and idiopathic GP. There are also published observations when post-vagotomy GP patients have substantial improvement in symptoms after GES. A subcategory for the indication for GES in diabetic GP is when renal and/or pancreatic transplants are being considered, and GES implantation, by stopping vomiting and allowing immunosuppressant to be absorbed, will prevent rejection of the transplanted organ(s).

Mechanism of Action

Studies have confirmed that the improvement in GP symptomatology is explained by the role of vagal activity based on the power spectral analysis of heart rate variability (HRV) and documentation by PET scanning. The thalamus, caudate lobe, and vagal tractus solitarius are all influenced by GES. The accepted mechanisms for GES improvement of GP symptoms are as follows:

1. Stimulation of the visceral afferent component of the vagal nerve fibers transmits impulses to the nucleus tractus solitarius (NTS), which then projects to the thalamus and caudate nuclei via the reticular formation, and that in turn exerts an inhibitory influence on nausea and vomiting control mechanisms.
2. Enhancement of vagal autonomic function, based on change in the sympatho-vagal ratio, increases gastric accommodation, which allows for improved food intake, by promoting postprandial adaptation and relaxation and decreased gastric sensitivity to volume distention.

Patient Selection

GP patients must have a record of suffering with symptoms including nausea or vomiting for more than 1 year and must not have responded to or have only had a limited exposure to

prokinetic and antiemetic medications because of side effects. Those with predominate abdominal pain presentation need to be carefully re-assessed for any other etiology for such pain because they are not good candidates for GES as far as expecting relief of pain. Patients should also have scintigraphy documented delayed gastric emptying (>60% at 2 h and/or >10% at 4 h). A patient's significant weight loss and an inadequate nutritional status, requiring oral caloric supplements or even use of enteral or total parenteral nutrition, are other qualifying criteria for receiving GES therapy. Patients do not qualify for GES surgery if they are pregnant, undergoing peritoneal dialysis (hemodialysis is acceptable), or suffer from chemical dependency (opiate addiction). GES is not indicated for nausea and vomiting explained by other conditions such as rumination syndrome, cyclic vomiting syndrome, dumping syndrome, and/or bulimic/anorexia-related symptoms. Patients with a limited life expectancy, requiring frequent MRIs to control progression of co-existing conditions (GES contraindicates MRI), or who have occupations requiring physical contact and combat should also be excluded.

Preoperative Evaluation

All established surgical and anesthesia relevant criteria must be evaluated and scrutinized to avoid jeopardizing patients' comorbidities. Also, a recent (within 1 year) esophageal gastro-duodenoscopy (EGD) excluding presence of bezoar, ulcers, pyloric outlet obstruction, sprue, *H. pylori* infection, and other relevant diagnosis is required, in order to exclude or explain the reason for GI symptoms.

Technical Considerations

The GES system includes a small battery-powered (non-rechargeable) pulse generator (Medtronic Enterra Therapy Model 3116/Model 37800 Implantable Neurostimulator) and two 35-cm-long intramuscular leads with 1-cm-long electrodes on the ends (Medtronic Model 4351). The GES pulse generator is 2.2″ (55 mm) × 2.4″ (60 mm) × 0.4″ (10 mm) and weighs 45 g (1.6 oz) (Fig. 44.1).

The system is placed surgically by either Da Vinci robotic-assisted laparoscopy or through an open laparotomy approach. Two permanent electrodes are placed on the greater curvature of the stomach, 9 and 10 cm proximal to the pylorus (Fig. 44.2). The electrodes are secured into the muscularis propria layer of the stomach, avoiding penetration into the lumen, which is confirmed by intra-op EGD. The other ends of the electrodes are inserted into the pulse generator, which is then secured by sutures in a subcutaneous pocket above the abdominal wall fascia. This system is

Fig. 44.1 Medtronic ENTERRA II device, two electrodes, and N'Vision Clinician Programmer

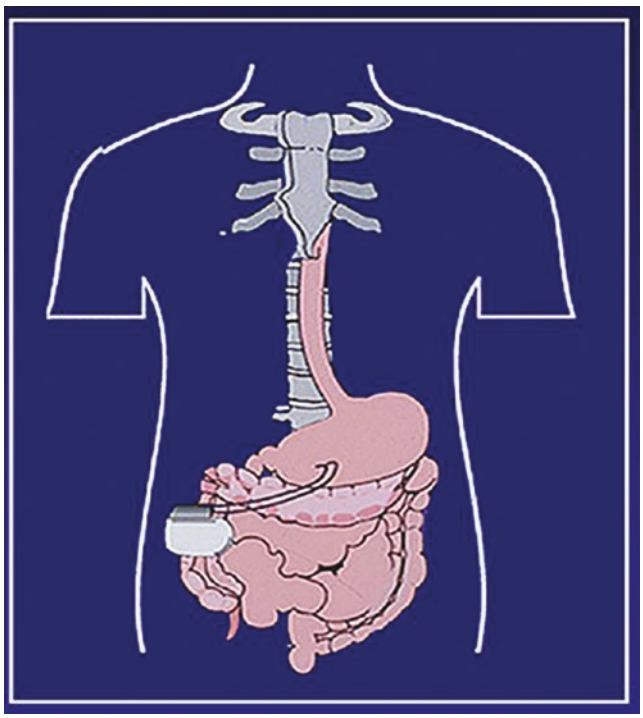

Fig. 44.2 The specific location of two electrodes and the pulse generator

activated within 48–72 h and is accessed with a handheld external programmer (N'Vision Clinician Programmer Medtronic Model 8840) to adjust parameters based on obtained readings, especially impedance between two electrodes (200–800 Ω are normal values) and patients' clinical presentation. Default settings are seen here in Fig. 44.3.

GES therapy is the only currently available gastric stimulation system utilizing parameters which have been recog-

The pulse generators standardized/default parameters:
Current- amplitude, 5 mA;
Pulse width, 330 ms (microseconds);
Rate 14 Hz;
Cycle ON: 0.1 seconds; cycle OFF: 5.0 seconds

Fig. 44.3 This figure demonstrates placement of electrodes in the antrum 10 centimeters from the pylorus with subcutaneous implantation fo the pulse generator

nized as a short pulse with low energy (microseconds) and frequencies 3–4 times higher than physiologic slow waves (12 cycles/min) called "neurostimulation." The approach improves nausea and vomiting in GP patients without a significant acceleration in gastric emptying, and does not reverse slow wave dysrhythmias.

Outcomes

Investigators have reported an improvement in all GP symptoms after GES implantation and use. The Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS) demonstrated an improvement in weekly vomiting frequency (WVF) and quality of life (QoL) in gastroparetics using the GES system. Additional clinical parameters that have improved by long-term follow-up of patients receiving GES include HbA1c in diabetics, increase in BMI, as well as improvement in physical and mental components of QoL-36 scores. Results showed that diabetic and postsurgical patients had superior (>50%) reduction in their GP symptoms scores compared to the idiopathic GP group (60% vs. 59% vs. 49%, respectively) during the follow-up to 5 years by a single center (Lee et al. 2020).

A database generated by the NIH/NIDDK-funded Gastroparesis Clinical Research Consortium showed that 15% of enrolled GP patients received GES, and they have significantly improved GCSI scores after 48 weeks of follow-up over those that did not receive the treatment. Interestingly, the most recent publication from April 2021 of the European Society for Neurogastroenterology and Motility included GES in their proposed schematic algorithm of GP management as an example of antiemetic for patients who are refractory to D2, 5HT3, and NK1 antagonists.

GES System-Related Complications

The most common adverse events (AE) are (1) dislodgement of GES electrodes (trauma, twisting/braiding of the lead(s)) and (2) penetration of electrodes through the gastric mucosa. They required removal of the whole GES system and waiting for at least 3 months before reinserting so all infected tissue is restored. Other adverse events include (3) lead insulation damage; (4) flipping of the neurostimulator with or without migration of the leads, occurring during the first 2–3 years; (5) bowel obstruction requiring surgical correction; and (6) skin erosion.

Postoperative Considerations

The main complication is a 6% risk of infection at the pulse generator site, which can occur in the immediate postoperative setting or at any time within the first 2 years of placement, particularly in diabetic GP patients. Trauma can trigger a hematoma at the pulse generator site, leading to an abscess which could then lead to a systemic infection. A temporary self-limiting, postsurgical, or posttraumatic seroma or hematoma can form at the pulse generator site and usually resolves without any sequela. Infection of the pocket is best diagnosed by ultrasound imaging. Withdrawal of fluid by aspiration could be carefully considered, as it would allow for culture sensitivity test, followed by appropriate antibiotics. If the infection of a pocket cannot be resolved, then the whole device will need to be removed because infection can spread thoroughly.

Healthcare Costs

The reduction of severe GP symptoms while using GES initiated a cascade of other outcomes, which showed to be very beneficial not only for patients but also for healthcare utilization. GES reduced frequency of hospitalizations (50 days/year before to 14 days after GES $p < 0.05$) and ED visits, allowed for the removal of jejunostomy tubes required for nutritional support, and reduced use of prokinetics. Such results provided evidence of the positive economic impact of GES therapy on long-term clinical outcomes in gastroparetic patients not responding to standard medical therapy.

A recent study of 33 DMGP patients revealed that symptom relief persisted at follow-up after at least 4 years. Quality-adjusted life years improved after GES, which was cost-effective after 24 months.

Specific Considerations

Life expectancy of the battery is 5–10 years, but this is influenced by the GES settings of the parameters, mainly voltage, which was responsible for changing current and energy use by the System. During all outpatient follow-up visits, the frequency (rate), pulse width, and time *on/off* were never changed. The decision to increase parameters, specifically

voltage and subsequently current, was only made if there was no other plausible and treatable explanation for an increase in nausea/vomiting, specifically infections, poor glucose control, renal failure, or use of narcotics. An unexplained abdominal pain should not be a reason for adjustment of any GES parameters.

Diathermy is contraindicated in patients with an implanted GES. The system should be deactivated prior to surgery, and GES patients should not have MRI performed at any time while the system is in place. All other diagnostic tests such as ultrasound, CT scans, X-rays, and treatment procedures are allowed, as they do not cause any injury to the system and do not damage surrounding tissues/organs. Sometimes, a standard electrocardiogram changes can reflect the rate of 12 cycles/min of the pulse generator, but it has no effect on cardiac function. However, it is important to be aware of those cardiogram findings, which could be immediately reassessed by repositioning of ECG electrodes, so they don't cover a stomach area.

Surgical Pyloroplasty

Multiple recent studies demonstrate that pyloroplasty (PP) serves as an effective primary therapeutic approach for gastroparesis (GP). Pyloric contractions seen on manometry are of higher amplitude and longer duration in diabetics with GP. PP reduces the barrier function to gastric emptying. Outcomes of PP demonstrate normalization of gastric emptying times in a majority of patients, although this objective measurement has poor correlation with symptoms resolution.

Indications for Pyloroplasty

Stand-alone PP is reported as an effective treatment for early-stage GP, while other studies describe triage indications based on symptoms. PP alone is best suited for postsurgical GP resulting from damage of the vagus nerve. Damage to the vagus nerve causes functional gastric outlet obstruction with intact gastric contractions. Botulinum toxin injection and stenting at the pylorus can be used selectively to determine the efficacy of stand-alone PP. Interval response to endoscopic interventions can be predictive of a positive response to PP. Selection for PP should include assessment of validated symptoms scores (gastroparesis cardinal symptom index GCSI) and demonstration of delayed gastric emptying (>60% at 2 h and/or >10% at 4 h). Parkman also reports use of the EndoFLIP (Medtronic) dynamic manometry to measure pyloric compliance as an indicator of favorable improvement with PP.

Recent comparison of stand-alone PP to gastric electrical stimulator (GES) outcomes by Marowski et al. (2021) suggests that bloating was the only symptoms that was durably improved in the PP group. This analysis found that those with early satiety were best treated with GES. Analysis by Zoll et al. (2020) demonstrates that refractory nausea and emesis were best treated by combined GES + PP therapy with greater symptom improvement in the diabetics compared with the idiopathic subtype. Parkman also reports use of the EndoFLIP (Medtronic) dynamic manometry to measure pyloric compliance as an indicator of favorable improvement with PP.

Operative Technique

Standard PP technique was first described by Heineke and Mikulicz in 1886 for the treatment of a perforated pyloric ulcer. Other techniques, including the Jaboulay and Finney, were developed to treat strictures in the pyloro-duodenal complex. Delayed emptying in GP is alleviated by the creation of an anterior gastro-duodenostomy (longitudinal or organo-axial) that divides the pyloric muscle, thereby separating muscular columns. Diamond-shaped transverse closure (mesentero-axial) renders the valve incompetent and increases the outlet diameter. This technique resolves delayed gastric emptying by increasing the functional outlet size and permanently separating the pyloric muscle with a mucosal bridge.

Studies commonly report laparoscopic and robot-assisted techniques that allow either single-layer full-thickness closure or double-layer closure. Technique starts with suspension of the cephalic and caudal ends of the pyloric ring followed by creation of a longitudinal or organa-axial incision through the pylorus. The incision is carried 2 cm or more on the antrum and an equal distance across the pyloric band into the duodenum (Fig. 44.4). This incision is routinely performed with a harmonic scalpel or electro-cautery shears to achieve hemostasis. Special care should be exerted to prevent injury to the back wall of the stomach and duodenum.

Proper closure is dependent on the incision extending onto the stomach with a length of 2 cm or greater and matching length onto the anterior duodenal wall. The gastro-duodenostomy is closed in a transverse fashion. Authors or recent laparoscopic and robotic approaches differ in closure techniques. Shada describes a running full-thickness absorbable suture starting from the center of the wound extending to each corner. Davis et al. (2017) creates an inner running absorbable suture layer starting at each corner and meeting in the center followed by a second layer of interrupted permanent suture placed in a lembert fash-

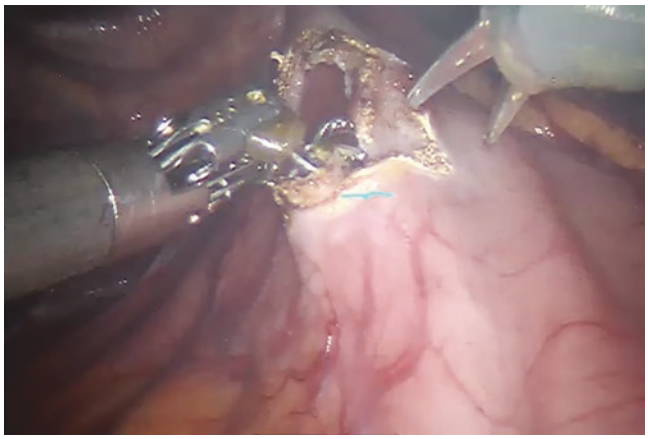

Fig. 44.4 Creation of a gastro-duodenostomy is pictured using robot assistance with electrocautery shears with extension of 2 cm onto the antrum

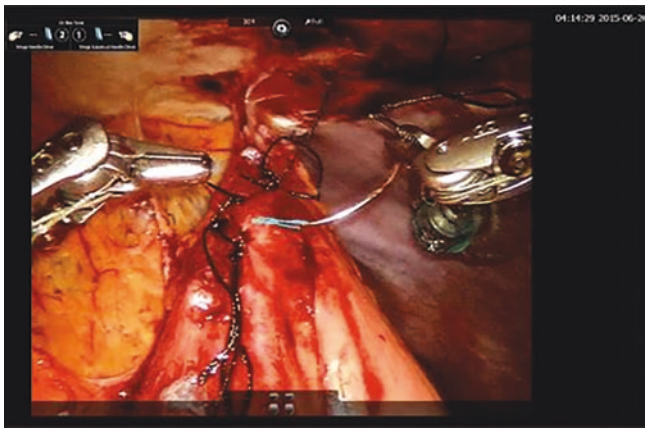

Fig. 44.5 Robotic pyroplasty closure is pictured to create a lembert stitch layer of permanent suture with telestration marking showing the path of the needle

ion, which dunks the mucosal closure (Fig. 44.5). Precise suturing is recommended to prevent leak for the surface of the repair, which can lead to fistula formation and delayed pocket site infections. Intraoperative endoscopy can be utilized to test for leaks and assess for pyloric channel diameter. Current studies on the effects of this surgery fail to correlate the size of the PP with improved gastric scintigraphy, although surface area of the PP correlates with severity of dumping syndrome symptoms.

Complications

Dumping syndrome is the primary complication of PP and is easily treated with octreotide. Inaccurate closure of the gastro-duodenostomy or failure of the suture line can result in fistula formation. Fistulas may require long-term drainage and parenteral versus post-pyloric tube-based enteral nutrition. Fistulas from the PP site are especially hazardous in patients with existing GES with resulting stimulator pocket site infections.

Excessively high 4-h retention on preoperative GES (53.7% in contrast to 32.9% for resolution by PP alone) often serves as a predictor of PP failure as a primary treatment for GP. Demonstrated failure to improve based on scintigraphy findings also predicted recalcitrant daily nausea and abdominal pain. Evidence suggests that PP is more successful in cases that do not represent end-organ failure of the stomach. Individuals with greater than 50% retention of 4-h GES should be considered candidates for subtotal or completion gastrectomy.

Outcomes

PP can result in normalization of gastric emptying in 71% resulting in an 83% improvement in symptoms at 1 month with an overall improvement rate of 92% at 3-month follow-up (75% idiopathic GP) as reported by Hibbard et al. (2011). According to Toro et al. (2014), subjective symptoms improve in 82%, with normalization of gastric emptying scintigraphy in 54%, utilizing laparoscopic PP (90% non-diabetic GP). The largest series with a 5-year follow-up is reported by Shada et al. (2016), demonstrating improvement in eight out of nine GP symptom domains in 89% of patients. Despite improvement in gastric emptying, 13% of patients in their series proceeded to undergo additional procedures for refractory symptoms. Propensity matching by Landrenau et al. (2019) prospectively compares laparoscopic to endoscopic PP, demonstrating equivocal results with lower complications and length of stay in the endoscopic group. Recent large-series retrospective comparison of GES and PP by Zoll et al. (2020) (132 patients) demonstrates that patients with symptoms of early satiety and postprandial fullness had the most significant improvement with pyloric surgery.

Simultaneous Pyloroplasty with Gastric Electrical Stimulation

Simultaneous GES placement and PP demonstrate exceptional long-term results with 71% symptom resolution (Davis et al. 2017). Critique of this technique has occurred due to concerns of delayed stimulator pocket infection secondary to bacterial contamination. Data reported by Davis et al. indicate that a robot-assisted approach resulted in shorter hospital stays with a median of 4.8 days, compared with laparotomy at 12.9 days' duration. Narcotic sparing techniques and

enhanced recovery protocols may further advancements and application of the surgical solution for GP.

Conclusions

GES therapy is one of the best antiemetics in the world, but it does not change electrical rhythm or the rate of gastric emptying. This technology continues to evolve; hence it could be anticipated that combinations of true gastric "pacing" and electrical neurostimulation, plus possibly pyloroplasty, may not only reduce GP symptoms but also be very predictable with improving a gastric emptying rate. Such treatment approaches could deliver the best long-lasting therapy to successfully address the proper control of chronic and debilitating symptoms of GP. Surgical pyloroplasty has proven benefits for a subset of patients with gastroparesis that have functional contractions of the gastric body and antrum absent relaxation of the pyloric complex. Clinical evidence is largely weighted toward patients with postsurgical and idiopathic etiologies. GES and PP can safely be completed simultaneously with low complication rates in those presenting with refractory GP symptoms and evidence of gastric dilation and ineffective contractions indicative of end-organ failure.

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Cyclic Vomiting Syndrome, Dumping, and Marijuana-Induced Hyperemesis Syndrome

45

Thangam Venkatesan and William L. Hasler

Cyclic Vomiting Syndrome

Introduction

Cyclic vomiting syndrome is a chronic disorder of gut-brain interaction (DGBI), which affects both children and adults [1]. This pattern of "fitful vomiting" was first described in 14 children in 1882. CVS was initially thought to be a pediatric disorder with ~80% outgrowing their symptoms and developing migraine headaches as young adults. However, it is now clear that CVS also affects adults and can present with symptoms in early adulthood. Of historical interest, even Charles Darwin was reported to have cyclic vomiting syndrome. The mean age of onset of CVS symptoms in adults is 37 years in adults and 5 years in children. CVS affects both males and females with a female preponderance in some studies in adults, though the data are conflicting.

The prevalence of CVS in adults is 2% in the USA, 1% in Canada, and 0.7% in the UK, according to a recent population-based study [2]. To put this in perspective, it is as common as celiac disease in the USA. Unfortunately, many patients are misdiagnosed and labeled as having frequent attacks of gastroenteritis, gastroparesis, or other diagnoses. A recent study in an outpatient gastroenterology clinic noted that the prevalence of CVS was 10.8% [3]. More importantly, only 4 of 99 (4%) of these patients were accurately diagnosed with CVS, underscoring the lack of recognition of this disorder.

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Etiology

The etiology of CVS is not known but is thought to be centrally mediated [4]. This is supported by clinical data showing that CVS attacks are often triggered by stressful events. Translational studies with functional magnetic resonance imaging (fMRI) have shown significant differences in functional connectivity of the nausea network between CVS patients and healthy controls following emotional stress. Other studies have shown differences in functional connectivity between the salience brain network and the mid-/posterior insula, a brain region important for viscerosensory and pain processing in CVS patients compared to controls.

Abnormalities in the endocannabinoid system (ECS) and the hypothalamic-pituitary-adrenal (HPA) axis have also been proposed. The ECS is important in the regulation of stress, nausea, and vomiting. The ECS consists of two endogenous ligands, *N*-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG); their respective G-protein-coupled cannabinoid receptors (CB1 and CB2); and related synthetic and degradation enzymes [5].

Preliminary findings of the ECS in CVS revealed that endocannabinoids were not significantly elevated during an attack of CVS as might be expected compared to the interepisodic phase [6]. The ECS also interacts with the HPA axis, and differences in salivary cortisol and alpha amylase were noted in CVS patients with cannabis use compared to non-users with CVS. Typically, the ECS is engaged during period of stress, and this helps bring the host back to homeostasis. Findings from this study suggest that patients with CVS may have a relative endocannabinoid deficiency as demonstrated by their inability to significantly increase endocannabinoids during a CVS attack.

The exact cause for ECS dysfunction in CVS is not known, and this might be due to a gene-environment interaction. A case-control study of adults with CVS showed a significantly increased risk of CVS among individuals with AG and GG genotypes of CNR1 rs806380, whereas the CC genotype of CNR1 rs806368 was associated with a decreased

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risk of CVS [7]. The CNR1 gene encodes for cannabinoid receptor type I, which is part of the ECS. In addition to genetic factors, chronic cannabis use is quite prevalent in patients with CVS and appears to be associated with hyperemesis and worsening of symptoms. The role of cannabis in CVS is discussed in another section in this chapter.

Other factors that have been thought to play a role in CVS include mitochondrial dysfunction. Studies in pediatric CVS showed an association with two mitochondrial DNA 13519T and 6010A. However, these earlier studies likely had a referral bias as these were primarily subjects seen in a pediatric genetic clinic with an emphasis on mitochondrial disorders. These studies have not been duplicated in adults or in children, and this association remains to be elucidated. In summary, the pathophysiology of CVS is not known but is likely due to both genetic and environmental factors with stress playing a central role.

Diagnosis

Clinical Features

The hallmark of CVS is stereotypic episodes of nausea, vomiting, and often abdominal pain lasting several hours to days, with patients returning to baseline in between episodes. A CVS episode consists of four phases, the prodrome, emetic, recovery, and the inter-episodic phase, as shown in Fig. 45.1 [8]. During the prodrome, patients experience multiple symptoms including nausea, sweating, abdominal pain, fatigue, weakness, hot and cold flashes, shivering, intense thirst, loss of appetite, burping, lightheadedness, and paresthesia. Many patients also have symptoms that are consistent with panic and an impending sense of doom. The prodromal phase can last from a few minutes to several hours. It is important to recognize this phase as patients can take abortive or rescue medications in this phase and prevent a full-blown episode. The emetic phase is characterized by intense nausea and vomiting, and patients are often disabled due to their symptoms. Of note, patients sometimes exhibit a drinking/guzzling behavior where they ingest large amounts of water and then induce emesis by sticking their fingers in the throat.

A hot-water bathing pattern where patients take several hot showers/baths during an episode is very characteristic of CVS. Of note, this pattern is associated with cannabis use but is also seen in about half the patients with CVS who not use cannabis [9]. This results in symptomatic relief, and after, the patients completely evacuate gastric contents and should not be misconstrued as malingering. This is then followed by the recovery phase when patients slowly resume eating and other activities and return to the well or inter-episodic phase. The transition from an episode to the well phase can be quite sudden like an on-off switch, which itself is a clue to the diagnosis.

Given the lack of biomarkers, *the diagnosis of CVS is made based on Rome IV criteria* [10] shown below:

- Stereotypical episodes of vomiting regarding onset (*acute*) and duration (*less than 1 week*), which are abrupt in onset, occurring at least 1 week apart.
- Three or more discrete episodes in the prior year.
- Two episodes in the past 6 months.
- Absence of nausea and vomiting between episodes (but other milder symptoms can be present between episodes).

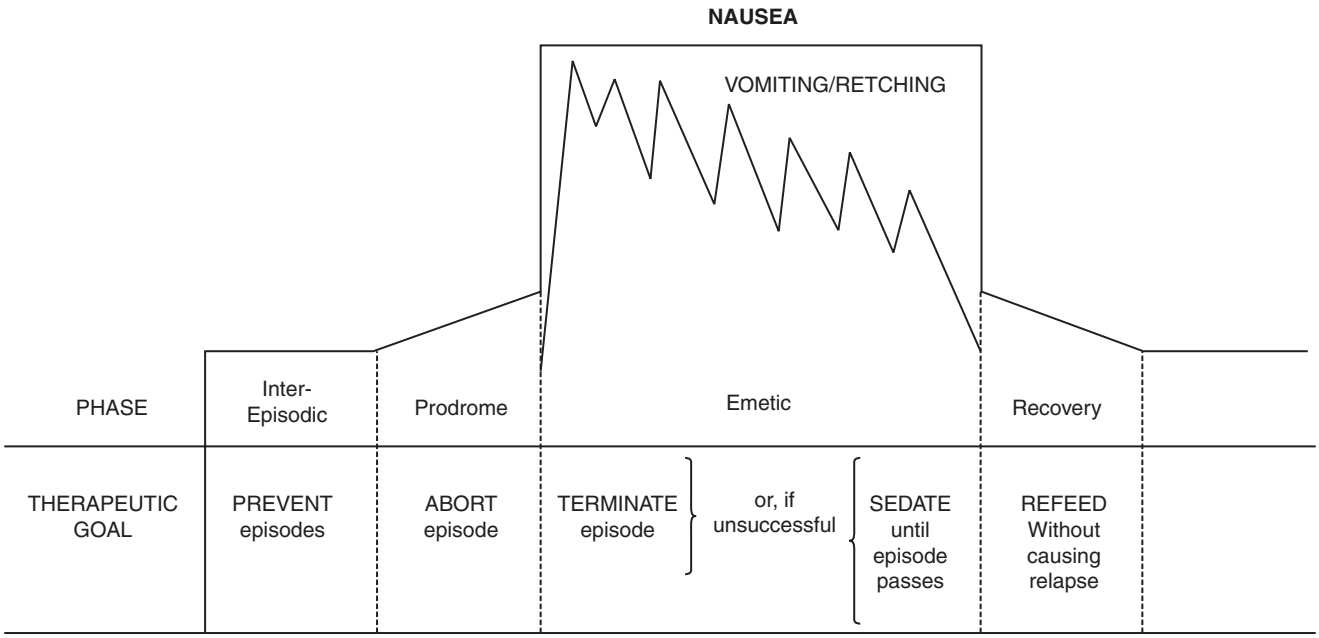

Fig. 45.1 Phases of CVS. The four phases of CVS as described by David Fleisher are shown above. (Adapted from Ref. [8])

- No metabolic, gastrointestinal, central nervous system structural, or biochemical disorders.

Criteria fulfilled for the last 12 months with symptom onset at least 6 months before diagnosis.

Comorbid Conditions and Impact of CVS

CVS is associated with multiple comorbid conditions including anxiety, depression, and autonomic dysfunction, which can further compound the problem [11]. Though mortality in CVS is low, it is associated with a significant morbidity and has a significant negative impact on patients, families, and the healthcare system. Patients suffer from multiple debilitating attacks of CVS, which results in delay in higher education, job loss, absenteeism, and disability in a third of patients. It is also associated with high healthcare utilization, with subjects reporting a median of 15 emergency department (ED) visits during their illness. Another study noted that the cost of hospitalizations from CVS annually was $200 million and does not take into account unnecessary procedures and other futile investigations [12]. In addition, about 20–30% of patients have had cholecystectomies for symptoms of CVS.

Management

We recommend a biopsychosocial model of care, with both pharmacotherapy and other therapies aimed at addressing associated psychological problems and other comorbidities. Recent guidelines have streamlined management of CVS and emphasized the need for prophylactic medications in the treatment of moderate-severe CVS [13]. Abortive medications such as antiemetics (such as ondansetron), triptans (sumatriptan), and benzodiazepines (lorazepam) are often needed to abort attacks and should be offered to most patients. *An algorithm for the management of CVS is shown in* Fig. 45.2 [14]. Of note, the guide-

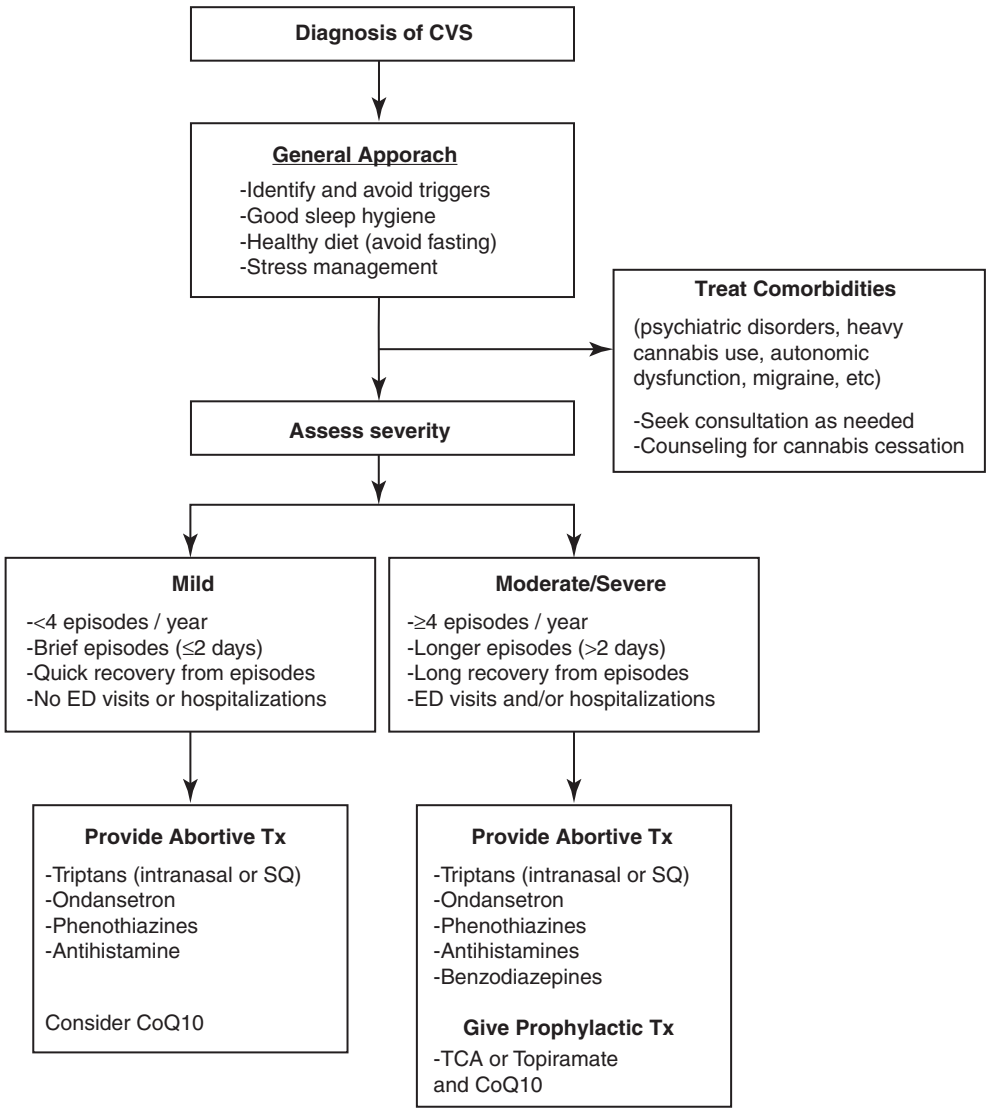

Fig. 45.2 Algorithm for treatment of cyclic vomiting syndrome: an approach to management of CVS based on severity of disease is shown. (Adapted from Ref. [12])

lines for the management of CVS are based on GRADE methodology. However, there were no randomized controlled trials of medications in CVS at the time of the guideline development, and most studies were either open-label or retrospective studies. Nevertheless, tricyclic antidepressant (amitriptyline), antiepileptic drugs (topiramate), and NKI receptor antagonists (aprepitant) are effective in reducing the number of CVS episodes, ED visits, and hospitalizations. Amitriptyline can be associated with anticholinergic side effects, daytime sedation, and constipation; in addition, the QT interval should be monitored. Topiramate is an effective prophylactic medication but can be associated with significant side effects, mostly cognitive dysfunction, which can result in discontinuation of the medication. Aprepitant is generally the most well-tolerated medication but is not FDA approved for the treatment of CVS, and associated costs can be prohibitive. It can reduce the efficacy of oral contraceptive pills, and women in the reproductive age group must be cautioned about this [13].

Anxiety and depression are seen in a significant number of patients, and referral to appropriate mental health personnel is recommended. A subset of patients also has autonomic dysfunction, and in addition to lifestyle measures, referral to a neurologist with expertise in autonomic dysfunction can be helpful. Approximately 40% of patients with CVS report cannabis use. One in five has significant chronic cannabis use, and these patients must be counseled about the adverse effects or cannabis exacerbating their symptoms.

Conclusion

In summary, CVS is a chronic disorder of gut-brain interaction and can be disabling. It is important to recognize the recurrent pattern of symptoms and diagnose patients using the Rome IV criteria, which provides a standard framework. Investigations should be limited to exclude organic causes and usually include an EGD and imaging studies of the abdomen and pelvis. Prophylactic agents such as amitriptyline, topiramate, and aprepitant should be initiated in patients with moderate-severe CVS, and abortive agents should be offered to most patients. A biopsychosocial model of care and a good rapport with these patients with an educated and dedicated team should improve patient-reported outcomes. Research and funding for elucidating the pathophysiology of CVS are needed. Ongoing efforts and FDA trials for therapies in CVS should further expand the available therapies for this debilitating disorder and improve the quality of life in these patients.

Dumping Syndrome

Features of Dumping Syndrome

Dumping syndrome traditionally is considered to reflect a constellation of gastrointestinal symptoms coupled with vasomotor manifestations. The condition was first described more than a century ago as a consequence of gastroenterostomy and was subsequently reported to develop after other surgeries involving vagotomy and/gastric drainage procedures [15]. Two distinct clinical forms have been described. The early dumping syndrome represents 75% of reports and presents with fecal urgency, diarrhea, abdominal discomfort, and nausea coupled with tachycardia, light-headedness, presyncope, and occasionally syncope beginning within 15–30 min of a meal usually consisting of soft or liquid simple carbohydrates. The late dumping syndrome occurs less commonly with a later onset 1–3 h after eating a similar meal and is characterized by diaphoresis, weakness, flushing, clumsiness, and cognitive impairments. Risks of developing dumping syndrome are dependent on the procedure performed with the highest rates observed after Roux-en-Y gastrojejunostomy (50–70%), followed by partial gastrectomy (15–20%), truncal vagotomy (6–14%), and proximal vagotomy (<1%). Many of these dumping complications improve with time after surgery, suggesting adaptive processes as well as learned dietary restrictions to limit symptoms. More recent studies of patients undergoing bariatric surgery for obesity suggest that dumping syndrome occurs in 0.3–14.6% of cases. Dumping syndrome also complicates fundoplication for gastroesophageal reflux disease both in adults and children.

The underlying presumed mechanism for induction of both early and late dumping syndrome is the abnormally rapid delivery of nutrients (usually liquids) into the small intestine with induction of nerve-mediated reflexes and release of several neurally and hormonally active mediators. The early dumping syndrome has been proposed to result from postprandial small bowel distention and induction of active phasic contractions, which can underlie pain, nausea, urgency, and diarrhea [16]. Meal-induced stimulation of intestinal serotonin, neurotensin, pancreatic polypeptide, peptide YY, enteroglucagon, and glucagon-like peptide release may further increase gut mucosal secretion, augmenting diarrheal symptoms as well as causing rapid fluid shifts and intravascular depletion as well as vasodilation, which underlie vasomotor symptoms such as light-headedness and presyncope. The late dumping syndrome occurs because of exaggerated insulin release from abrupt intestinal mucosal exposure to simple carbohydrates that leads to reactive hypoglycemia [16, 17].

In addition to postsurgical causes, rapid gastric emptying has been observed in cyclic vomiting syndrome (35% of cases) followed by functional dyspepsia (25%), type 2 diabetes (13%), and probable irritable bowel syndrome (10%). The relation of gastric motor disturbances to symptom development in these conditions is unproven, and no therapies targeting this dysmotility have demonstrated efficacy in controlled trials. With publication of these reports, the clinical definition of dumping syndrome has morphed from a symptom-based condition to one based purely on a physiologic abnormality—rapid gastric emptying. As a result, most recent publications refer to dumping syndrome as any condition which is associated with rapid emptying of gastric contents into the intestine. Because of this evolution in clinical practice, most patients currently diagnosed as having dumping syndrome are not categorized as having early versus late dumping and are commonly not reported to experience the vasomotor or neuroglycopenic manifestations of patients given the diagnosis based on prior standards.

Rapid Gastric Emptying in Cyclic Vomiting Syndrome

Epidemiology of Rapid Gastric Emptying

Over the past few decades, several case series have reported a high prevalence of rapid gastric emptying in CVS patients. Accelerated emptying was documented in 40% of children with CVS in one report using scintigraphic testing [18]. However, an older study employing ultrasound observed normal emptying profiles in a small pediatric cohort. This finding has been more extensively evaluated in adult CVS patients, with numerous series reporting prevalence rates of rapid gastric emptying ranging from 45% to 80%. Table 45.1 shows a comparison of rapid emptying in pediatric versus adult CVS from one recent report. The variability of these findings likely stems from inconsistent criteria for defining rapid gastric emptying. Although standards have been suggested by expert groups, these have not been uniformly adopted in all studies. Furthermore, this increased prevalence rate is similar to that observed in functional dyspepsia and in functional vomiting—a Rome III diagnosis denoting a condition with more regular vomiting rather than the episodes typical in CVS (Table 45.2). Other clinical factors have been associated with rapid gastric emptying in adult CVS including older age, anxiety, and symptoms of irritable bowel syndrome.

Table 45.1 Comparison of rapid gastric emptying in pediatric versus adult patients with CVS

Gastric emptying profile at 2 h	All CVS patients *N* (%)	Pediatric CVS patients *N* (%)	Adult CVS patients *N* (%)
Rapid	32/67 (48%)	6/15 (40%)	26/52 (50%)
Normal	29/67 (43%)	5/15 (33%)	24/52 (46%)
Delayed	6/67 (9%)	4/15 (27%)	2/52 (4%)

Adapted from Ref. [18]

Table 45.2 Comparison of rapid gastric emptying in adults with CVS versus functional vomiting

Gastric emptying profile at 2 h	CVS patients *N* (%)	Functional vomiting patients *N* (%)
Rapid	21/47 (45%)	16/35 (46%)
Normal	24/47 (51%)	13/35 (37%)
Delayed	2/47 (4%)	6/35 (17%)

Adapted from Choung RS, Locke GR, Lee RM, et al. Cyclic vomiting syndrome and functional vomiting in adults: association with cannabinoid use in males. Neurogastroenterol Motil 2012;24:20-e1

Pathogenic Role of Rapid Gastric Emptying

The cause of rapid gastric emptying in CVS patients has not been definitively identified. Autonomic nervous system abnormalities have been characterized in both children and adults with CVS. These appear to mostly involve predominantly sympathetic pathways, although vagal cholinergic dysfunction also has been observed. Sympathetic imbalance is believed to increase susceptibility to central nervous system emetic stimulation. Dysautonomia has been postulated to cause accelerated gastric emptying. In one study, rapid emptying was associated with autonomic dysfunction in patients with gastrointestinal symptoms suspicious for dysmotility [19]. However, another group found similar autonomic impairments in CVS patients with rapid versus normal emptying. Other groups propose neurohumoral factors as contributors to rapid gastric emptying in CVS. Concentrations of ghrelin, a gut hormone with gastrokinetic capability, are elevated in some adult CVS patients with rapid emptying.

Likewise, the importance of rapid gastric emptying as a cause of any of the clinical features of CVS is unproven. Alternatively, it remains unresolved whether rapid emptying is a marker of another pathogenic abnormality or it is merely an unrelated epiphenomenon. In functional dyspepsia, nausea and vomiting are more often associated with delayed gastric emptying, while accelerated emptying more often relates to other dyspeptic symptoms. Furthermore, rapid gastric emptying cannot be the sole cause of symptoms as all studies that have documented this finding have been conducted during intervals between CVS attacks when patients are mostly asymptomatic. When gastric emptying has been measured during episodes, it has been found to be delayed. These findings should be viewed skeptically given the acuity of severe symptoms and the possibility they were influenced by antiemetic and other medications given during a CVS attack. Other researchers have proposed including

rapid gastric emptying as a supportive criterion for CVS diagnosis, but these observations do not support this recommendation [20].

Contrast of Gastric Emptying Abnormalities in Cyclic Vomiting Syndrome vs. Cannabinoid Hyperemesis

Gastric emptying findings in CVS should be contrasted with those in patients with a related condition, cannabinoid hyperemesis syndrome (CHS). Although reliable data are sparse, gastric emptying rates have shown delays in CHS. These observations parallel observations of the motor effects of exogenous cannabinoids. In rats, cannabinoid CB_1 receptor activation decreases gastric contractions and slows emptying. In humans, gastric emptying is slowed by tetrahydrocannabinol in clinical doses used to treat emesis and also was significantly delayed in a placebo-controlled trial of dronabinol.

Cannabinoid Hyperemesis Syndrome

Introduction

Cannabinoid hyperemesis syndrome (CHS) is a disorder that is similar to CVS but is characterized by chronic heavy cannabis use. The association between cannabis and hyperemesis was first recognized by Allen et al. who reported symptoms of cyclic vomiting in 18 adolescents and adults with heavy cannabis use [21]. These patients also resorted to a peculiar hot-water bathing behavior where they would have very hot showers/baths several times during an episode. Following this, there were numerous case reports and case series of CHS in the literature. Initially, the hot-water bathing behavior was thought to be pathognomonic of CHS, but subsequent studies have shown that this can also be seen in ~50% of patients who do not have chronic cannabis use [9]. The diagnosis of CHS varied considerably in the literature, which has led to significant confusion about this disorder.

CHS is now diagnosed using Rome IV criteria and are listed below [10]:

- Stereotypical episodic vomiting resembling (CVS) in terms of onset, duration, and frequency.
- Presentation after prolonged, excessive cannabis use.
- Relief of vomiting episodes by sustained cessation of cannabis use.

Supportive remarks:

- May be associated with pathologic bathing behavior (prolonged hot baths or showers).

Criteria must be fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.

While the Rome criteria help in establishing a diagnosis of CHS, there are limitations to this approach. The main challenge is that patients perceive benefits of cannabis with many being reluctant to stop cannabis use. Given this, it would be impossible to determine if a patient has CHS based on Rome criteria. In one study of 141 patients with CVS who used cannabis, 86% abstained from cannabis for at least a month, but only one patient had resolution of symptoms. This patient subsequently resumed cannabis with a higher CBD/THC ration and remained symptom-free [22]. Gaps in knowledge about the effects of cannabis use preclude more precise recommendations about how long patients need to abstain and the amount and duration of use that might lead to hyperemesis.

Pathophysiology

Role of Cannabinoids in CHS and CVS

Cannabinoids consist of (a) phytocannabinoids (derived from plants), (b) endocannabinoids (synthesized by humans), and (c) synthetic cannabinoids such as nabilone and dronabinol that are manufactured. Cannabis is the most commonly used illicit drug in the USA and is being increasingly used for perceived health benefits [23]. This is usually derived from *Cannabis sativa* or *Cannabis indica* and consists of almost 200 constituents, but Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most important. THC is the major psychoactive ingredient in cannabis in contrast to CBD which does not have any psychoactive properties and acts via 5HT1A receptors. Several clinical and preclinical studies demonstrate that cannabis has antiemetic properties. Paradoxically, cannabis has also been associated with hyperemesis, and there are several potential mechanisms that might explain these effects.

The potency of cannabis products has increased exponentially with time, and the THC content in a joint has increased for ~4% in the 1990s to 15% currently [24]. Further, the availability of cannabis concentrates such as wax, oils, and resins which contain concentrations of THC that range between 40% and 80% can substantially alter its properties and its effects on human physiology. It is postulated that cannabis has a biphasic effect with antiemetic effects at low doses and emetic effects at high doses. The paradoxical effects of cannabis leading to CHS may be due to the down-regulation of cannabinoid receptor type 1 (CB1R) signaling as a result of chronic THC exposure, leading to loss of an inhibitory control in the neurological circuit that regulates emesis.

Variation in the effects of cannabis could also be due the genetic variability among individuals to cannabis, which might explain symptoms in some individuals but not others.

Is CHS a Distinct Disorder?

While CHS is considered a separate entity, the current data does not support this notion. Prevalence rates have varied widely from 7 cases among 5931 adults surveyed in the USA, the UK, and Canada in a recent population-based study to 2.75 million people affected annually [2]. However, the latter study by Habbouseh et al. has major flaws as the criteria for CHS was made based on the presence of vomiting in the context of near-daily cannabis use. Even the recurrent pattern of vomiting was not required to make a diagnosis of CHS in this study, and this could have led to an erroneous diagnosis of CHS in these cases. Further, features that suggest that CHS is a subset of CVS include the similarity in clinical presentation. Both disorders are characterized by recurrent episodes of nausea and vomiting with symptoms of normalcy in between episodes. Hot-water bathing is a peculiar phenomenon that was thought to be pathognomonic of CHS but is also seen in ~50% of CVS patients without cannabis use.

A recent systematic review of reported CHS was done to determine the number of cases that met Rome IV criteria for CHS. Of a total of 105 individual case reports and 25 case series (n = 271), only 15.7% or approximately 1/6 of the cases of "CHS" reported in the literature met the Rome IV criteria for the same [25]. While the exact duration of abstinence from cannabis for resolution of symptoms is not known, a minimum cutoff of 4 weeks was used in this study [25]. This exemplifies the limitations of the current literature in CHS and considerable heterogeneity in how CHS is diagnosed, which makes it difficult to know if cannabis truly leads to hyperemesis. More research is needed to understand the risks vs. benefits of cannabis.

However, there are some differences between patients with CVS and CHS that are noteworthy. CVS affects mostly females, while CHS afflicts mostly young males who are more likely to be heavy cannabis users. The prevalence of cyclic vomiting visits in the emergency department doubled from 41 per 113,262 ED visits to 87 per 125,095 ED visits after marijuana liberalization in the state of Colorado [26]. Also, patients with cyclic vomiting in the post-liberalization period were more likely to have cannabis use documented than patients in the pre-liberalization period (odds ratio = 3.59, 95% CI = 1.44–9.00). This suggests that cannabis might worsen or cause hyperemesis and needs further clarification.

Management

Patients who are diagnosed with CHS, particularly those who are heavy (daily) users, should be encouraged to reduce their intake and abstain. This should be done in a nonjudgmental manner to achieve positive outcomes. While this might be difficult in a busy clinical setting, institutions and hospitals need to recognize this need and provide resources for substance abuse and addiction medicine. It is also important that patients are advised not to use cannabis concentrate as this is associated with significant adverse effects including high rates of addiction and withdrawal and cognitive side effects in addition to possible hyperemesis. Patients with presumed CHS should be treated similar to CVS patients with prophylactic agents like amitriptyline for moderate-severe disease and an abortive regimen [13]. While there are some reports of the efficacy of topical capsaicin cream and haloperidol, data is sparse to make any firm recommendations regarding their use. Comorbid conditions such as anxiety and depression are also prevalent in CHS, and appropriate referral for mental health services should be done.

Conclusion

In summary, CHS is a condition that is indistinguishable from CVS and should be considered in the context of heavy daily cannabis use. Cannabis products, particularly concentrates which have a high THC/CBD ratio, should be avoided, and patients should be screened for possible cannabis use disorder and addiction. Patients should be treated with medications that are used in CVS when needed. Systematic enquiry about the different types and potency of cannabis products used, effects of abstinence on symptoms long term, and the relationship between cannabis and hyperemesis are needed in the future.

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Part VI

Gastric Cancer and Other Gastroesophageal Disorders

Gastric Cancer Epidemiology, Genetics, and Screening

46

Brittany G. Sullivan, John D. Karalis, Sam C. Wang, and Maheswari Senthil

Objectives

1. Understand the variations in gastric cancer incidence based on geographical region, demographics, and socioeconomic status.
2. Understand familial gastric cancers and their associated genetic mutations.
3. Understand gastric cancer molecular profiling efforts and their implications for precision oncology.
4. Understand screening for gastric cancer based on high-risk regions and high-risk populations.

Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide and is the fourth leading cause of cancer-related death. While overall incidence of GC is declining, the prevalence of disease is increasing due to an overall aging population. Despite advances in treatment, the overall prognosis for GC remains poor with 5-year overall survival rate of 20%. The 5-year survival rate is 69.5% for patients with localized disease, 32% for regional disease, and only 5.5% for metastatic disease. In this chapter, we will review the epidemiology of sporadic and familial GC, recent advances in genomic profiling of the disease and their implication for treatment, and current recommendations for screening.

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Epidemiology of Sporadic Gastric Cancer

Ninety percent of GC cases are sporadic, and most are diagnosed between the ages of 60 and 80. Males are 2–3 times more likely to be affected than females. GC is broadly classified as cardia and non-cardia cancer based on anatomic location, and these subtypes differ in terms of their risk factors, genetic profile, and geographic distribution. The discovery of the association of *H. pylori* infection and GC in the early 1980s has dramatically changed our understanding of GC pathogenesis. *H. pylori* infection causes chronic gastric inflammation contributing to gastric mucosal genetic instability that may progress to cancer. Up to 65–80% of non-cardia GC cases are associated with *H. pylori* infection. However, although more than half of the world population is affected with *H. pylori*, only 5–6% of patients develop GC, likely due to differences in host response to infection, the phylogeographic origin of *H. pylori*, and environmental factors. Other factors for GC include high-salt and high-nitrite diet, smoking, and alcohol consumption. Cardia GC are associated with obesity, gastroesophageal reflux disease, and atrophic gastritis.

The overall incidence of GC has steadily declined worldwide over the past five decades, primarily due to the decreased incidence of non-cardia GC, which is partly attributed to *H. pylori* eradication efforts. Other reasons for the decline in incidence are likely due to increased worldwide availability of refrigerators which has led to better storage, increased availability of fresh foods, and reduced need for salt-based meat preservation. However, while the incidence of non-cardia GC is declining, the incidence of cardia GC has increased by sevenfold, especially in high-income countries likely due to the increased incidence of obesity and gastric dysbiosis due to prevalent use of proton pump inhibitors.

The incidence of early-onset, sporadic GC, defined as GC diagnosed before age 45, has also been increasing. Recent studies from the United States reported an increased incidence of GC among young Hispanic men. Early-onset GC

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accounts for up to 30% of all cases diagnosed in the United States as of 2018. It is associated with signet-ring cells and diffuse histology, higher grade, and metastatic disease at diagnosis. However, only a small portion of early-onset GC cases have an identifiable hereditable cause.

Variations in Incidence and Mortality of Gastric Cancer

The incidence and mortality of GC varies widely by geographic region (Figs. 46.1 and 46.2). The highest incidence of GC is observed in East Asia, Eastern Europe, and parts of South America, whereas Northern Europe and North America have much lower incidence. Japan and Mongolia have the highest per-capita incidence of GC in men and women, respectively (Fig. 46.1). Per-capita GC mortality rates are highest in Mongolia and Tajikistan (Fig. 46.2).

Low- and middle-income countries, such as Vietnam and Colombia, have a twofold increased risk of GC due to a high prevalence of risk factors, namely, smoking, obesity, and a diet low in fruits and vegetables. GC survival has also been associated with socioeconomic status as it influences the exposure to risk factors, access to healthcare, and stage at diagnosis.

Multiple studies have evaluated the effect of migration patterns on GC incidence. Studies from the United States that have explored the effect of acculturation on the incidence of GC have reported that immigrants from high-incidence GC regions such as Japan, Korea, and the Middle East retain a higher risk of GC compared to the native population; however, subsequent generations born to immigrants show racial/ethnic variations in incidence. For example, second-generation Americans of Middle Eastern origin exhibit a similar incidence to Non-Hispanic Whites, whereas subsequent Japanese-American generations continue to have a higher risk, highlighting the multifactorial roles of environmental and biological causes of GC. The observed variations in the incidence and mortality of GC among various race/ethnic subgroups transcend geographic differences and represent a complex interplay of biological, behavioral, and sociocultural factors. The most common type of GC among South Americans is non-cardia GC of Lauren intestinal subtype. Although the prevalence of *H. pylori* infection in this geographic region may explain the high incidence of non-cardia GC, recent studies have confirmed that certain single nucleotide polymorphisms enriched in this ethnic group affect the host response to *H. pylori* infection and risk of GC.

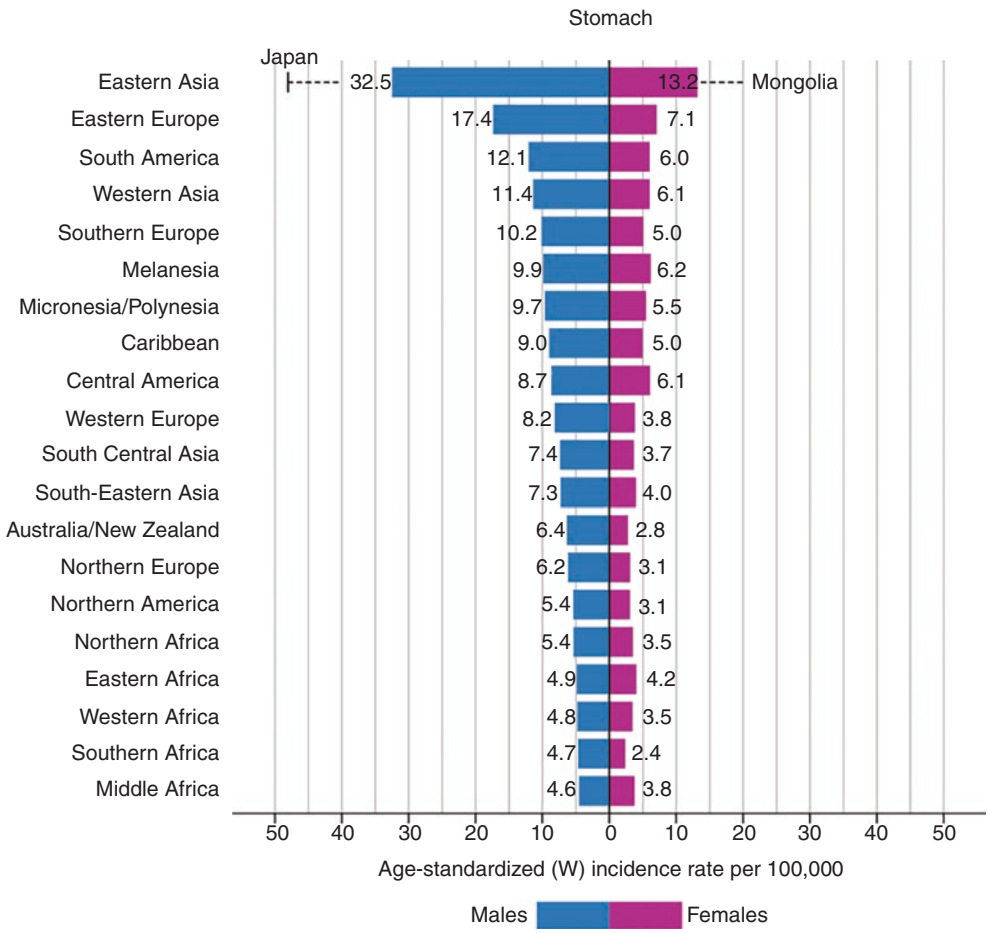

Fig. 46.1 Region-specific incidence age-standardized rates by sex for stomach cancer in 2020. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries

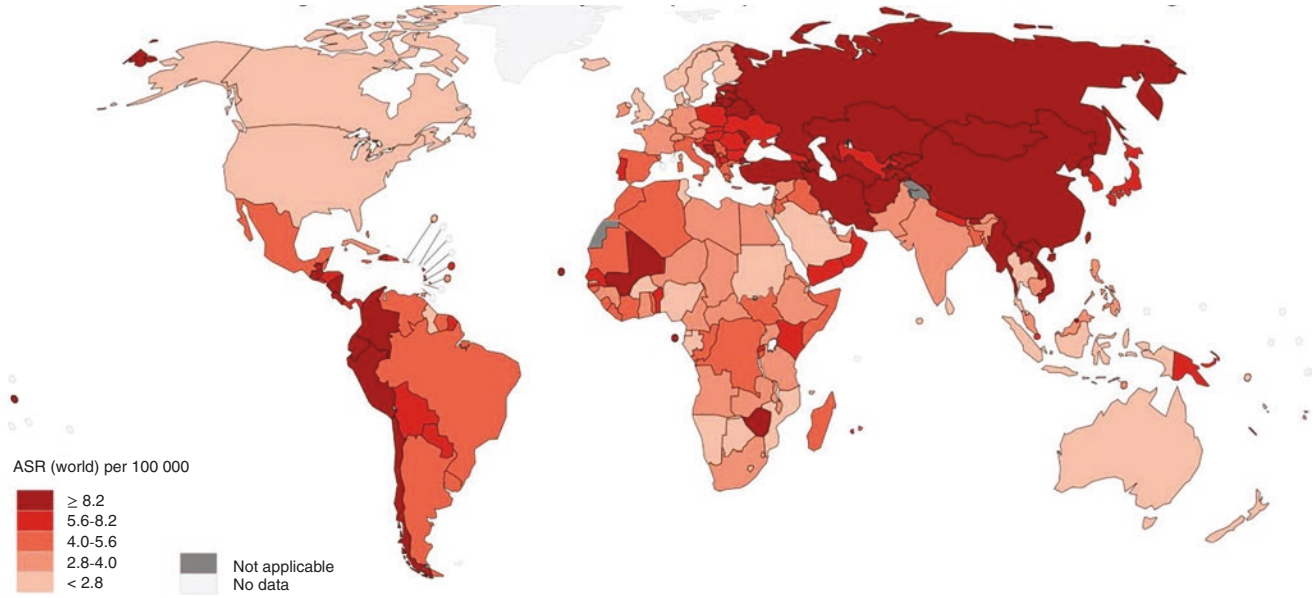

Fig. 46.2 Map shows estimated age-standardized mortality rates (World) in 2020 for stomach cancer, both sexes and all ages. (Data source: GLOBOCON 2020. Graph production: IARC (http://gco.iarc.fr/today) World Health Organization)

Familial Gastric Cancer

Ten percent of GC cases show evidence of familial inheritance and are classified as familial GC. However, only 1–3% of familial GCs have an identified pathogenic germline mutation. Familial GC is comprised of three known syndromes, hereditary diffuse GC (HDGC), gastric adenocarcinoma with proximal polyposis of the stomach (GAPPS), and familial intestinal GC (FIGC), which are summarized in Table 46.1. Additionally, GC risk is increased in multiple other hereditary cancer syndromes with known genetic causes.

Hereditary Diffuse Gastric Cancer

HDGC was the first of the familial GC syndromes to be recognized and is characterized by early-onset, multigenerational, diffuse GC (DGC) and invasive lobular breast cancer (ILBC). HDGC was first described in 1964, when a Māori tribal family in New Zealand was noted to exhibit a high rate of GC which displayed an autosomal dominant pattern of inheritance. Three decades later, loss-of-function germline *CDH1* variants, which code for the cell-cell adhesion protein E-cadherin, were identified as the causative mutation. Mutations of *CTNNA1*, which encodes α-E-catenin, were identified as another cause of HDGC in a small minority of patients, likely emulating the functional significance of mutated *CDH1*.

Notably, in HDGC families, invasive lobular breast cancer (ILBC) is the second most frequently occurring cancer type. Both DGC and ILBC exhibit high penetrance with approximately 72% of males and 56% of females developing GC and 42% of women developing breast cancer by age 80. The International Gastric Cancer Linkage Consortium (IGCLC) released revised guidelines for the diagnosis and management of HDGC in 2020, based upon a consensus of leading HDGC researchers, genetic counselors, and clinicians. In contrast to previously used clinical criteria, HDGC is now defined by presence of a pathogenic *CDH1* or *CTNNA1* variant in an isolated individual with DGC or in a family with one or more DGC cases in first- or second-degree relatives. Patients should be referred for genetic testing if they meet any of the following family or individual criteria:

Family criteria:

- ≥2 cases of GC in family regardless of age, with at least one diffuse GC (DGC)
- ≥1 case of DGC at any age and ≥1 case of lobular breast cancer at age <70 years, in different family members
- ≥2 cases of lobular breast cancer in family members <50 years of age

Individual criteria:

- DGC at age <50 years
- DGC at any age in individuals of Māori ethnicity
- DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate
- History of DGC and lobular breast cancer, both diagnosed at age <70 years

Table 46.1 Summary of familial gastric cancers

	HDGC	GAPPS	FIGC
Germline Mutation	*CDH1, CTNNA1*	*APC* Promoter 1B	Likely polygenic
Inheritance Pattern	Autosomal dominant	Autosomal dominant	Autosomal dominant
Associated Cancer	Invasive lobular breast cancer	None known	None known
Management Recommendations	Prophylactic gastrectomy or yearly endoscopy beginning at age 20-30 years. For females: yearly breast imaging starting at age 30 or bilateral risk-reducing mastectomy	Determined on a patient-specific basis	Determined on a patient-specific basis

- Bilateral lobular breast cancer, diagnosed at age <70 years
- Gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age

IGCLC guidelines recommend that patients with confirmed cases of HDGC undergo a prophylactic total gastrectomy between 20 and 30 years of age. For patients wishing to avoid or postpone gastrectomy, yearly endoscopy at an expert center is recommended, and if appropriate, *H. pylori* eradication must be confirmed. However, prior to adopting this approach, patients should be acutely aware that endoscopic screening has been shown to frequently miss early DGC. Moreover, young asymptomatic patients with *CDH1* and *CTNNA1* variants undergoing prophylactic gastrectomy have been found to harbor foci of intramucosal DGC, although the time to progression is unknown.

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

GAPPS was first described in a 2012 case series in which the authors observed a carpeting polyposis of the proximal stomach, in the absence of duodenal or colorectal polyps, in three independent families. GAPPS displays an autosomal dominant inheritance pattern; however, penetrance is incomplete. The polyps displayed in GAPPS patients often harbored dysplasia, and affected patients had a significantly increased risk of developing intestinal-type adenocarcinoma. Interestingly, when compared to other gastrointestinal polyposis syndromes such as familial adenomatous polyposis (FAP), the malignant potential of any individual polyp in GAPPS appears to be significantly higher. The polyposis observed in GAPPS stands in contrast to sporadic FGPs which rarely progress to dysplasia or carcinoma and are diagnosed in approximately 5% of all endoscopic studies of the stomach, often in patients requiring chronic proton pump inhibitor (PPI) therapy. The clinical diagnostic criteria for GAPPS include:

- Gastric polyps restricted to the body and fundus with no evidence of duodenal or colorectal polyposis
- >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first-degree relative of another case
- Mainly fundic gastric polyps, some with regions of dysplasia (or a family member with either dysplastic fundic gastric polyps or gastric adenocarcinoma)
- Autosomal dominant pattern of inheritance
- No evidence of another heritable gastric polyposis syndrome

Accepted management strategies for GAPPS include endoscopic surveillance and prophylactic total gastrectomy. The risks and benefits of each approach should be determined on a patient-specific basis. While no specific age-based screening protocol has been established, it should be noted that the polyposis phenotype with focal areas of dysplasia was evident on endoscopic examination in patients as young as age 10, and the earliest case of gastric adenocarcinoma observed occurred at age 33. No causal germline mutation has been definitely established; however, point mutations of *APC* promoter 1B have emerged as the most likely candidate.

Familial Intestinal Gastric Cancer

FIGC is characterized by predominance of intestinal-type GC that clusters in families and displays an autosomal dominant inheritance pattern. No causal germline mutation has been identified thus far; however, contemporary studies have postulated a likely polygenic cause. As such, there is no genetic testing currently available and no consensus for management of patients at risk for FIGC; however, the clinical criteria for diagnosis are:

- ≥2 cases of GC in first- or second-degree relatives, with at least one confirmed case of intestinal histology in someone younger than 50 years
- ≥3 confirmed cases of intestinal GC in first- or second-degree relatives, independent of age

Gastric Cancer Genetics

Genomic profiling offers insights into GC biology that may guide clinical care. However, association of the molecular features of gastric adenocarcinoma to patient clinical characteristics has been complicated by the highly heterogeneous nature of the disease. Multiple classification systems have been developed in an attempt to account for the observed heterogeneity, with arguably the most notable being the still-widely used Laurén histologic classification system published in 1965 by Dr. Pekka August Laurén. While the Laurén classification provided an early insight into the spectrum of GC biology, ultimately, histologic evaluation alone incompletely captures the molecular complexity of the disease. Five decades later, large-scale sequencing efforts, most notably the landmark study carried out by The Cancer Genome Atlas (TCGA) Research Network, have generated a wealth of genetic data. These efforts have provided key insights into the diverse molecular profile of GC and have elevated opportunities for developing personalized GC treatments.

Molecular Classification Systems

Recent large-scale next-generation sequencing efforts have provided insights into the genomic landscape of GC. In 2014, the TCGA published the largest GC sequencing effort to date, which proposed a molecular classification system comprised of four distinct subtypes (Fig. 46.3): Epstein-Barr virus-positive (EBV), microsatellite instable (MSI), chromosomal unstable (CIN), and genomically stable (GS).

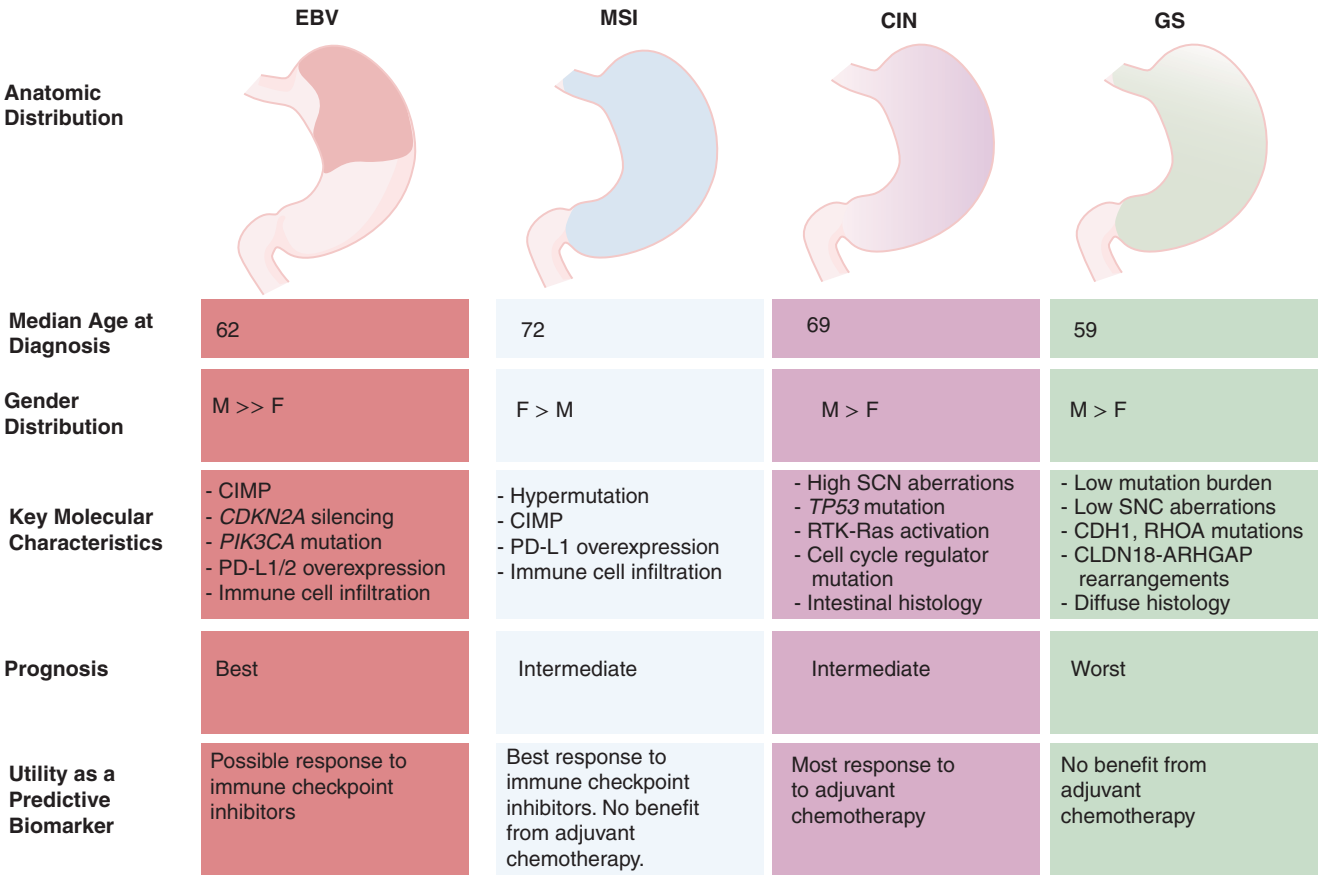

Fig. 46.3 Molecular and clinical characteristics of TCGA subtypes

- *EBV* (9% of patients): The distinguishing molecular characteristics of EBV subtype tumors include Epstein-Barr virus positivity, CpG island methylator phenotype (CIMP), *CDKN2A* promoter hypermethylation, and frequent *PIK3CA* (80%), *ARID1A* (55%), and *BCOR* (23%) mutations. Phenotypically, EBV tumors exhibit intestinal-type histology, high PD-L1 expression, and significant immune cell infiltration. Patients with EBV tumors have a relatively young age of diagnosis (median age 59), and there is a marked gender imbalance with males harboring 81% of EBV tumors. Patients with EBV tumors have the best prognosis of the four subtypes, which may be associated with the high degree of immune cell infiltration.
- *MSI* (22%): MSI tumors exhibit *MLH1* silencing, a hypermutated genome, and a high degree of DNA methylation. Mutations in *PIK3CA* are also common in MSI tumors (42%) although not as common as what is observed in the EBV subtype (80%). MSI tumors are more prevalent in elderly patients, with a median age of diagnosis of 72 years, and exhibit a slight female predominance, at 56%. Additionally, MSI tumors are associated with a high degree of lymphocyte infiltration and PD-L1 overexpression. Clinically, MSI tumors have an intermediate prognosis and have the highest response rate to immune checkpoint inhibitors and a lack of response to standard cytotoxic chemotherapy.
- *CIN* (50%): CIN tumors have a high degree of copy number alterations and are most frequently located at the gastroesophageal junction and cardia. *TP53* is commonly mutated (73%), and CIN tumors harbor amplification of many receptor tyrosine kinase genes, including HER2 and cell cycle regulators, which represent potential opportunities for targeted therapies. Phenotypically, CIN tumors over-index for intestinal-type histology. Compared to the other three molecular subtypes, CIN tumors have an intermediate prognosis and are the most responsive to adjuvant chemotherapy following surgical resection.
- *GS* (20%): GS tumors harbor a low rate of somatic copy number mutations and a low mutational burden. GS tumors exhibit a higher rate of *CDH1* (37%) and *RHOA* (30%) mutations as well as *CLDN18-ARHGAP* rearrangements (30%) than the other subtypes. Additionally, GS tumors over-index for diffuse-type histology. GS tumors are more prevalent in younger patients, with a median age of 59, and have the worst prognosis of the four subtypes.

One notable limitation of these molecular classification systems, however, is the underrepresentation of racial and ethnic minorities. This is important because GC biology has been shown to differ between patients of different races and ethnicities, for example, Asian patients show superior clinical outcomes when compared to Western populations, even after adjusting for prognostic clinical and pathologic variables. Importantly, the predominance of non-Hispanic White and Asian patients in the TCGA and ACRG studies has likely biased our understanding of the molecular landscape of GC, which has clinical consequences. For example, in the 440-patient TCGA cohort, only 5 Hispanic patients were included. A subsequent sequencing effort demonstrated that Hispanic patients have a significantly higher proportion of GS tumors and a high rate of *CDH1* germline variants, when compared to the predominantly non-Hispanic White and Asian patients in the TCGA cohort, which may explain the worse clinical outcomes observed in Hispanic patients. Recent reports found that single nucleotide polymorphisms that are enriched in certain ethnic groups influence host response to *H. pylori* infection and the subsequent development of cancer. For example, TNF-A-857*T polymorphism is associated with an increased risk of gastritis and GC in Costa Rican patients. Another study found that rs4733616 in chromosomal region 8q24 is associated with poorly differentiated GC in Venezuelan patients. As such, genetic predisposition and increased susceptibility to GC may explain the increased rates in certain racial/ethnic subgroups, regardless of immigration to low-incidence countries. These discoveries will help identify high-risk groups for targeted screening and customize treatment. This underscores the importance of considering the diversity of patient representation when evaluating the external validity of genetic studies.

Precision Oncology

GC patients are treated in a nearly uniform fashion regardless of the unique biology of their disease. As such, biomarkers are needed to improve treatment precision and guide clinical decision-making. To date, only three biomarkers have been shown to be predictive of therapy response in GC patients. Patients with HER2-amplified GC benefit from trastuzumab; however, only 10–20% of patients have HER2-amplified tumors. Additionally, MSI status and PD-L1 combined positive score (CPS) have been used to select patients who may benefit from immune checkpoint inhibition, but their predictive utility is limited.

Molecular profiling provides prognostic and predictive information about tumor biology which has the potential to guide clinical care. Indeed, the four molecular subtypes proposed by the TCGA have been found to inform clinical outcomes in a retrospective analysis of multiple independent

cohorts, with EBV tumors having the best prognosis, followed by MSI and CIN, and GS having the worst prognosis. The TCGA subtypes have also been shown to have predictive value as well. In a retrospective analysis of GC patients who underwent surgical resection, patients with CIN tumors were found to derive the greatest benefit from adjuvant chemotherapy, with a 3-year recurrence-free survival of 59% for patients who received chemotherapy vs. 34% for patients who did not. In contrast, patients with GS tumors were found to derive no benefit from adjuvant chemotherapy, and the GS subtype is enriched for genes which likely confer resistance to chemotherapy.

While recent comprehensive molecular profiling studies have advanced our understanding of the complexity and heterogeneity of GC, it should be emphasized that achieving the objective of personalized medicine will require contextualizing each patient in terms of their unique biologic, socioeconomic, and environmental factors. Ultimately, the development of a prospectively validated genomic-based assay capable of improving the outcomes of GC patients is the aspirational goal of precision oncology research.

Screening Recommendations

GC screening recommendations vary because the effectiveness of screening is dependent on the incidence and prevalence in a given population. The two primary GC screening modalities include upper endoscopy and contrast radiography. Upper endoscopy allows for direct visualization of the gastric mucosa and for tissue biopsies to be obtained, aiding in the diagnosis of not only GC but precancerous lesions and *H. pylori* infection. Upper endoscopy is the most sensitive screening modality for GC (69–88%) with similar specificity as contrast radiography (85–96%). Endoscopy is an invasive procedure, requiring conscious sedation, and is costly. The cost-effectiveness of screening endoscopy is debated and varies by geographic location and population incidence. Contrast radiography is a less invasive and less expensive method of GC screening. It requires patients to ingest barium contrast and then undergo digital radiography for visualization of suspicious lesions. The downside of this screening modality is a lower sensitivity for detection of early GC, when compared to endoscopy.

Despite the high prevalence of GC in many countries, population-based screening guidelines are currently implemented only in Japan and Korea. The Japanese Gastric Cancer Treatment Guidelines recommend upper endoscopy every 2–3 years for individuals 50 years of age and above. The Korean National Cancer Screening Program recommends upper endoscopy or contrast radiography every 2 years for patients 40 years and older. Screening in these high-incidence countries improves GC mortality and is cost-effective. The impact of screening is highlighted by the overall survival rates of 65% and 71.5% in Japan and Korea, respectively, compared to 20% worldwide.

Studies done in Costa Rica in the early 2000, to assess the effectiveness of screening with upper GI contrast radiography, showed a 50% reduction in GC mortality. However, similar studies done in Venezuela, utilizing the same screening method, resulted in no changes in GC mortality. Despite these conflicting results, extrapolation of evidence from other high-incidence regions would indicate that a population-based screening program will be beneficial in Central and South America, similar to Japan and Korea. However, the high cost of GC screening is a barrier for implementation in low- and middle-income countries.

In the United States, a low-incidence country for GC, there are currently no general population-based screening recommendations. Current American Gastroenterological Association (AGA) guidelines recommend testing for and eradication of *H. pylori* in patients with gastrointestinal metaplasia (GIM). However, it recommends against routine, short interval endoscopy screening in GIM and advocates for a shared decision-making regarding endoscopic surveillance in high-risk groups.

Eradication of *H. pylori* has been shown to reduce the incidence of GC. As such, *H. pylori* population screening and treatment, similar to GC screening, may be cost-effective in high-risk populations. However, to date, no country has implemented a population-based *H. pylori* screening program; rather, it is reserved for high-risk individuals. The 2020 Taipei global consensus guidelines for screening and eradication of *H. pylori* recommend consideration of screening for high-risk populations.

Individuals with certain hereditary cancer syndromes represent a high-risk population for the development of GC. These syndromes include Lynch syndrome, Li-Fraumeni syndrome, MUTH-associated polyposis, familial adenomatous polyposis (FAP), juvenile polyposis syndrome, and Peutz-Jeghers syndrome. Screening recommendations for patients with each of these syndromes are summarized in Table 46.2.

Table 46.2 Hereditary cancer syndromes associated with an increased risk of gastric cancer

	Lynch Syndrome	Familial Adenomatous Polyposis	MUTYH-associated Polyposis	Li-Fraumeni Syndrome	Juvenile Polyposis Syndrome	Peutz-Jeghers Syndrome
Associated Mutations	*MLH1, MSH2, MSH6, PMS1, PMS2, EPCAM*	*APC*	*MUTYH*	*TP53*	*SMAD4, BMPR1A*	STK11
Age of Initial Screening	30-35	10-15	25-30	25, or 10 years before earliest onset in family	15	8
Screening Modality	EGD with biopsy of gastric antrum	EGD	EGD	EGD	EGD	EGD
Repeat Screening Interval	Every 2-3 years	None	Every 1-5 years	Every 2-5 years	Every 1-2 years	Every 3 years if polyps found. In absence, repeat at age 18

Summary

GC is an important global health problem due to high incidence and mortality. Incidence varies by region, race/ethnicity, and socioeconomic status and is affected by the complex interplay of environmental, lifestyle, and biological risk factors. Genomic discoveries have shown that gene mutations may explain some of the variation in incidence by race and ethnicity. One of the most notable epidemiologic trends is the increasing incidence of early-onset GC. Population-based screening for GC has proven to be cost-effective and successful in high-incidence regions; however, economic barriers make implementation of screening programs in low-income countries more challenging. The benefit of population-based screening and eradication of *H. pylori* is controversial; nevertheless, there is a role for *H. pylori* eradication in young adults residing in high-incidence regions. Whether a similar strategy should be considered for immigrants who migrate from high-incidence regions to low-incidence countries requires further investigation.

Questions

1. Which of the following is *not* a risk factor for non-cardia gastric cancer?
   A. *H. pylori*
   B. Fruits and vegetables
   C. Nitrites
   D. Low socioeconomic status

Answer: B

2. All of the following genetic syndromes are associated with an increased risk of gastric cancer *except*:
   A. Lynch syndrome
   B. Peutz-Jeghers syndrome
   C. Li-Fraumeni syndrome
   D. von Hippel-Lindau syndrome
   E. Hereditary diffuse gastric cancer syndrome

Answer: D

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Diagnosis and Management of Gastric Intestinal Metaplasia

47

Ji Yoon Yoon, Dan Li, and Shailja C. Shah

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide. The majority of gastric cancers originate in the noncardia region of the stomach and are histologically classified as intestinal-type adenocarcinoma. Intestinal-type noncardia gastric adenocarcinoma (NCGA) generally develops from a series of histologically identifiable stages referred to as the "Correa cascade" (Fig. 47.1). Chronic infection with *Helicobacter pylori* (*H. pylori*) causing non-atrophic gastritis is the most common initial insult to trigger the cascade, although other less common etiologies exist. In some individuals, particularly if there is persistent *H. pylori* infection or other etiologies for ongoing mucosal insult, such as autoimmunity against parietal cells, there may be progression to loss of normal gastric glands and atrophy with or without replacement of non-native glands, known as metaplasia, the most common form of which is gastric intestinal metaplasia (GIM). Both atrophic gastritis and GIM are considered premalignant changes and are associated with an increased risk of dysplasia and NCGA. Based on a recent meta-analysis, the baseline annual risk of gastric cancer in patients with histologically confirmed GIM is approximately 0.16% per year, although it may be higher than this depending on additional risk factors, such as persistent *H. pylori* infection; smoking; excess intake of salted, preserved, or processed foods; family history; non-white race/ethnicity; and GIM location and severity, among other factors. Accordingly, it is critical that both providers and patients recognize GIM as a precancerous condition requiring thoughtful management consideration in order to reduce and ideally prevent gastric cancer-related mortality.

In countries where gastric cancer screening does not routinely occur, such as the United States, NCGA is most often diagnosed in the advanced stage when symptoms prompt workup. Unfortunately, advanced-stage NCGA is associated with a dismal prognosis. By contrast, if NCGA is diagnosed in the early, and generally asymptomatic, stage prior to submucosal invasion, resection with curative intent is possible. The slow sojourn time of GIM to NCGA coupled with the fact that GIM is readily diagnosed on endoscopy with histological confirmation offers opportunity for endoscopic surveillance for early NCGA detection. This approach is not dissimilar to the models of surveillance of Barrett's esophagus and post-polypectomy surveillance for the prevention/early detection of esophageal and colorectal cancer, respectively.

Objectives

The primary objectives of this chapter are to:

- Discuss the epidemiology and risk factors for GIM
- Discuss the endoscopic and histologic diagnosis of GIM
- Discuss factors associated with neoplastic progression of GIM
- Discuss current recommendations for GIM management

We will note that while we use the term "progression" in this chapter to describe the subsequent diagnosis of NCGA in patients with histologically confirmed GIM, we acknowledge that it is debated as to whether GIM is simply a surrogate marker for increased gastric neoplasia risk or if GIM is truly a precursor lesion that undergoes neoplastic transformation, or both.

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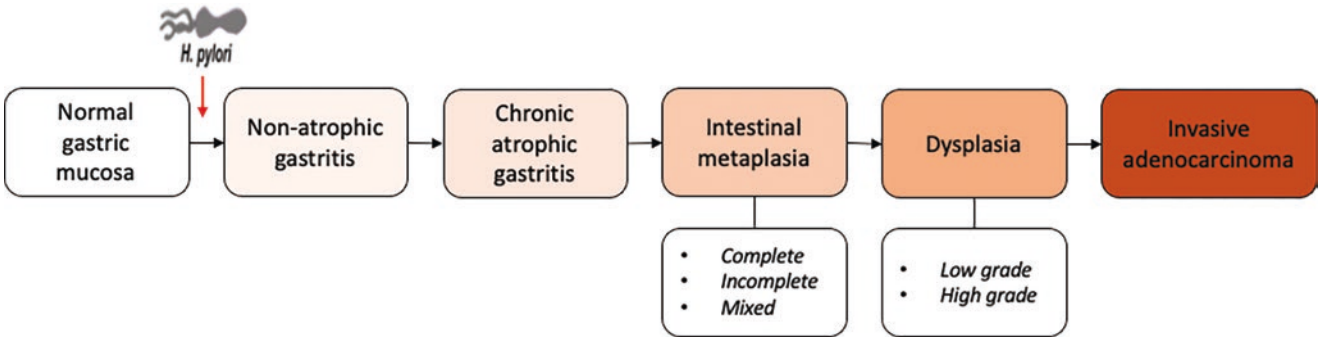

Fig. 47.1 Correa cascade

Epidemiology

Studies reporting on the prevalence of GIM within the United States are limited. Because a diagnosis of GIM requires upper endoscopy with histological confirmation, selection bias is important to consider when interpreting prevalence estimates. Most studies also do not report on whether GIM is limited to the antrum or if there is corpus involvement, which is an important distinction to make given that the latter is associated with a higher risk of NCGA. One large study from a national pathology of 895,293 people undergoing upper endoscopy and gastric biopsies for any indication reported that the prevalence of any GIM was 4.9%. A recent meta-analysis of pooled studies from the United States, which was overwhelmingly influenced by the large sample size of this one study using a pathology database, reported a pooled GIM prevalence of 4.8% (95% CI 4.8–4.9%). In smaller studies, the prevalence for GIM is higher, ranging between 4.9% and 19%. An important point to emphasize is that there are identifiable populations within the United States who have higher prevalence of GIM. Factors associated with higher prevalence of GIM include *H. pylori* exposure (25%, 95% CI: 24–26%), non-white race/ethnicity (23.3%, 95% CI 36.6–63.4%, in Hispanics vs 12.2%, 95% CI 9.7–15.0%, in non-Hispanic whites), and immigration from countries where NCGA and *H. pylori* are endemic. The likelihood of GIM also increases with age, male sex, tobacco use (RR 1.57, 95% CI 1.24–1.98), alcohol use (RR 1.29, 95% CI 1.12–1.50), and probably dietary factors. Certain *H. pylori* virulence factors appear to present additional risk, consistent with the association of these same virulence factors with gastric cancer. For example, *cytotoxin-associated gene A* (CagA)-positive strains are associated with a higher prevalence of GIM than CagA-negative patients, although the lowest prevalence is still in patients without prior *H. pylori* infection.

Pathophysiology

The progression of normal gastric mucosa to noncardia gastric adenoma (NCGA) is outlined by the Correa cascade, which describes a distinct pathologic sequence as follows: normal gastric mucosa → non-atrophic gastritis → chronic atrophic gastritis → intestinal metaplasia (complete, incomplete, mixed) → low grade dysplasia → high grade dysplasia → invasive adenocarcinoma, which occurs in only a small minority (<1–3%) of those infected with *H. pylori* (Fig. 47.1). As noted above, the most common trigger for the Correa cascade is *H. pylori* infection, although other less common causes of chronic inflammation exist, including autoimmune gastritis (AIG) and bile acid reflux. AG is defined as the loss of oxyntic or mucosecreting glands from the body and antrum, respectively. Years of mucosal inflammation result in atrophy of the gastric glands, which are replaced with connective tissue (non-metaplastic atrophy), or metaplastic epithelium. GIM refers to the replacement of the gastric epithelium with one that resembles that of the intestine. Other forms of metaplasia do occur, such as pancreatic metaplasia, but are rarer and do not appear to be clinically relevant. GIM arises on a background of AG and implies the presence of AG, although the presence of background AG is inconsistently documented in pathology reports.

Histologic Features

GIM can be classified based on histological subtype as complete, incomplete, or mixed type. The complete type resembles the small intestinal epithelium, displaying enterocytes with a characteristic brush border, interspersed well-developed goblet cells, and organized, straight crypt architecture, often with Paneth cells at the crypt base. Incomplete-type GIM demonstrates irregular crypt architecture, no brush border, goblet cells of variable sizes, and

columnar cells with mucin at various stages of differentiation. Not uncommonly, both types are present in the biopsy specimen. While both complete and incomplete GIM are associated with elevated gastric cancer risk, incomplete GIM has a 3.3-fold (RR 3.33, 95% CI 1.96–5.64) higher risk compared to complete GIM. Histologic subtyping is not currently routinely reported in clinical practice in the United States. Given its utility for risk stratification at minimal additional cost (discrimination can be made on routine H&E staining), routine subtyping of GIM should be considered.

GIM can also be classified based on mucin staining according to a system proposed by pathologists Filipe and Jass in 1981. This system relies on Alcian blue pH 2.5 (AB)/periodic acid-Schiff (PAS) and high iron diamine (HID)/AB to classify GIM type I, II, and III. AB/PAS stain identifies neutral mucins, normally in the stomach (stains magenta), and acid mucin, normally in the intestinal mucosa (stains blue). HID/AB stain identifies sialomucin, normally present in the small intestine and colon (stains blue), and sulfomucins, normally in the colon (stains brown). This system is mostly for research purposes, but there is clinical correlation with respect to risk of gastric cancer. Type I corresponds to complete-type GIM, and types II and III correspond to incomplete GIM.

Diagnosis and Management of GIM

Endoscopic Diagnosis

The endoscopic appearance of both AG and GIM may be subtle, and attention to optimizing the quality of endoscopic exam is a priority. General measures to improve mucosal visibility should be applied, including adequate insufflation, lavage, and use of defoaming agents such as simethicone. Adequate withdrawal time and careful photo-documentation should be emphasized. While the diagnosis of AG/GIM requires histopathological confirmation, their endoscopic features should be recognized to help with the diagnosis and also for appropriately targeting biopsies to improve yield, since both AG/GIM can have a patchy distribution. In East Asia, image-enhanced endoscopy, including chromoendoscopy, and high-resolution magnification endoscopy are routinely used for improved endoscopic diagnosis of AG/GIM; however, these techniques and expertise are not widely available in the West. In general, we recommend using high-definition white light endoscopy (HD-WLE) in combination with image-enhanced techniques such as narrow-band imaging (NBI) to optimize the endoscopic diagnosis of AG/GIM. Traditional chromoendoscopy using dyes including acetic acid, indigo carmine, and methylene blue is associated with improved diagnostic yield of GIM, but with the drawback of adding to procedure time and unclear advantage over HD-WLE and image-enhanced techniques.

With NBI, normal gastric mucosa displays homogeneously sized round pits with regular arrangement of collecting venules (RACs), which are highly predictive of the absence of *H. pylori* infection (Fig. 47.2). In the setting of chronic *H. pylori* infection, these pit patterns become elongated and irregular in shape and size, with RACs becoming difficult to discern due to inflammation. In AG, gastric mucosa typically appears pale with increased prominence of vessels due to mucosal thinning, and there may be a loss of gastric folds (rugae) if the gastric corpus is involved (Fig. 47.2).

The appearance of GIM can be subtle on white light endoscopy and therefore easily overlooked. HD-WLE has high specificity (>90%) but low sensitivity (53–75%) for GIM. HD-WLE in combination with NBI which emphasizes the mucosal pit pattern has shown improved detection of GIM. Areas of GIM may appear as mildly nodular patches, with ridged or tubulovillous mucosal patterns (Fig. 47.2). The presence of "light blue crest" (LBC) sign, defined as fine, blue-white lines on the crests of the epithelial surface, is characteristic of GIM, with sensitivity and specificity of approximately 90%. LBC signs are best visualized with magnification endoscopy but may also be seen with near-focus HD-WLE.

Biopsies should also be obtained according to the updated Sydney protocol in order to determine the extent/severity of AG/GIM involvement, as well as the histologic subtype of GIM if possible. The updated Sydney protocol advocates a total of five sets of biopsies from the following locations: the lesser and greater curve of the antrum, lesser and greater curve of the corpus, and the incisura. The biopsies should be placed in separate jars, although if cost is a consideration, these can be combined into jars labelled "antrum/incisura" and "body," to allow evaluation of extent of disease and full risk stratification as outlined below. Targeted biopsies should be taken from any suspicious lesions and placed into separately labeled jars. A combination of HD-WLE and NBI should be used to guide biopsies for GIM, define the extent of gastric atrophy, and interrogate the mucosa for possible synchronous gastric neoplasia.

Risk Stratification

Based on pooled analysis of mostly non-US studies, among patients with GIM, the cumulative incidence of gastric cancer was 0.1%, 1.1%, and 1.6% at 3, 5, and 10 years, respectively, which provides rationale to also offer surveillance

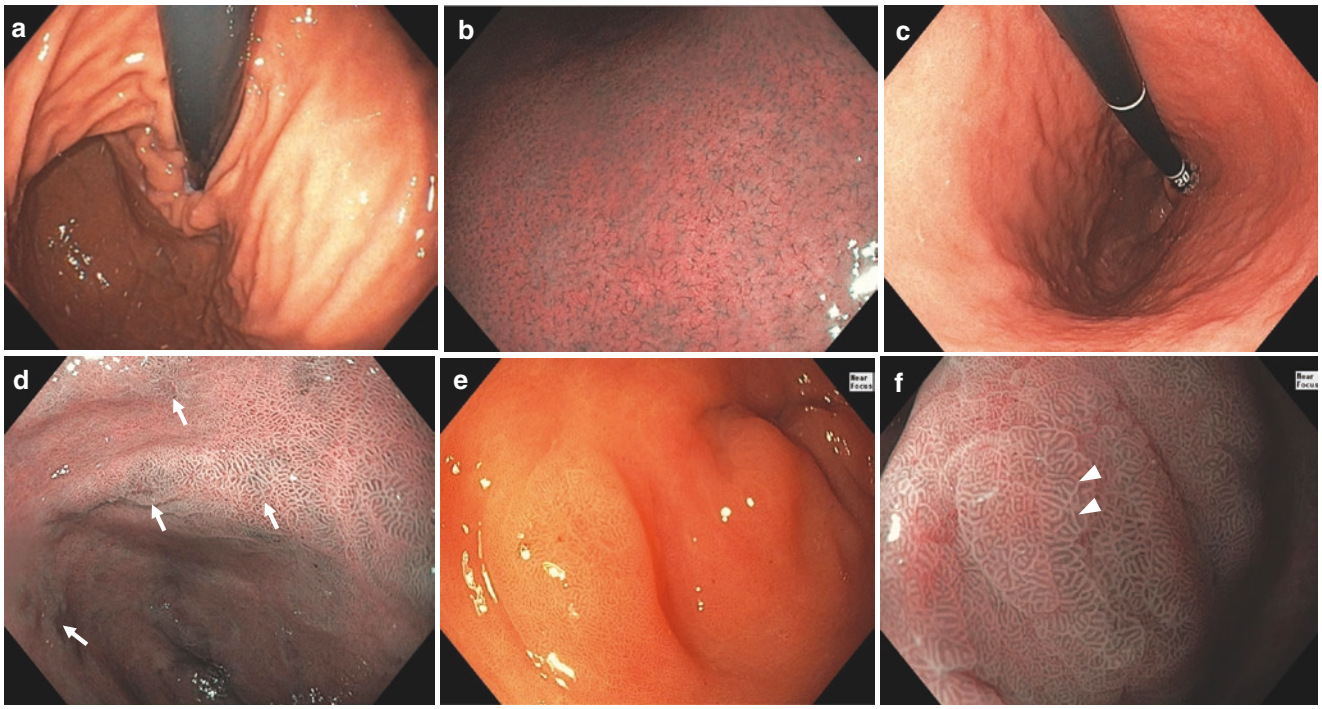

Fig. 47.2 Endoscopic appearance of normal stomach, atrophic gastritis, and gastric intestinal metaplasia (GIM). (**a**) Normal gastric mucosa with smooth mucosal texture and normal rugae. (**b**) Regular arrangement of collecting venules (RACs) under NBI. RACs appear as numerous tiny spidery vessels and are highly predictive of absence of *Helicobacter pylori* infection. (**c**) Atrophic gastritis with loss of gastric rugae. (**d**) Multiple foci of GIM under NBI (arrow heads). (**e**) Close-up view of GIM using near-focus WL-HDE. The area of GIM appears mildly nodular, with ridged or tubulovillous mucosal patterns. (**f**) GIM under near-focus NBI. The "light blue crest" sign, defined as fine, blue-white lines on the crests of the epithelial surface and characteristics of GIM, is visible

endoscopy for patients with GIM. However, given the high prevalence of AG/GIM even in regions with overall low-intermediate incidence of NCGA, a balance much be reached between the economic cost/patient risks associated with endoscopic surveillance and the potential benefits with respect to early cancer detection and opportunity for potentially curative treatment. Other than clinical risk factors such as race/ethnicity, *H. pylori* infection, smoking, family history, AG/GIM extent/severity, and perhaps dietary factors, our understanding of risk factors for progression once AG/GIM are identified remains very limited. Indeed, we are not yet able to predict who will vs will not go on to develop gastric cancer. The following section outlines the identified risk factors and histologic features that help identify subgroups of patients at elevated risk for gastric cancer who might benefit from surveillance. We follow this section with a summary of current guidelines for surveillance of AG/GIM.

Continued inflammation of the gastric mucosa with persistent *H. pylori* infection is the greatest modifiable risk factor. While AG is more likely to be reversible with possible restoration to normal gastric mucosa following *H. pylori* eradication, it is still debated as to whether GIM is reversible. Ideally, *H. pylori* eradication is achieved prior to the development of AG/GIM, thus substantially mitigating the risk of subsequent NCGA. Even in patients with GIM or more advanced histologic changes, *H. pylori* eradication and confirmation of eradication are still recommended to reduce the likelihood of subsequent NCGA, even if these changes are not reversible. With or without GIM, treatment of *H. pylori* demonstrated a lower risk of incident gastric cancer compared to placebo (RR 0.68, 95% CI 0.48–0.96). When this analysis was limited to patients with GIM, there was a statistically non-significant trend toward higher risk of incident NCGA with treatment of *H. pylori* vs placebo, which implicates other factors in progression that are not yet well-defined. After eradication, the risk of NCGA remains elevated, particularly in patients with severe or extensive atrophy, and accordingly, patients with GIM even after *H. pylori* eradication may still benefit from endoscopic surveillance.

As noted above, certain subgroups of patients with GIM have a higher than the baseline risk of 0.16% annual risk of progression to NCGA. Based on the AGA technical review, these include the following subgroups: Compared to no family history of gastric cancer, a positive family history was associated with 4.5-fold increased odds of gastric cancer (OR 4.53, 95% CI 1.33–14.56). Compared to complete GIM, incomplete GIM had 3.3-fold increased risk of gastric cancer (RR 3.33, 95% CI 1.96–5.64). Compared to limited GIM, extensive GIM had a twofold increased risk of gastric cancer, though this was not statistically significant (RR 2.07, 95% CI 0.97–4.42). In pooled analysis of studies based in North America, racial and ethnic background (non-Hispanic white,

black, Hispanic, Asian, other) demonstrated no significant difference in GIM progression to gastric cancer. Similarly, dietary factors, smoking, and pernicious anemia are associated with gastric cancer, but did not demonstrate significant differential risk based on pooled analysis.

Staging Systems

Extensive GIM, involving the corpus, has a higher risk of NCGA vs limited GIM, which is confined to the gastric antrum/incisura. The Operative Link on Gastritis Assessment (OLGA) staging system integrates the degree and extent of atrophic gastritis. Higher OLGA stages (such as OLGA III/IV) correlate with risk of gastric cancer, but routine use of the OLGA staging system is limited by low interobserver agreement. GIM by contrast is more easily identified on histology than atrophy, and modifying the OLGA staging system by replacing the main parameter of the staging system from atrophy to intestinal metaplasia ("Operative Link on Gastric Intestinal Metaplasia" (OLGIM)) has demonstrated improved interobserver agreement. There is an additional benefit of lower technical requirements for the processing of biopsy specimens to identify GIM. Although this staging system does not consider the histologic subtype (complete vs incomplete) of GIM, there is a significant association between presence of incomplete GIM and increased GIM severity according to OLGIM. OLGA and OLGIM stage III and IV are associated with an increased risk of gastric cancer vs stage 0/I/II. Unfortunately, despite clear prognostic value, these systems have not gained a foothold in the routine clinical practice in the United States.

Management

Currently, there is wide variation in the knowledge and management of GIM among US-based gastroenterologists. This reflects the lack of high-quality data specific to the United States to inform practice. The American Gastroenterological Association (AGA), British Society of Gastroenterology (BSG), Management of epithelial precancerous conditions and lesions in the stomach (MAPS II) guidelines published by the European societies, and the Kyoto global consensus report on *H. pylori* gastritis provide relevant guidance, which will be reviewed in the following section. A focused comparison of these guidelines is provided in Table 47.1.

Eradication of *H. pylori*

In patients with or without GIM, eradication of *H. pylori* demonstrates a pooled relative risk reduction of gastric cancer of 32% (RR 0.68; 95% CI 0.48–0.96) and 33% pooled relative risk reduction of gastric cancer mortality (RR 0.67; 95% CI 0.38–1.17). The impact of *H. pylori* treatment specific to patients with GIM is not fully defined; however, eradication of *H. pylori* eradication has been shown to reverse mucosal changes in non-atrophic gastritis and mild gastric atrophy compared to placebo (RR 1.29, 95% CI 1.12–1.48), although in some studies, the effect was attenuated in severe gastric atrophy with or without GIM, potentially indicating a "point of no return."

AGA and BSG guidelines recommend testing for and eradication of *H. pylori* in patients with AG/GIM. MAPS II recommends eradication in atrophic and non-atrophic gastritis associated with *H. pylori* and for providers to consider *H. pylori* eradication in patients with established GIM, though it

Table 47.1 Summary of International Guidance on management of gastric intestinal metaplasia management

	United States (AGA 2020)	British (BSG 2019)	European (MAPS II 2019)	Japanese (Kyoto 2015)
Methodology (GRADE)	PICO	AGREE II	Delphi	Delphi
H. pylori eradication	Yes *Strong, moderate*	Yes *Strong, high*	Yes *Strong, high*	Yes *Strong, high*
Endoscopic surveillance is recommended according to:				
Family history	Consider	Yes	Yes	NR
Age, sex	NR	NR	NR	NR
Race, ethnicity, immigration	Consider	NR	NR	NR
Extensive GIM	Consider	Yes	Yes	CR[a]
Incomplete GIM	Consider	NR	CR	NR
Pernicious anemia with GIM	NR	Yes	Yes	NR
Gastric atrophy	NR	CR	CR	CR[a]
OLGA/OLGIM III/IV	NR	NR	CR	CR[a]
Suggested endoscopic surveillance interval	3–5 years	3 years	3 years	NR
Endoscopy quality	NR	Yes	Yes	NR

NR not reported, *CR* conditional recommendation
In italics: strength of recommendation, quality of evidence (GRADE)
[a] Not a statement that was agreed upon under Delphi consensus process, but the authors state that due to higher gastric cancer risk subgroups of patients (stage III or IV of OLGA/OLGIM, extensive gastric atrophy), endoscopic surveillance should be offered to patients in these subcategories

specifies that this is a weaker recommendation due to evidence that eradication once GIM is established does not appear to significantly reduce the risk of gastric cancer. *H. pylori* eradication is associated with a reduced risk of metachronous gastric cancer. The Kyoto guidelines recommend all individuals who test positive for *H. pylori* receive eradication therapy, citing the additional benefit of reduced transmission to other individuals in regions with high prevalence.

If biopsies are negative for *H. pylori*, an alternative non-serological test, such as the urea breath test or *H. pylori* stool antigen test, can be considered, given that *H. pylori* colonization of gastric mucosa may be patchy and is not uncommonly absent from overt areas of GIM. Following *H. pylori* treatment, providers should confirm that eradication was successful using a non-serological *H. pylori* test.

Short-Interval Endoscopic Evaluation

GIM is sometimes diagnosed incidentally, and unfortunately, the index endoscopy may not provide sufficient information to complete the risk assessment. For example, if biopsies obtained from the body and antrum were placed in the same jar, the extent (limited vs extensive) of GIM is not known. A short-interval repeat endoscopic evaluation for the purpose of risk stratification is not routinely recommended by GI societies (AGA, MAPS II); however, if there is concern about the initial quality of the exam, then a repeat endoscopy provides an opportunity for careful, systematic examination for synchronous lesions such as an early-stage gastric cancer which may be subtle in appearance and can be overlooked. The BSG suggests that patients with elevated risk for gastric cancer, including patients with AG and GIM, undergo full endoscopic evaluation with photographic documentations and pathology using the updated Sydney protocol.

Endoscopic Surveillance

Although there is a lack of prospective, randomized controlled trials to support the benefits of surveillance for GIM in reducing gastric cancer-related morbidity and mortality, the strong association between AG/GIM (particularly extensive AG/GIM) and increased risk of NCGA based on multiple observational studies justifies endoscopic surveillance in patients after risk stratification (discussed below).

The AGA does not recommend routine endoscopic surveillance for patients with GIM but suggests that patients who are at higher risk of progression to gastric cancer (incomplete GIM, extensive GIM, or family history of gastric cancer) or patients at overall increased risk for gastric cancer (racial/ethnic minorities, immigrants from high incidence regions), those who put a high value in potential reduction of gastric cancer risk and a low value on risk associated with repeat endoscopic surveillance, may consider endoscopic surveillance every 3–5 years. The BSG recommends endoscopic surveillance every 3 years in patients with extensive gastric atrophy or GIM. In AG/GIM limited to the gastric antrum, surveillance is only recommended if there are further risk factors, including family history of gastric cancer, or persistent *H. pylori*. MAPS II does not recommend patients with GIM at a single location (antrum or corpus) undergo regular endoscopic surveillance, although surveillance in 3 years can be considered if the patient also has additional risk factors for gastric cancer, including family history, incomplete IM, or persistent *H. pylori* gastritis. MAPS II guidelines recommend endoscopy every 3 years in patients with severe atrophic changes or IM in both antrum and corpus, or OLGA III/IV disease, and suggest that patients with advanced atrophic gastritis and a family history of gastric cancer may benefit from more intensive endoscopic surveillance, every 1–2 years.

The Kyoto guidelines suggest that endoscopic surveillance be offered to patients with elevated gastric cancer risk despite *H. pylori* eradication, including those with advanced OLGA/OLGIM stage, pepsinogen I <70 ng/mL, and pepsinogen I/II ratio <3. The surveillance interval is not specified in this guideline; however, a population-based biennial screening program for gastric cancer exists in Japan.

Healthcare Cost Considerations

Similar to colorectal cancer, gastric premalignant lesions have a reasonably sufficient lead time to the development of gastric cancer, and effective endoscopic interventions for dysplastic lesions or early cancer are available. In the United States, in the absence of a structured screening program, gastric cancer is diagnosed once symptoms prompt evaluation. Gastric cancer typically only causes symptoms, which are most often nonspecific, once in the advanced stage. The predominant advanced-stage presentation explains the dismal 5-year survival rate of 31% of gastric cancer in the United States. In contrast, in East Asian countries such as Japan and South Korea where endoscopic screening and surveillance programs have been implemented, the 5-year overall survival is approximately 70% and is attributed to higher proportion of gastric cancer diagnosed in an early stage when curative resection is possible.

A systematic review of decision analytic studies on gastric cancer screening and gastric precancer surveillance identified 17 studies and demonstrated that endoscopic screening was cost-effective across all studies conducted in high-incidence countries (greater than 10 cases per 100,000 persons) and generally cost-effective in targeted screening of high-risk populations in otherwise low-to-intermediate incidence countries. The United States is considered a low-to-intermediate incidence country for gastric cancer, and a population-based screening and surveillance approach is not considered to be cost-effective. However, the incidence of gastric cancer demonstrates significant variability across racial/ethnic subpopulations in some countries. For example, within the United

States, in comparison with the non-Hispanic white majority, Hispanics and non-Hispanic blacks demonstrate a twofold higher incidence rate, and in some Asian American groups, an estimated 14.5-fold higher. Migrants from high-incidence countries retain an elevated risk of gastric cancer compared to the native population. Although broad population-based screening does not meet the willingness-to-pay thresholds in low-to-intermediate incidence countries such as the United States, risk-stratified targeting screening that incorporates objective variables (age, sex, race/ethnicity, smoking status, immigration details) may reach the cost-effectiveness threshold in these countries.

Conclusion

GIM represents an important precancerous mucosal change in the multistep cascade in gastric cancer pathogenesis. It is associated with an approximately 0.16% annual risk of progression to gastric cancer, which may be higher in the presence of additional risk factors. A finding of GIM is significant and should not be ignored. The long sojourn time of progression to gastric cancer presents important opportunities for endoscopy surveillance of GIM, which allows early detection and intervention of gastric cancer at a curable stage. Individuals with GIM should be carefully risk stratified. Higher risk features include incomplete GIM, extensive disease, racial/ethnical minorities, and family history of gastric cancer. Careful endoscopic examination and adequate biopsies are paramount to inform risk stratification. Enhanced imaging, such as NBI, in addition to high-definition white light endoscopy improves detection rate and should be employed routinely. In addition, all individuals with GIM should be tested for *H. pylori* and treated if positive, with confirmation of eradication post treatment. Future studies are awaited to further improve the precision in the diagnosis, surveillance, and management of patients with GIM.

Questions

1. Which of the following individuals would be an appropriate candidate for surveillance according to current US guidelines? (Choose two)
   A. Patient with complete intestinal metaplasia confined to the antrum
   B. Patient with incomplete intestinal metaplasia confined to the antrum
   C. Patient with limited intestinal metaplasia, first generation migrant from East Asia
   D. Patient with limited intestinal metaplasia, H pylori positive

Answer: B and C. Current US guidelines suggest that endoscopic surveillance be considered in patients with advanced intestinal metaplasia (extensive involvement of both antrum and corpus, or incomplete intestinal metaplasia on histology) or family history of gastric cancer, due to higher risk of progression (Option B). Surveillance may also be considered in patients with overall elevated risk of gastric cancer outside of GIM severity, including patients of racial/ethnic minority background and those from high-incidence regions (option C).

2. What are the endoscopic features of GIM? (Choose two)
   A. Loss of rugal folds
   B. Regular arrangement of collecting venules
   C. Nodular areas with tubulovillous mucosal pattern
   D. Light blue crest sign

Answer: C and D. Option A is suggestive of atrophic gastritis and not intestinal metaplasia. It is important to note that atrophic gastritis is considered a precursor state of GIM, while the presence of GIM almost invariably implies the diagnosis of atrophic gastritis. Option B represents healthy gastric mucosa and strongly suggests lack of H pylori infection. Options C and D are typical endoscopic features of GIM.

3. What is the appropriate endoscopic biopsy protocol for risk stratification of GIM? (Choose two)
   A. Biopsies from the lesser and greater curvature of the antrum and body, plus the incisura, in separate jars
   B. Biopsies from the antrum, incisura, body, and fundus in separate jars
   C. Biopsies from the antrum/incisura and body, in two jars
   D. Biopsies from the antrum, incisura and body, in one jar

Answer: A and C. Option A is the updated Sydney protocol that allows determination of the extent of GIM for risk stratification. Option C is an abbreviated protocol which can be followed for cost considerations.

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Endoscopic Staging and Resection for Early Gastric Cancer

48

Jason Samarasena, Anastasia Chahine, and Joo Ha Hwang

Case Presentation

Mrs. N is a 68-year-old Japanese American female who presents to her gastroenterologist for symptoms of intermittent heartburn and bloating. She undergoes an upper endoscopy at which time a 3 × 2 cm lesion in the greater curvature of the antrum is noted (Fig. 48.1). What are the next appropriate steps in the management of this lesion?

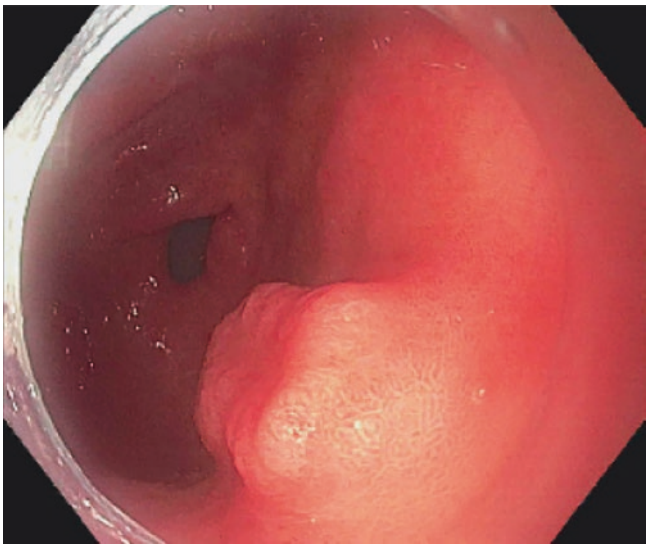

Fig. 48.1 Endoscopic view of a gastric antral lesion

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Introduction

Globally, gastric adenocarcinoma afflicts nearly one million people yearly and is the third leading cause of global cancer mortality and the leading cause of infection-associated cancer death [1, 2]. Early gastric cancer (EGC) accounts for 15–57% of incident gastric cancer and is defined as invasive gastric cancer that invades no more deeply than the submucosa [3–6]. EGC has driven the development of novel endoscopic imaging technologies for early neoplasia detection and advanced endoscopic resection techniques, such as endoscopic submucosal dissection. The following is an evidence-based review of the contemporary methods of endoscopic staging and resection for early gastric cancer.

Endoscopic Evaluation of EGC

Whenever gastric cancer is suspected, endoscopic evaluation of the gastric lining is performed using upper endoscopy for diagnosis and staging. Accurate diagnosis and precise staging of gastric lesions is essential in guiding therapy. In order to determine whether endoscopic resection for early gastric cancer is warranted, gastric lesions should be assessed for size, depth of invasion, presence of ulceration, and histopathological type [7].

To improve lesion assessment in EGC, several devices have been used to assist conventional endoscopy in evaluating early gastric lesions. These developments in diagnostic endoscopy include white-light endoscopy (WLE), chromoendoscopy, narrow-band imaging (NBI), magnifying endoscopy (ME), confocal laser endomicroscopy (CLE), and artificial intelligence (AI) programs.

Evaluation of EGC lesions differs in Asian and Western countries [8] and depends on the devices available. In Asia, endoscopists use ME to assess a lesion [8], whereas in Western countries, endoscopists rely mainly on conventional endoscopy with WLE and NBI. Magnification endoscopes are capable of magnifying an image up to 150 times its original size signifi-

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cantly higher than the standard endoscope [9]. These endoscopes have an adjustable lens attached to the tip of the endoscope capable of producing an optical zoom magnification. This produces an enlarged image without decreasing the resolution of the image [9]. Magnifying endoscopy is usually combined with dye-based chromoendoscopy or more commonly virtual chromoendoscopy to enhance visualization [9]. Virtual chromoendoscopy uses technology built into the endoscope to achieve a similar result as dye application with the ease of only pressing a button. The most widely used system is NBI (Olympus Corporation), which applies a red-green-blue light filter to the target mucosa. The NBI is based on the optical phenomenon that the depth of light penetration into tissue depends on the wavelength; the shorter the wavelength, the more superficial the penetration. Whereas standard WLE uses light at wavelengths of 400–700 nm, NBI applies shorter wavelengths (400–540 nm) to maximally highlight the surface mucosa and vascular pattern [10]. Additionally, this narrower spectrum is matched to the maximum absorption of hemoglobin, so that structures with high hemoglobin content will appear dark (surface capillaries appear brown; submucosal vessels appear cyan) compared to the brighter surrounding mucosa. Virtual chromoendoscopy such as NBI improves lesion classification by allowing the endoscopist to better visualize the mucosal and vascular structures [11, 12]. When image-enhanced endoscopy is used in combination with magnification endoscopy, the accuracy for differentiation of superficial gastric cancer increases since the microsurface architecture and microvasculature patterns can be better assessed [12].

Assessment of Margins

Assessing the margins of a lesion during initial evaluation is critically important when performing endoscopic resection [7, 13] as this allows for accurate marking of the lesion prior to ESD, thereby increasing the likelihood of a curative resection [13].

When relying on WLE, studies have shown that the borders of EGC lesions are accurately predicted in 50–66.9% of the cases and that the size of the lesion is usually underestimated [13].With chromoendocopy, the addition of dyes such as indigo carmine or acetic acid to conventional endoscopy improves the accuracy of demarcating the lateral margins of EGC [14, 15], with studies showing its ability to detect the borders of 80% of EGC lesions [7].

Studies have demonstrated the usefulness of NBI in predicting the horizontal margins of EGC lesions. Combining NBI with ME enables visualization of the microvasculature and allows endoscopists to better delineate the borders of the lesion [16, 17]. Nagahama and colleagues reported that in 18.9% of EGC lesions, chromoendoscopy was not able to delineate the horizontal margins reliably. When ME-NBI was used to examine these lesions, 72.6% were successfully demarcated [16]. However, the literature is conflicting when it comes to comparing the effectiveness of chromoendoscopy and ME-NBI. Some studies have proven superiority of ME-NBI in demarcating horizontal margins [18], while other studies show similar effectiveness in both techniques [19]. The most challenging lesions to assess horizontal margins remain undifferentiated EGC, whereby even ME-NBI often is inadequate [16]. Guidelines recommend doing targeted biopsies around such difficult lesions in order to determine the margins [7].

A disadvantage of current image-enhanced endoscopy is that it does not provide true microscopic level visualization [11, 20]. Confocal laser endomicroscopy (CLE) allows endoscopists to view the microscopic architecture of lesions in real time with increased magnification. Endoscopy with CLE improves assessment of EGC margins prior to ESD [11, 20]. In a prospective randomized controlled study, Park et al. compared probe-based confocal laser endomicroscopy (pCLE) and WLE with chromoendoscopy to assess margin delineation in EGC for ESD. The complete resection rate was similar in both groups; however, lateral margins in EGC lesions with superficial flat morphology were better assessed using pCLE compared to chromoendoscopy. A significant ($p = 0.007$) reduction in median distance from the marking to the margin was achieved with pCLE (0.5 mm) compared to chromoendoscopy (3.1 mm) [21].

With the advancement in AI technology, highly trained endoscopic algorithms have gained popularity in gastroenterology. Several studies have shown promising results when evaluating the usefulness of AI in the assessment of EGC lesions. In one of the studies [22], ENDOANGEL, a real-time fully convolutional neural network, was trained and evaluated for its accuracy in margin demarcation of EGC lesions. When the algorithm was tested on chromoendoscopy and WLE images, ENDOANGEL showed a margin delineation accuracy of 85.7% and 88.9%, respectively. When evaluated using ESD video clips, ENDOANGEL was able to draw margins for all areas of high-grade intraepithelial neoplasia and cancers. Compared to ME-NBI, ENDOANGEL was superior in predicting the resection margin [22]. In a meta-analysis of 16 studies, evaluating the performance of AI in diagnosing EGC, AI was more accurate in diagnosing EGC when compared to endoscopists. As for depth of invasion, AI was capable of identifying the depth of EGC invasion but hasn't been shown to be superior to conventional endoscopy [23].

Staging: Depth of Invasion and Lymph Node Involvement

Staging of gastric cancer is done following the TNM classification of the American Joint Committee on Cancer [24]. EGC are lesions that are limited to the mucosa and submucosa of the gastric wall. All T1 lesions regardless of lymph node metastasis are considered EGCs; however, lymph node involvement affects treatment selection for EGCs. As such, clearly identify-

ing the depth of invasion and assessing for lymph node metastasis is crucial for staging of gastric cancer and for determining which lesions are amenable for endoscopic resection.

Conventional endoscopy with white-light and indigo-carmine dye (chromoendoscopy) has been commonly used to determine the depth of invasion [7]. In a study by Choi et al., conventional endoscopy with WLE was shown to be 78% accurate in estimating the depth of invasion of EGC by assessment of the microsurface and morphology. During endoscopic evaluation, careful evaluation of the tumor base, borders, and converging folds can help determine the depth of invasion. Based on this study, when a lesion has a smooth surface depression or protrusion, a slightly raised margin, and slippery tapering of converging folds, it is most likely a mucosal cancer. In contrast, submucosal cancers are depicted as having an irregular surface, notable raised margins, and sudden cutting or merging of converging folds [25].

Zhou et al. evaluated the effectiveness of ME-NBI in accurately detecting the depth of invasion. In some studies, ME-NBI showed a high accuracy in detecting the vertical margins of EGCs that are limited to the superficial mucosa and are histologically well differentiated, while other studies showed less accuracy. However for undifferentiated EGCs, similar to when evaluating horizontal margins with ME-NBI, vertical margin assessment is difficult [13].

Endoscopic ultrasound (EUS) has been also used as a diagnostic tool for measuring depth of invasion. EUS offers information about the layers of the gastric lining as well as lymph nodes and thus has been largely used for T and N staging of gastric cancers. The importance of EUS in determining the depth of tumor invasion and thus T staging of EGC remains controversial. Studies have shown that EUS does a fair job in detecting shallow submucosal invasion of EGC; however, its sensitivity and specificity in detecting focal areas of invasion deeper than the submucosa is low [12]. In addition, EUS has not been proven to be superior in diagnosing vertical margins when compared to WLE [12, 13]. EUS is however especially useful in determining regional lymph node involvement by detecting any enlargement of lymph nodes. EUS-guided fine-needle aspiration can then be used to classify nodal status as a reactive versus metastatic process.

In our experience, both conventional endoscopy with white-light imaging and EUS often fall short, and the most accurate method to stage gastric cancer is still endoscopic resection. In addition to treating EGCs, ESD enables en bloc resection of tumors, which helps clarify staging by providing true pathological results [26].

Indications for Resection of EGC

When the diagnosis of EGC is made, lesions should be removed with either endoscopic resection or surgical treatment [7]. In this section, we will review the general recommendations of the updated 2020 Japanese Guidelines for endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) for EGC. Overall, when lymph node metastasis is not suspected, and when there is high likelihood of achieving en bloc resection according to size and location assessment, endoscopic resection is favored over gastrectomy since long-term outcomes are similar to surgery with lower morbidity [7].

Absolute, Expanded, and Relative Criteria for Endoscopic Resection

For all the mentioned indications, it is presumed that there is no evidence of lymph node invasion: "all lesions are presupposed to have a <1% risk of lymph node metastasis."

Absolute Indications for EMR or ESD

1. Differentiated-type carcinomas
2. Greatest dimension measuring ≤2 cm
3. Absence of ulceration or ulcer scar (UL0)
4. Limited to the mucosa: clinically intramucosal (cT1a)

Absolute Indications for ESD

1. Differentiated-type carcinomas
2. Greatest dimension >2 cm (no upper limit)
3. Absence of ulceration or ulcer scar (UL0)
4. Limited to the mucosa: clinically intramucosal (cT1a)

Or

1. Differentiated-type carcinomas
2. Presence of ulceration or ulcer scar (UL1)
3. Greatest dimension measuring ≤3 cm
4. Limited to the mucosa: clinically intramucosal (cT1a)

Or

1. Undifferentiated-type carcinomas
2. Greatest dimension ≤2 cm
3. Absence of ulceration or ulcer scar (UL0)
4. Limited to the mucosa: clinically intramucosal (cT1a)

Expanded Indications for ESD

In the current updated edition of the Japanese Guidelines, the expanded indications for endoscopic resection from previous guidelines have been combined with the absolute indications as recent multicenter studies showed a similar prognosis [7, 8, 27, 28].

In this edition, the expanded indications for ESD involve local recurrence: "only in cases of differentiated-type carcinomas, lesions can be regarded as expanded indications for

ESD, provided that the absolute indication lesions locally recur as intramucosal cancer after initial ESD/EMR with a C-1 grade of endoscopic curability (eCura)" [7].

Relative Indications

When lesions do not meet the criteria for absolute or expanded indications, endoscopic resection can still be used in some EGC lesions. Preoperative diagnosis and staging are not always reliable especially when the histopathologic report indicates submucosal invasion (pT1b). In cases where a precise histopathologic diagnosis of lesions before surgery cannot be made and when a patient's condition makes surgery a high risk, endoscopic resection is optimal [7].

Submucosal Invasion

Many studies have investigated the risk of lymph node metastasis (LNM) for differentiated EGC lesions that invade into the upper third of the submucosa (SM1). Some studies have shown low risk of LNM, while others reported the risk to range between 4% and 20% [8].

In 2018, a meta-analysis of 12 studies and 9798 patients was conducted by Abdelfatah et al. to evaluate the incidence of LNM in EGC that met the expanded criteria of the National Cancer Center. These expanded criteria comprised differentiated lesions, ≤3 cm in size, as well as submucosal invasion of <500 μm. The incidence of LNM in patients who met these criteria was significantly higher than that of LNM in patients who met the absolute criteria of the 2014 Japanese Guidelines (cT1a differentiated adenocarcinomas, without ulceration, and size ≤2 cm). The values were 2.5% for the expanded criteria vs 0.35% for the absolute criteria with a relative risk reduction of 6.30 when applying the absolute vs expanded criteria [29]. For such patients with differentiated EGCs with SM1 invasion, the relative risks of surgery versus frequent surveillance after ESD should be balanced when choosing between treatment options [29].

Undifferentiated Adenocarcinoma

Undifferentiated-type adenocarcinoma generally denotes signet-ring adenocarcinoma or poorly differentiated adenocarcinoma [30]. The Japanese Guidelines have included T1a undifferentiated adenocarcinomas that are ≤2 cm with no evidence of ulceration as part of the absolute indications for EGC resection with ESD [7].

In the 2018 meta-analysis by Abdelfatah et al., the incidence of LNM in those lesions was shown to be significantly higher than LNM in absolute indications group (T1a differentiated adenocarcinomas, without ulceration, and size ≤2 cm). Of the undifferentiated EGCs, 2.6% had LNM versus 0.11% from the absolute indications group. As such, it was concluded that when dealing with these undifferentiated lesions, assessment of surgical risk compared to endoscopic resection should be carefully made [8, 29].

In order to assess the safety and efficacy of ESD for undifferentiated EGC, Takizawa et al. conducted a multicenter, single-arm trial of cT1a lesions, ≤2 cm in size, with no ulceration, no lymph node invasion, and histologically showing undifferentiated adenocarcinoma (UD-EGC). The primary outcome was the 5-year overall survival. Ninety-nine percent of the lesions were resected en bloc. If there was evidence of noncurative resection after ESD, gastrectomy was performed. Of the 275 patients with histologically proven UD-EGC, 71% had a curative resection, and the 5-year overall survival was 99.3% [28]. As for adverse events, 7.3% of the patients had delayed bleeding, 3.8% had intraoperative perforation, and 1.7% had delayed gastric perforation. However, there was no ESD-related Grade 4 adverse events reported. As referenced by the updated Japanese guidelines, this large, prospective multicenter study substantiated that ESD can be performed instead of gastrectomy for certain patients with undifferentiated EGC. As such, this category was moved from the expanded criteria to the new absolute indications for ESD [7, 28].

Techniques for Resection

Endoscopic Mucosal Resection

Technique of EMR was initially described in 1984 and has been commonly used and recommended by guidelines for endoscopic resection of EGC [31]. The current absolute indication of Japanese Guidelines for using EMR for EGC resection is the following: differentiated carcinomas, limited to the mucosa (cT1a) with a size of 2 cm or less and with no signs of ulceration or lymph node invasion [7]. Lesions larger than 2 cm are difficult to resect in one piece using EMR and are more likely to develop local recurrence [11, 20, 31]. To ensure complete resection with EMR, marking of the lesion's margins is done first. Then, a snare is used to resect the area in an en bloc manner [32]. There are different techniques described to perform EMR, but injection-assisted EMR is most commonly used for EGC resection. In this technique, the submucosa is targeted for injection with a liquid agent to expand the submucosal layer to prevent injury to the muscularis propria layer at the moment of snare cautery resection.

In patients with EGC who undergo EMR, high cure and survival rates have been shown.

In one study by Choi et al., the 5-year survival rate and risk of recurrence were similar when comparing patients who had EMR versus gastrectomy for intramucosal EGC

lesions. Patients undergoing EMR had increased risk of metachronous gastric cancers when compared to the surgical group, but this did not affect the overall survival rate as these cancers were re-treated successfully [33].

Guaranteeing en bloc resection is the major determinant to whether EMR is performed. Based on the size limitation of snares, incomplete resection of lesions greater than 2 cm in size becomes a major disadvantage for EMR. Studies have shown an increased risk of local recurrence for lesions resected in piecemeal fashion [20]. Also, when resecting a lesion, the cut should be deep enough to ensure a curative resection, and this is hard to achieve with EMR. Because of these limitations, endoscopists resorted to a newer technique, ESD, for EGC removal.

Endoscopic Submucosal Dissection

The ESD technique was developed in Japan and was initially described in 1999 [7]. It has been widely used to treat EGC as an alternative to surgical treatment when lesions meet the indications for resection with ESD. Its use first became popular in Asia and then expanded to Western countries [7]. In Japan, around 60% of all EGC treatments are performed by endoscopic resection, and in 2015, it was reported that more than 90% of these resections were done by ESD [31]. During ESD, a needle knife is used to cut through the submucosa to remove the lesion, which allows for a deeper resection. However, ESD is more challenging than EMR [32] and requires training and experienced endoscopists to achieve desired results. A study assessing the learning curve for ESD found that in the West, more time is required to learn ESD than in Asia [34]. Approximately 150 gastric ESDs are needed to reach a resection speed of >9 cm^2/h. Their study showed that to achieve a rate of en bloc resection of more than 90% and a R0 resection rate of more than 80%, approximately 250 ESD cases need to be completed [34].

In a meta-analysis in 2018 by Zhao et al., ESD was associated with prolonged procedure time and higher risk of gastric perforation when compared to EMR [35]. However, ESD was superior to EMR in accomplishing en bloc resections with better complete resection rates and lower risk of local recurrence [31, 35].

Technique

ESD requires several steps to ensure en bloc resection. First the boundaries of the lesion should be marked. Then a solution is injected into the submucosa to lift the mucosal lesion. An electrosurgical knife is then used to make a circumferential incision in the mucosal surface around the lesion. Next, dissection through the submucosa is performed to detach the mucosal lesion from the gastric wall. Endoscopists often utilize devices to provide additional traction and retrieval devices to help to achieve en bloc resections (Fig. 48.2) [32].

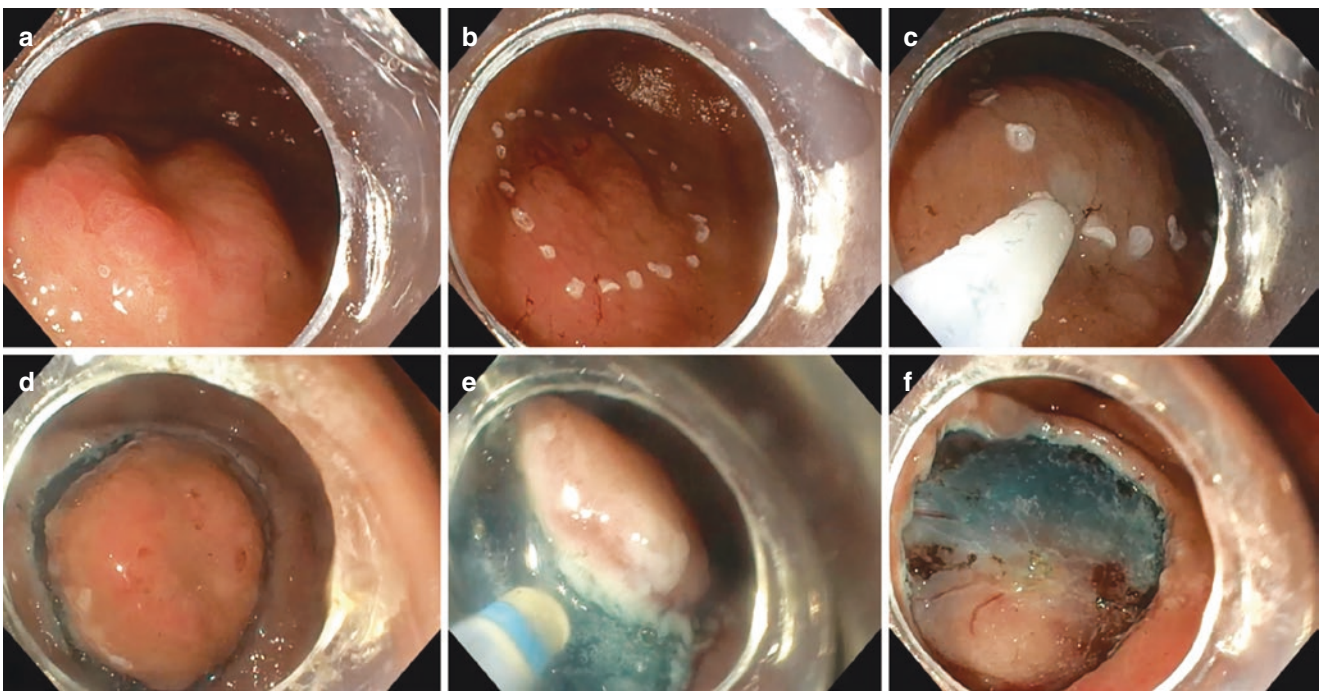

Fig. 48.2 ESD procedure: (**a**) gastric antral lesion; (**b**) cautery marks to delineate the borders; (**c**) submucosal lifting; (**d**) complete circumferential incision; (**e**) submucosal dissection; (**f**) post-ESD

Surveillance Post-treatment

Curative Resection

It is important to assess the margins of a specimen after endoscopic treatment to confirm complete resection. A Japanese evaluation system, endoscopic curability (eCura), was developed in 2017 in order to help guide endoscopists' next steps after EGC resection with ESD [8]. This system evaluates curability and is divided into three categories: eCura A, B, and C (Table 48.1) [7].

Adapted from: Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Digestive Endoscopy. 2021;33(1):4–20

Ly0 negative lymphatic infiltration, *HM0* negative horizontal margins, *VM0* negative vertical margins, *V0* negative venous infiltration

[a] Confined to en bloc resection and HM0, VM0, Ly0, and V0. pT1a (M), intramucosal cancer (histopathological diagnosis); pT1b (SM), submucosally invasive cancer (histopathological diagnosis). UL, finding of ulceration (or ulcer scar); UL0, absence of ulceration or ulcer scar; UL1, presence of ulceration or ulcer scar

Classification into these levels depends on the initial indication for ESD (absolute or expanded) and on the outcome (curative versus noncurative resection). Levels A and B denote a curative resection, and guidelines recommend surveillance of patients with frequent follow-up to evaluate for lesion recurrence and metachronous gastric cancers [7, 8].

In order to detect early signs of malignant change, Min et al. suggest repeating EGD with abdominal CT scan every 6–12 months for at least the first 5 years post a curative ESD resection with absolute and expanded indications (2014) [8, 36].

As per the Japanese Gastric Cancer Association 2018 guidelines, repeat EGD is recommended following eCura A and B resections once or twice per year [37] in order to identify any metachronous gastric lesions. Additional follow-up with abdominal ultrasound or CT scans is recommended for eCura B resections to identify any metastatic lesions [37].

These recommendations are in alignment with the latest American Gastroenterological Association clinical practice update on surveillance after pathologically curative endoscopic submucosal dissection of early gastrointestinal neoplasia in the United States (Table 48.2) [38].

Noncurative Resection

Level C of the endoscopic curability evaluation system denotes noncurative resection after endoscopic treatment and is divided into two categories: eCura C-1 and eCura C-2.

When the lesion resected is of differentiated type and fits the criteria for eCura A or B but was incompletely resected or had evidence of positive horizontal margins, it is classified as eCura C-1 [7, 37]. All other resections that do not meet the criteria for eCura A, B, and C-1 are categorized as eCura-C2 [7, 37].

Deciding on the treatment option for of eCura C-1 and C-2 resections is highly dependent on the risk of lymph node metastasis. The eCura scoring system assesses the risk of lymph node metastasis after ESD according to several features: tumor size and depth, presence of lymphatic or venous invasion, and positive vertical margins. A numerical score ranging from 0 (low risk of metastasis) to 7 (high risk of metastasis) is then assigned to the resection and guides subsequent treatment [7, 8, 39]. In general, for C1 resections, the possibility of lymph node metastasis is considered low, and this allows for a variety of treatment options. Repeat ESD, surgery, ablative therapy, or close surveillance can be done [7, 8, 37]. For eCura-C2 lesions, surgical treatment with

Table 48.1 Evaluation of curability according to tumor-related factors

Depth of Invasion	Ulceration	Differentiated Type		Undifferentiated Type	
pT1a (M)	UL0	≤ 2 cm	> 2 cm	≤ 2 cm	> 2 cm
	UL1	≤ 3 cm	> 3 cm	Any Size	
pT1b1 (SM1)		≤ 3 cm	> 3 cm	Any Size	
pT1b2 (SM2)		Any Size		Any Size	

eCureA *

eCureB *

eCureC-2

Table 48.2 Suggested surveillance for gastric dysplasia and adenocarcinoma removed by ESD that met histopathologic criteria for curative resection (absolute and expanded Japanese criteria used)

	First follow-up endoscopy (months)	Second follow-up endoscopy (months)	Subsequent endoscopic exams	Need for EUS surveillance	Need for radiographic surveillance	Estimated risk of LN metastasis (affected by size, ulceration) (%)
LGD	6–12	12	Annually	No	No	0
HGD	6–12	6–12	Annually	No	No	0
T1a EGC[a]	6	6	Annually	No[a]	No[a]	<1–5.1
T1b, Sm1 EGC (<500 μm submucosal invasion)	3–6	3–6	Annually	Yes CT chest/abdomen and/or EUS, every 6–12 months for 3–5 years		2.6–10.6

Adapted from: Wang AY, Hwang JH, Bhatt A, Draganov PV. AGA Clinical Practice Update on Surveillance After Pathologically Curative Endoscopic Submucosal Dissection of Early Gastrointestinal Neoplasia in the United States: Commentary. Gastroenterology. Forthcoming 2021.
ESD endoscopic submucosal dissection, *LGD* low-grade dysplasia, *HGD* high-grade dysplasia, *EGC* early gastric adenocarcinoma, *EUS* endoscopic ultrasound, *CT* computed tomography, *LN* lymph node
[a] CT scans and/or EUS may be considered for T1a EGCs

lymphadenectomy is recommended, as the risk for recurrence and metastasis is high [7, 37].

Helicobacter pylori (*H. pylori*) Infection

In patients who test positive for *H. pylori*, eradication therapy is recommended [7, 8, 37].

Several randomized controlled trials have reported a decreased incidence of metachronous gastric cancer after endoscopic resection in patients who have been treated for *H. pylori* [40, 41].

Case Conclusion

With respect to the introductory case, Mrs. N. underwent endoscopic ultrasound where it demonstrated a T1 lesion with no evidence of lymphadenopathy and therefore amenable to endoscopic resection. No biopsies of the lesion were performed prior to resection in order to minimize any scarring of the lesion and to increase success of an uncomplicated resection. Given the size of the lesion, the decision was made to perform ESD over EMR, given there would be a higher likelihood of an en bloc resection. An en bloc resection was performed of the 3 cm lesion, and pathology revealed a T1a well-differentiated gastric adenocarcinoma with clear margins and no lymphovascular invasion. This resection was curative and meets the criteria of eCura A. Endoscopic and cross-sectional imaging surveillance will be performed.

In closing, it is a new and exciting time for the West as ESD techniques and training for en bloc resection of EGC are being realized. It is important, however, for those physicians who choose to enter into this type of practice to understand and appreciate the history of this procedure and the tireless work performed by our colleagues in Asia to shape the optimal techniques and best practice guidelines that we use today.

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Laparoscopic Total and Subtotal Gastrectomy

49

Stephen Stopenski, Luigi Bonavina, and Brian R. Smith

Objectives

1. Discuss the indications and contraindications for a laparoscopic total or subtotal gastrectomy.
2. Discuss preoperative planning for patients with gastric adenocarcinoma.
3. Review the technical components of a laparoscopic gastrectomy and lymphadenectomy.
4. Review postoperative care and management of early common postoperative complications.

Introduction

Definitions and Indications

Gastrectomy is frequently performed for malignant gastric tumors located more than 2 cm below the esophagogastric junction (EGJ). Total and subtotal gastrectomy with a D2 lymph node dissection is the "standard" oncologic resection for gastric adenocarcinoma and less common tumors such as lymphoma and sarcoma. A total gastrectomy is used for invasive lesions of the proximal stomach, whereas subtotal gastrectomy with the removal of over two thirds of the distal stomach is often possible for early distal tumors. With advances in laparoscopic instrumentation and surgeon experience, a variety of techniques have been developed to drive the implementation of total laparoscopic gastrectomy.

Although gastric adenocarcinoma is by far the most common indication for gastrectomy, other less common indications include other gastric tumors (neuroendocrine/carcinoid, gastrointestinal stromal tumors (GIST), or leiomyosarcoma), hereditary diffuse gastric cancer (CDH1 mutation), refractory hemorrhage that fails endoscopic management, or intractable symptoms related to prior partial gastrectomy or previously failed antireflux procedures. If the indication for gastrectomy is benign, GIST, or prophylaxis, lymphadenectomy is not necessary. For rare gastric carcinoid, a lymph node dissection is generally recommended, but no large studies are available to guide the extent of dissection. In the setting of malignancy, contraindications to total gastrectomy include peritoneal seeding, distant metastasis, and local invasion into the aorta, celiac axis, or hepatic artery. Direct invasion into adjacent structures such as the transverse colon, pancreas, left lobe of the liver, and spleen does not preclude multivisceral resections; however, operative candidacy requires individualization by a multidisciplinary tumor board, surgical expertise, and intraoperative judgment.

Since gastrectomy is most commonly performed in the setting of malignancy, a thorough understanding of the management and workup of gastric adenocarcinoma is needed. This chapter will review gastric adenocarcinoma, relevant perioperative considerations, laparoscopic surgical technique, and postoperative considerations.

Gastric Adenocarcinoma

Gastric cancer is the fifth most common cancer worldwide with over a million new cases in 2020 and the fourth leading cause of cancer death. The worldwide incidence of gastric cancer varies greatly, and although not as common in North America and Europe, over 50% of cases occur in Eastern Asia. Men are disproportionately affected with a twofold higher incidence compared to women. It is predominantly a

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disease of the elderly with a peak incidence in the seventh decade of life. Over the past few decades, prognosis has improved modestly due to advances in neoadjuvant treatment, surgery, and postoperative care. In endemic areas, screening with endoscopy is common and has contributed to a decrease in mortality. Western countries, such as the USA, have not adopted screening due to the relatively low incidence, and no reliable biomarker has been identified.

Chronic inflammation plays an important role in gastric adenocarcinoma pathophysiology, with the largest risk factor being chronic infection with *Helicobacter pylori* or Epstein-Barr virus. Additional risk factors include nitrosamine consumption, low intake of fruits and vegetables, smoking, obesity, and gastric adenomas. A smaller proportion of patients (10–15%) will have a family history of gastric cancer. Identified syndromes include hereditary diffuse gastric cancer (CDH1 mutation), Lynch syndrome, and familial adenomatous polyposis. Patients with a CDH1 mutation are unique in that a prophylactic gastrectomy is recommended after the age of 20. Histologically, the Lauren classification is most commonly adopted. It divides adenocarcinomas into either intestinal or diffuse (poorly differentiated). The diffuse subtype can lead to the classic "linitis plastica" and carries a poorer prognosis due to early peritoneal seeding.

Gastric cancer treatment incorporates a multidisciplinary approach, but adequate surgical resection remains the only potential curative option. According to the most recent 2018 Japanese Gastric Cancer Treatment Guidelines, for tumors that invade the muscularis propria or have clinically positive lymph nodes, either a distal subtotal gastrectomy or a total gastrectomy is appropriate. The extent of resection is determined by tumor location, histology, and stage. A gross margin of 2–5 cm is recommended to decrease the likelihood of positive microscopic margins and unsatisfactory resection.

Preoperative Evaluation

Symptoms related to gastric cancer are vague and can mimic other gastrointestinal disorders. Diagnosis is usually not made until after symptom onset or incidentally when imaging or endoscopy is performed for a separate indication. Due to this, over 50% of newly diagnosed cases in the USA have evidence of regional or distant metastasis. Diagnosis is made by endoscopy with biopsies of suspicious lesions. Endoscopy also assesses the proximity of the tumor to the gastroesophageal junction. Tumors in close proximity pose unique challenges and are managed uniquely. Staging includes abdominal/pelvic computed tomography (CT) imaging to evaluate for metastatic disease. Tumors invading the muscularis propria ($T \geq 2$) and/or have positive lymph nodes (N+) are referred for neoadjuvant therapy, which has been shown to improve overall survival, disease-free survival, and reduced local recurrence. The benefits of neoadjuvant therapy highlight the importance of accurate locoregional staging. Endoscopic ultrasound (EUS) and positron emission tomography (PET) scan may provide additional clinical information but are not routinely performed. EUS is a useful adjunct to assess tumor depth (T stage) and peri-gastric nodal involvement (N stage); however, accuracy is user-dependent, particularly for mid-stage tumors. In experienced hands, EUS may be most useful in early gastric cancer to guide potential neoadjuvant therapy. PET scan may be used in the event of equivocal findings on cross-sectional imaging. Lastly, a diagnostic laparoscopy is indicated to assess for peritoneal or liver metastases as these small lesions can be missed on CT scan in up to 44% of cases. This can be performed as a separate procedure or the same day as the planned gastrectomy. Patient's with T3/T4 disease or those with a high nodal burden are at highest risk for peritoneal metastasis and likely those that benefit most from neoadjuvant therapy.

Laparoscopic Approach

The first laparoscopic gastrectomy was reported in 1994 and has gained significant popularity ever since. For many high-volume centers, a total laparoscopic approach has become standard. This trend is supported by several observational and randomized trials comparing open to laparoscopic gastrectomy. In a large meta-analysis evaluating 17 randomized controlled trials of both early and advanced gastric cancer, the laparoscopic gastrectomy had similar mortality (0.3% versus 0.2%), severe morbidity (2.7% versus 3.0%), lymph node harvest, and oncologic outcomes compared to open gastrectomy. Laparoscopic gastrectomy has been reported to have shorter hospital length of stay, lower blood loss, and lower overall morbidity but longer operative time. Although technically demanding, laparoscopic gastrectomy with a D2 lymphadenectomy has comparable outcomes to open gastrectomy. Surgeon experience is crucial for favorable outcomes, and some studies suggest a learning curve of up to 100 cases to achieve proficiency.

More recently, robotic-assisted gastrectomy has gained popularity at specialized centers to overcome some of the conventional drawbacks associated with laparoscopy. Robotic surgery offers three-dimensional visualization and articulating instruments for improved dexterity. Several studies have reported the feasibility and safety of robotic surgery. Early literature comparing laparoscopic to robotic gastrectomy suggests similar short-term outcomes at the expense of longer operative times and increased cost.

Lymphadenectomy

The extent of optimal lymph node dissection for gastric adenocarcinoma is an area of significant debate. A more extensive lymph node dissection has been shown to provide more accurate staging and better overall survival but at the risk of higher perioperative complications in some series. Gastric-related lymph nodes are classified into 16 stations (Table 49.1). A D1 dissection includes only the peri-gastric nodes (stations 1 though 6) taken en bloc with the specimen. A D2 lymphadenectomy involves an extended dissection of the left gastric, hepatic, celiac, splenic arterial, and portal lymph nodes (stations 1 through 12). A D3 dissection adds the para-aortic lymph nodes (stations 14, 15, and 16) and has been popularized in the Japanese medical literature. Several randomized controlled trials have compared outcomes between the three lymph node dissections for locally advanced gastric adenocarcinoma. In a Cochrane systematic review, D3 and D2 had similar outcomes, but D2 had an improved disease-specific survival compared to D1, albeit with a higher perioperative morbidity. Classically, a D2 lymphadenectomy included a distal pancreatectomy and splenectomy, but more recently this has been associated with increased morbidity without improvement in survival when performed routinely. Therefore, recent guidelines have removed it from recommendations and advocate for a spleen preserving D2 lymphadenectomy for gastric adenocarcinoma.

The National Comprehensive Cancer Network guidelines recommend removal and evaluation of at least 15 lymph nodes for accurate staging. Insufficient lymph node evaluation is associated with poorer survival after gastrectomy, and D2 dissection has been shown to be necessary in order to routinely yield ≥15 nodes. However, the vascular and lymphatic anatomy around the stomach is complex and variable, and dissection can pose a significant challenge. Near-infrared fluorescent (NIR) imaging after peritumor submucosal injection of indocyanine green (ICG) is a recent technique introduced to assist surgeons in lymph node mapping. The successful application of ICG with NIR light in laparoscopic devices enables more accurate lymph node identification compared to visible light. A recent randomized controlled trial of patients undergoing a laparoscopic gastrectomy with D2 dissection showed that ICG increased lymph node retrieval without an increase in perioperative complications. Although not yet a standard of care or Food and Drug Association (FDA)-approved for this use, ICG may help reduce lymph node yield non-compliance in the future.

Table 49.1 Gastrectomy lymph node stations and anatomic definitions

Station	Definition
1	Right paracardial LNs
2	Left paracardial LNs
3	Lesser curvature LNs
4	Greater curvature LNs (subdivided into 4sa, 4sb, and 4d)
5	Supra-pyloric LNs along the proximal right gastric
6	Infra-pyloric LNs along the proximal right gastroepiploic
7	LNs along the origin of the left gastric
8	LNs along the common hepatic artery (subdivided into anterior and posterior)
9	LNs along the celiac trunk
10	Splenic hilar LNs
11	Splenic artery LNs (subdivided into proximal and distal)
12	LNs along the proper hepatic ligament or hepatoduodenal ligament (subdivided into a, b, and p)
13	Posterior surface of the pancreatic head LNs
14	LNs along the superior mesenteric vein
15	LNs along the middle colic
16	Paraaortic LNs

LNs lymph nodes

Surgical Technique

Patient Positioning and Preoperative Considerations

Although many variations can be used, the core principles of technique remain constant. After induction with general anesthesia, appropriate preoperative antibiotic prophylaxis is administered. The patient can be positioned supine or split-leg in a low lithotomy position. Steep reverse Trendelenburg is used throughout the operation, and care is taken to avoid patient movement during surgery. For venous thromboembolism (VTE) prophylaxis, lower-extremity pneumatic compression stockings are placed, and preoperative subcutaneous heparin is administered. Ultrasound-guided transversus abdominis plane (TAP) block analgesia may reduce the use of postoperative opioids and improve early functional outcomes in the context of enhanced recovery programs. An intraoperative esophagogastroduodenoscopy utilizing carbon dioxide (CO_2) is performed to visualize the tumor. The peritumor submucosa is injected with 0.5 cc of ICG to aid in lymphadenectomy, taking great care to avoid trans-mural injection with resultant ICG in the free peritoneal cavity. Once endoscopy is complete, the stomach is fully decompressed prior to withdrawal of the endoscope. The surgeon stands on the patient's right and the first assistant on the patient's left.

Port Placement and Diagnostic Laparoscopy

Pneumoperitoneum is established via a Hasson or Veress needle technique. Most commonly, five ports are required. An initial camera port is placed 2/3 of the distance from the xiphoid to the umbilicus at the lateral edge of the left rectus muscle. The following additional four ports are placed under

direct vision: a 5 mm left lateral subcostal port, a right upper quadrant 5 mm midclavicular port, a 5 mm right lateral subcostal port for the liver retractor (versus 5 mm subxiphoid incision for a Nathanson retractor), and a 12 mm midline epigastric port for suturing and stapling (Fig. 49.1). When the indication is cancer, the first step of the operation is to perform a diagnostic laparoscopy. The surface of the liver, anterior stomach, omentum, and peritoneum are carefully inspected for the presence of tumor deposits. Peritoneal washings are sent for cytology, and any concerning lesions are biopsied and sent as frozen sections. Once metastatic disease has been excluded, total or subtotal gastrectomy can be carried out.

Omentectomy and Division of the Gastrocolic Ligament

Using a 5 mm laparoscopic bipolar device, the omentum is separated from the transverse colon and mesocolon. Although the prognostic and oncologic benefit of omentectomy is controversial, it is still routinely performed for T3 and T4 tumors as 5% of cases can harbor metastatic nodes. The remaining gastrocolic ligament is divided along the greater curve to the upper extent of the gastrectomy, exposing the lesser sac (Fig. 49.2). The avascular retrogastric adhesions can be divided to facilitate mobilization when present. The omentum is dissected along the greater curve toward the spleen. For total gastrectomy, dissection continues until a clear plane is visualized under the short gastric vessels to the level of the left crus. The perigastric lymph nodes along the greater curvature are left en bloc with the specimen (stations 2 and 4).

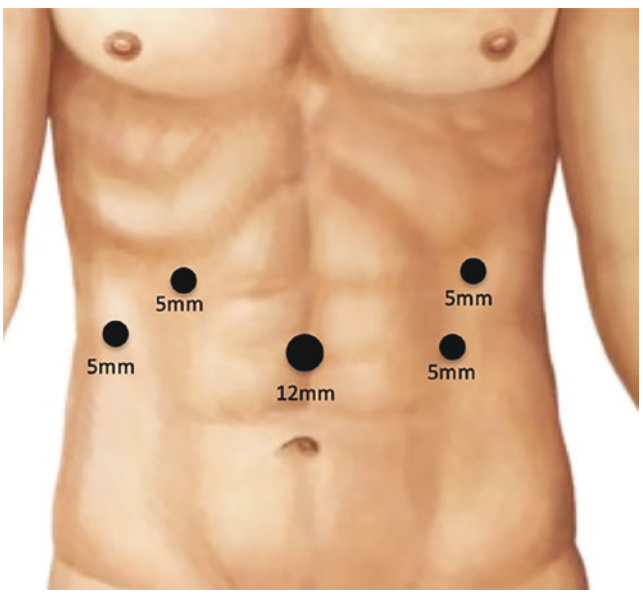

Fig. 49.1 Recommended laparoscopic port placement for total and subtotal gastrectomy

Division of the Hepatogastric Ligament

The left lateral segment of the liver is retracted superiorly to obtain appropriate exposure of the gastroesophageal junction while care is taken to avoid impingement on the portal structures. The assistant retracts the stomach caudally so the hepatogastric ligament can be divided and kept with the specimen (Fig. 49.3). The dissection begins above the caudate lobe and extends superiorly until the right crus is identified. Note that an accessory left hepatic artery originating from the left gastric artery may be encountered and may be sacrificed if not a true replaced left hepatic. For total gastrectomy, the dissection is continued posteriorly via a pars flaccida technique until the esophageal hiatus is clearly visualized and the entire abdominal esophagus is mobilized. Dissection is then continued down toward the hepatoduodenal ligament. The right gastric artery is identified, dissected, and ligated.

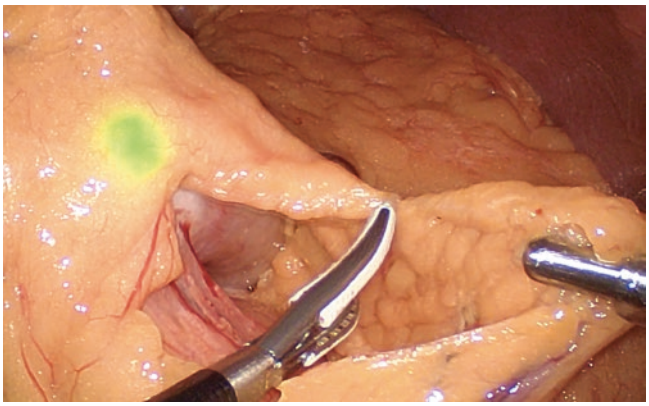

Fig. 49.2 Division of the gastrocolic ligament and entering the lesser sac, station 4 perigastric lymph nodes highlighted by indocyanine green (ICG) using Near-Infrared (NIR) fluorescent imaging

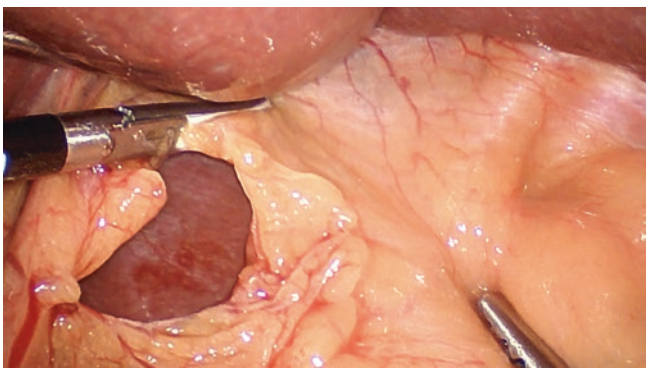

Fig. 49.3 Incision of the hepatogastric ligament and the lesser omentum

Division of the Right Gastroepiploic Pedicle and Gastric Resection

Following mobilization of the lesser curve and upper portion of the greater curve, dissection resumes along the remaining greater curvature toward the pylorus. Dissection is facilitated by ICG lymphatic mapping (Fig. 49.4) and carried around the right gastroepiploic pedicle containing the vessels and lymphatics (station 6), arriving at the first portion of duodenum (D1). The right gastroepiploic artery is identified, dissected, and divided with bipolar or clipped when appropriate. The inferior and superior borders of D1 are cleared, encircled, and divided 1–2 cm distal to the pylorus using an endoscopic linear stapler with staple line reinforcement to minimize staple line bleeding. The inferior and superior pyloric nodes (stations 5 and 6) are left en bloc with the specimen. The stomach can then be elevated and the remaining posterior gastric wall dissected free of any remaining pancreatic adhesions. The extent of proximal dissection is determined by the location and extent of tumor. For subtotal gastrectomy, a linear stapler with staple line reinforcement is used to divide the lesser curve vasculature just distal to the left gastric artery, with subsequent unreinforced stapling transversely across the stomach. For total gastrectomy, the left gastric artery is localized and ligated close to its origin at the celiac trunk, followed by transection of the distal esophagus with a linear thick-load stapler after placement of stay sutures in the distal esophagus to avoid retraction post-transection. Once the entire stomach has been fully mobilized and devascularized, the 12 mm epigastric port site is widened and wound protector placed, allowing for removal of the specimen. Proximal and distal margins are sent to pathology for frozen section review. If the indication for gastrectomy is a GIST, frozen sections are not necessary. The widened port site is closed and the 12 mm port reinserted.

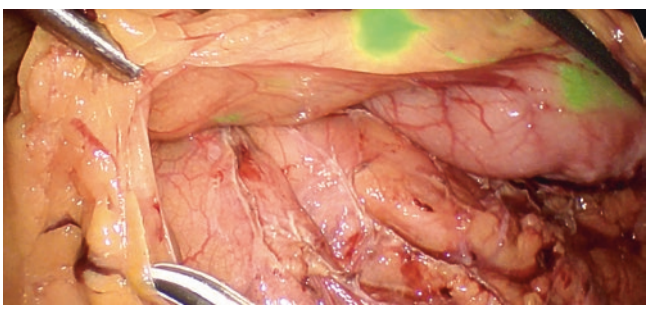

Fig. 49.4 Dissection of the right gastroepiploic pedicle guided by indocyanine green (ICG) and Near-Infrared (NIR) fluorescent imaging for removal of stations 4d and 6

Modified D2 Lymphadenectomy

While margins are being examined, the D2 dissection is completed. Starting at the nodal basin over the celiac artery (station 9), dissection continues laterally along the splenic artery (station 11), freeing up nodal tissue overlying and adjacent to the vessel. Common hepatic artery nodal tissue (station 8) resides anterior and superior to the vessel (Fig. 49.5), and care is needed to avoid injury to the left gastric (coronary) vein if subtotal gastrectomy is being performed (Fig. 49.6). Dissection continues to and around the origin of the gastroduodenal artery and then carried superior along the porta toward the hilum of the liver to remove the remaining station 12 nodes residing anterior to the porta.

Reconstruction

For a total gastrectomy, gastrointestinal reconstruction is performed with a Roux-en-Y esophagojejunostomy. This can be performed as either end-to-side or end-to-end via a circular stapler with the creation of a pouch or side-to side using a linear endostapler. For a subtotal gastrectomy, reconstruction can be performed either by a Roux-en-Y gastrojejunostomy or a Billroth II, depending on the amount of stomach remaining and presence of gastroesophageal reflux disease (GERD) prior to surgery (Billroth II results in bile reflux into the stomach, and close proximity of the anastomosis to the GEJ or pre-existing GERD is better served with Roux-en-Y reconstruction to avoid bile reflux esophagitis).

For a Roux-en-Y esophagojejunostomy, the ligament of Treitz is identified, and a 50 cm roux limb is measured to discourage bile reflux. The jejunum is transected, and the distal limb is brought up to the esophageal stump either

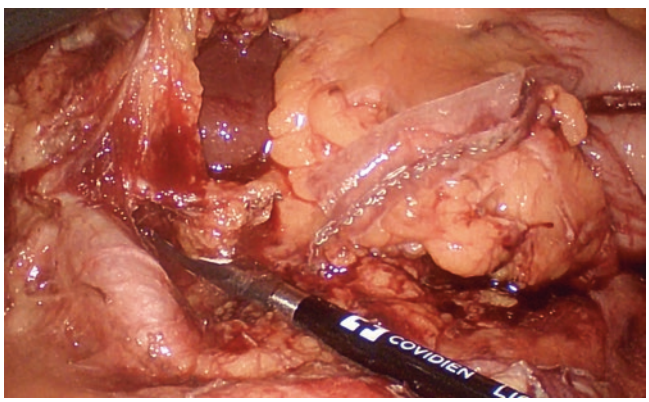

Fig. 49.5 Dissection of the station 8 nodes around the common hepatic artery

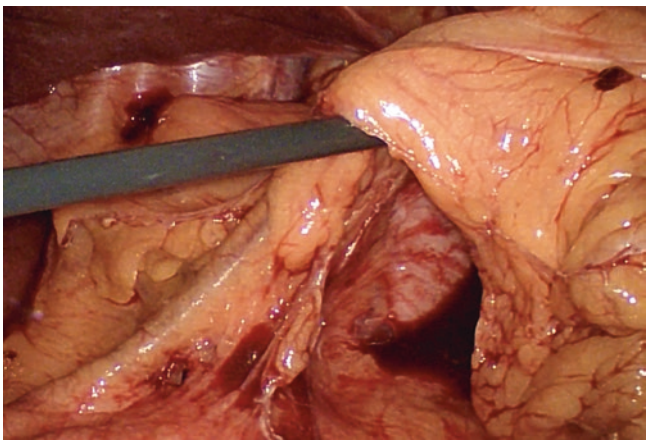

Fig. 49.6 Dissection of the left gastric artery

retro- or ante-colic. An OrVil 25 mm EEA Stapler Anvil (Medtronics, USA) is placed trans-orally by anesthesia and brought out through an esophagotomy in the central staple line and orogastric tube separated and removed. An enterotomy is created on the cut end of jejunal Roux and a 25 mm EEA XL stapler inserted into the jejunal stump. The stapler spike is advanced through the anti-mesenteric border of the Roux limb and docked to the OrVil anvil. Under direct visualization, a tension-free anastomosis is created, and the tissue donuts are evaluated for integrity. The open Roux limb is stapled closed, and an endoscopic air leak test is performed while the esophagojejunostomy is evaluated for hemostasis and Roux clamped. Next, the side-to-side Roux-Y jejunojejunostomy is created using a linear endoscopic stapler and mesenteric defect closed. A drain is left posterior to the esophagojejunal anastomosis. When indicated, a feeding jejunostomy tube is placed 20 cm distal to the roux-en-Y jejuno-jejunal anastomosis in selected patients based on the patient's nutritional status.

Postoperative Considerations

Postoperative Management

Patients are initially kept *nil per* os (NPO) and maintained on maintenance intravenous fluids. Pain can typically be managed with routine intravenous narcotics or multimodal regimen. On postoperative day 1, VTE chemoprophylaxis is resumed, and patients start ambulating. If a jejunostomy tube was placed, then tube feeds are started as ileus is uncommon. After total gastrectomy, routine gastrografin swallow study is performed on postoperative day 2, before initiating a clear liquid diet. Once clears are tolerated, patients are advanced to a full liquid diet for 7 days, followed by puree diet for another 7 days and eventually post-gastrectomy diet. All patients receive dietary counseling to limit weight loss and post-gastrectomy syndromes. Chronic gastric outlet obstructions treated with subtotal gastrectomy often experience delayed gastric emptying early in the postoperative period and making resumption of PO intake slow to tolerate.

Perioperative Morbidity and Anastomotic Complications

Although perioperative mortality has declined in recent years, morbidity related to gastrectomy remains high. Early surgical complications are primarily due to the anastomosis, and long-term complications include esophageal stricture, reflux, and post-gastrectomy syndromes such as dumping.

The most feared early complication of a total gastrectomy is disruption of the esophagojejunal anastomosis, which is an independent risk factor for poor survival. The distal jejunojejunal anastomosis is rarely problematic in experienced hands. Duodenal stump leakage can be treated conservatively if it is controlled and well-drained, without efferent limb obstruction. Early recognition, diagnosis, and treatment are key to mitigating damage and preventing mortality. Early clinical signs are nonspecific, but new onset of fever, tachycardia, abdominal pain, or leukocytosis are key indicators. The presence of amylase or bile-stained fluids in the abdominal drain is unequivocal evidence of a leak. The preferred method of diagnosis is by CT scanning with oral contrast. A contrast swallow can be used, but this test lacks sensitivity and risks a false-negative result. On CT, the presence of perianastomotic fluid/air is highly suggestive of a leak. CT also can identify other etiologies of sepsis such as intra-abdominal abscess or pneumonia. Upper endoscopy can be used to confirm a leak, assess viability of the anastomosis, and help guide endoscopic treatment options.

Treatment options for a leak include conservative management (antibiotics and NPO), percutaneous drainage of collections, endoscopic stenting, and surgery. There is no standard treatment algorithm due to lack of prospective evidence, and success often rests on multimodal therapies. Once diagnosed, a multidisciplinary approach including radiology, gastroenterology, and surgery should be applied. Surgery is typically reserved for patients with peritonitis, septic shock, or failure of less invasive options. Smaller leaks can be managed with antibiotics and percutaneous drainage of any fluid collections. There are a multitude of endoscopic techniques now available. The most commonly used and studied is the self-expanding covered metal stent, which has a reported success rate up to 88%. More recently, endo-VAC therapy has been shown effective, but experience is still limited, and this approach is resource-intensive. Specific complications to stents include migration and potential obstruction.

Conclusions

Laparoscopic total and subtotal gastrectomy are standard treatment options for malignant gastric tumors and rare benign conditions. Workup for gastric adenocarcinoma consists of endoscopy with or without EUS, cross-sectional imaging, and diagnostic laparoscopy. In experienced centers, a laparoscopic gastrectomy with a spleen preserving D2 lymphadenectomy has similar outcomes to open gastrectomy. The addition of ICG to aid in lymph node mapping and dissection can improve laparoscopic lymph node harvest. Postoperatively, patients are managed similar to other foregut operations with high suspicion for anastomotic complications and special attention to changes in diet and nutritional status.

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Laparoscopic Resection of Gastric and Esophageal Submucosal Tumors

50

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Objectives

1. To develop a fundamental understanding of the pathophysiology of submucosal tumors and basic management principles.
2. To create a better understanding of technical considerations in the approach to esophageal and gastric submucosal tumors, noting that a hybrid approach may be indicated.
3. To discuss surgical outcomes of patients undergoing open vs lap technique based on overall morbidity and mortality, post-op complications, tumor resection margins, and length of hospital stay.

Introduction

Submucosal tumors are tumors of mesenchymal origin and can be found anywhere along the gastrointestinal tract. The incidence of these lesions is not well-known; however, the prevalence is increasing likely due to increased screening methods. On imaging and endoscopy, SMTs are typically well circumscribed and have an intact overlying mucosa. Workup includes endoscopic ultrasonography (EUS), which allows observation of the size, layer of origin, echogenicity, and internal properties of SMTs.

In the esophagus, there are various types of submucosal esophageal lesions, which are characterized by location; most commonly found intramural lesions include leiomyoma, gastrointestinal stromal tumor (GIST), and schwannoma. Leiomyomas are the most commonly diagnosed mesenchymal tumor in the esophagus, originating from the inner circular muscle layer of the distal and mid-thoracic esophagus, particularly at the esophagogastric junction. They originate from the muscularis propria that is composed by bundles of spindle cells with rare mitoses. Typically, immunohistochemical analysis is positive for smooth muscle actin and desmin. The majority of esophageal leiomyomas remain asymptomatic and are found during screening for other unrelated workups. However, larger leiomyomas can cause mass effect and cause symptoms such as epigastric discomfort, dysphagia, regurgitation, heartburn, or atypical chest pain. The most common surgical procedure for esophageal SMTs is minimally invasive enucleation and reconstruction of the muscle layer through a thoracoscopic or laparoscopic approach.

Submucosal gastric tumors include gastrointestinal stromal tumors (GIST), leiomyomas, schwannomas, and lipomas. Of these, GIST and leiomyoma are the two more frequently encountered. Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors, accounting for 90% of all such tumors and representing 2–3% of all gastric malignancies. GISTs occur most frequently in the stomach (70% in gastric body, 15% in antrum, and 15% in cardia) or small intestine (30% in jejunum or ileum, 5% in duodenum) but may occur anywhere in the gastrointestinal tract. They arise from the interstitial cells of Cajal (ICCs) found in the muscularis propria and around the myenteric plexus and are derived from mutations in the tyrosine kinase receptor KIT. Each lesion is capable of malignant degeneration and are stratified as low-tumor-risk and high-tumor-risk GISTs based on mitotic index, tumor size, and tumor location. Unlike GIST, leiomyoma is a benign, submucosal tumor without associated risk of future progression to malignancy. GISTs can be endoluminal (growing preferentially inward, toward the gastric lumen), extra-luminal (growing predominately outward, toward the gastric serosa), or mixed (dumbbell shaped or centered on the gastric wall). While these lesions can be asymptomatic, they can present with upper gastrointestinal bleed, early satiety, acid reflux, and bloating depending on size and SMT features. The standard treatment of GIST without metastasis is surgical resection, whereas GIST with metastasis is treated with tyrosine kinase inhibitors upfront. Surgical approach to gastric SMTs varies by location and size.

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Epidemiology

Based on the National Cancer institute, GISTs are found within the sixth decade of life with (3:1) male predominance. In the United States, about 5000–6000 new cases of GISTs are diagnosed per year. As per Surveillance, Epidemiology, and End Results database, the incidence of GIST increased from 0.55/100,000 population in 2001 to 0.78/100,000 population in 2011. In Europe, the incidence of GIST varies from 6.5 to 14.5 per million per year. Esophageal submucosal tumors are usually found in patients aged 20–50 with a diagnosis of leiomyoma 70–80% of the time. The incidence of esophageal SMTs is low with a prevalence of less than 0.5%, with a ratio of men to women of 2:1.

Diagnosis/Pre-op Evaluation

Due to the increasing utilization of endoscopy and widespread availability of high-resolution imaging, submucosal gastric tumors are more frequently encountered. SMTs are mostly asymptomatic; however, when large, they can present as an upper gastrointestinal bleed, due to tumor ulceration from pressure necrosis. Symptoms vary based on size of lesion and locations (gastrointestinal or extra-gastrointestinal) and include abdominal pain, dysphagia, GI bleed, anemia, hematemesis, melena, and bowel obstruction. GISTs generally metastasize to the liver and intra-abdominal cavity and rarely metastasize to the lungs and bones. Leiomyomas of the esophagus account for roughly two thirds of all benign tumors. Most patients are asymptomatic; however, some present with dysphagia.

Workup for SMTs is based on patient symptoms. There are no confirmatory lab studies to diagnose these tumors preoperatively. Imaging studies and/or endoscopic evaluations are done based on the patient's clinical presentation. Barium swallow is the most commonly used radiologic test for esophageal lesions. The finding on barium swallow is a smooth filling defect in the esophageal lumen without a mucosal abnormality. CT is the most commonly used modality in the diagnosis of primary and metastatic GISTs. For SMTs of the stomach, contrast-enhanced CT may show an intramural endophytic or exophytic hypervascular mass in the gastric wall (Image 50.1). Small (<5 cm) GISTs are homogeneous, smooth-walled, and sharply margined masses, whereas large (>5 cm) GISTs are heterogeneous (due to hemorrhage, necrosis, or cystic degeneration) masses. On MRI, small GISTs are generally round and homogeneous with strong arterial enhancement, while large GISTs are usually lobulated and mildly heterogeneous with gradual enhancement due to hemorrhage, necrosis, and cystic changes. MRI is more useful in the evaluation of anorectal GISTs and metastatic hepatic GISTs. A baseline FDG-PET should be done prior to initiation of therapy. Endoscopically, GISTs appear as spherical or hemispherical smooth, subepithelial polypoid lesions; however, they can also degenerate and show features of hemorrhage and ulceration (Images 50.2 and 50.3). Tissue diagnosis should be done by EUS-guided fine-needle aspiration (FNA) for lesions greater than 1 cm or true cut biopsy (TCB) for lesions 2–5 cm in size, particularly if non-GIST histology such as a leiomyoma is suspected. EUS-guided FNA/TCB should be considered for a very large GIST needing neoadjuvant therapy with a tyrosine kinase inhibitor. Tissue acqui-

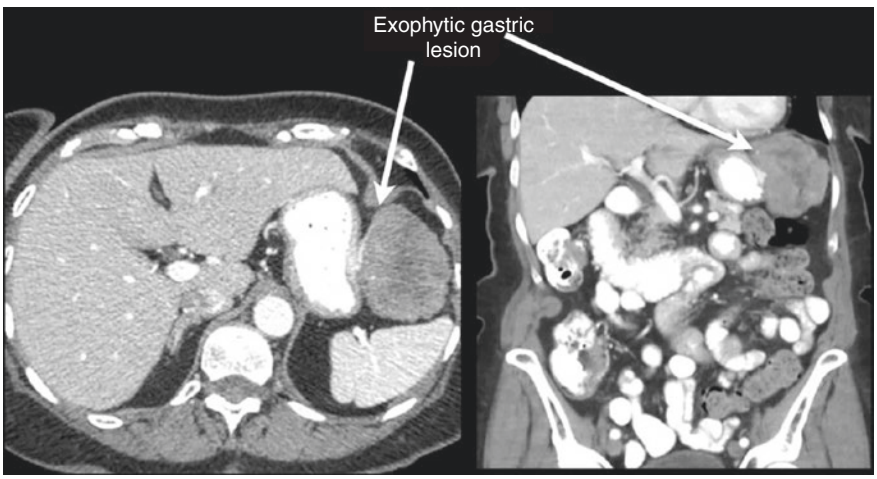

Image 50.1 CT showing a large gastric GIST

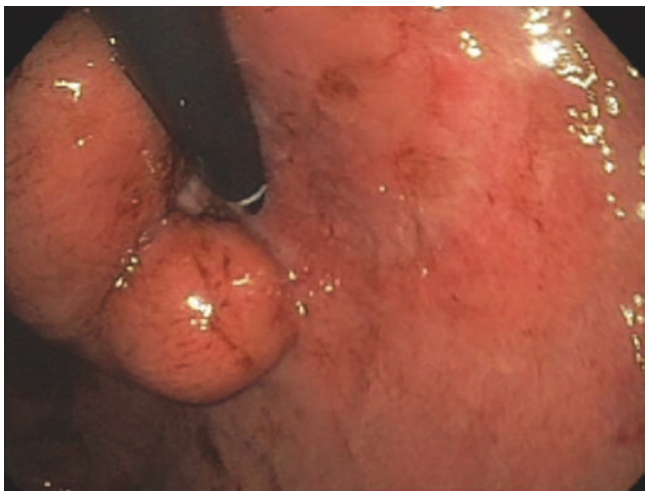

Image 50.2 Endoscopic view showing GEJ mass very close to the esophagus

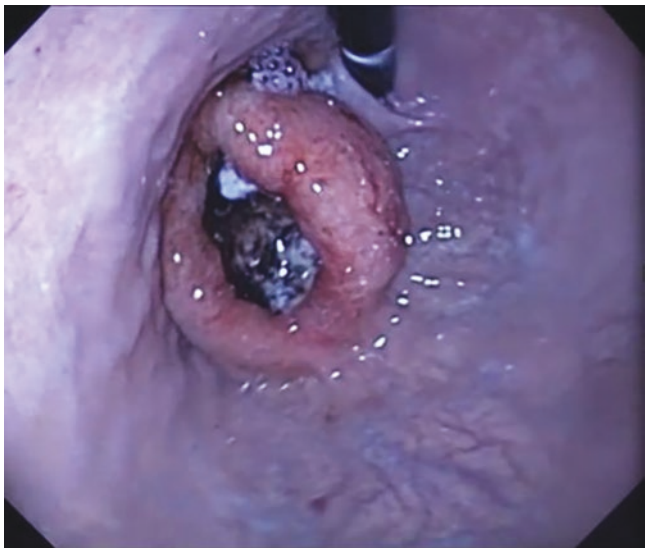

Image 50.3 Endoscopic view of ulcerated GIST mass in the cardia and fundus

sition may not be necessary if the lesion is very large and is a symptomatic GIST with malignant features on EUS that will need surgical resection irrespective of the FNA/TCB result. High-risk malignant features on EUS include large size of the GIST (≥2 cm), irregular borders, presence of heterogenous echogenicity, anechoic (cystic) spaces, ulceration, echogenic foci, and a marginal halo (Image 50.4).

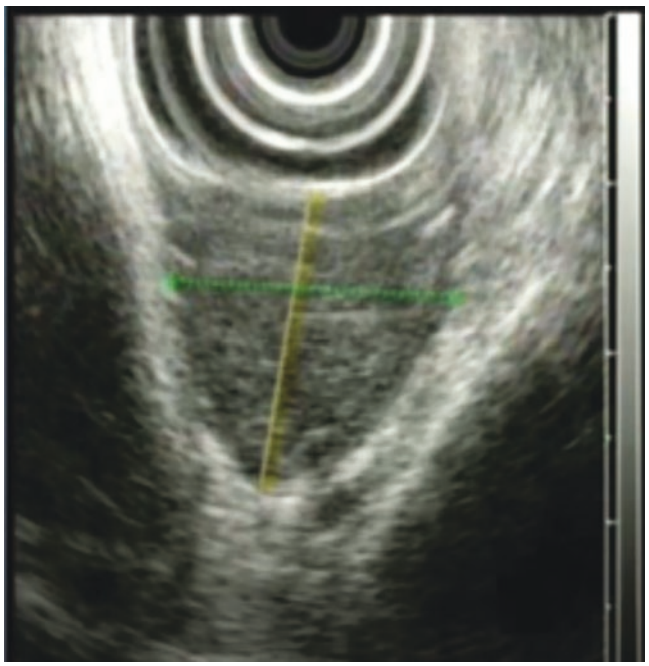

Image 50.4 EUS of esophageal mass

Indications/Patient Selection

Indication for resection of SMTs depends on accuracy of diagnosis which sometimes can be difficult with only biopsy specimens, symptoms, and malignant potential. All symptomatic SMTs, lesions where diagnosis is not certain, and lesions >3 cm should be resected. All GISTs great than >2 cm should undergo resection. There is no consensus on management of GIST <2 cm (NCCNN guidelines). According to the National Comprehensive Cancer Network (NCCN), asymptomatic patients with GISTs <2 cm with benign EUS features can be followed conservatively with annual EUS and/or esophagogastroduodenoscopy. An R0 resection (negative margin) of the GIST is the aim of surgery. As GISTs almost never metastasize to the lymph nodes, routine local lymph node dissection is not necessary unless suspected on imaging or EUS. The operative approach to SMTs is dependent on tumor size, location, and tumor growth characteristics.

Contraindications for Minimally Invasive Management

Other than the inability to tolerate abdominal insufflation or one lung ventilation, there are relatively no contraindications to laparoscopic surgical removal of SMTs. A tumor size limit, which was initially considered to be 2 cm, is now liberated in recent evidence and based on surgeon preference and the ability to obtain negative margins. A size limit for laparoscopic surgery has not been established for SMTs in other sites (esophageal, small intestine, colon, rectum).

Technical Consideration

Esophagus

Room Step-Up and Port Placement

Patient is placed in right lateral position. Monitors are over each shoulder of the patient. Port placement is typical VATS placement for esophageal surgery (Image 50.5).

Proximal and Mid-esophageal Tumors

Patients are intubated with a double-lumen endotracheal tube to allow for single-lung ventilation. A common surgical approach includes enucleation via a right video-assisted thoracoscopy (VATs). The use of intraoperative endoscopy allows for precise localization of the lesion via transillumination. A Penrose is placed to help with retraction and mobilization of the esophagus (Image 50.6). In cases were the tumor is proximal, division of the Azygous vein may be needed using a laparoscopic stapler with staple line reinforcements. Once the esophagus is appropriately mobilized, using a combination of blunt and harmonic dissection, the longitudinal muscles are incised, and tumor is exposed (Images 50.7 and 50.8). During enucleation, air insufflation of the esophagus is used to confirm mucosal integrity and safeguard against esophageal perforation. Care must be taken to preserve the tumor pseudocapsule. Reapproximation of the muscle layers after tumor enucleation is performed to prevent the development of a pseudo-diverticulum (Images 50.9 and 50.10).

Distal Esophageal Tumors

Tumors involving the gastroesophageal junction may require esophagogastric resection extending proximally onto the esophagus and may not be amenable to enucleation. Patients are placed in the supine position.

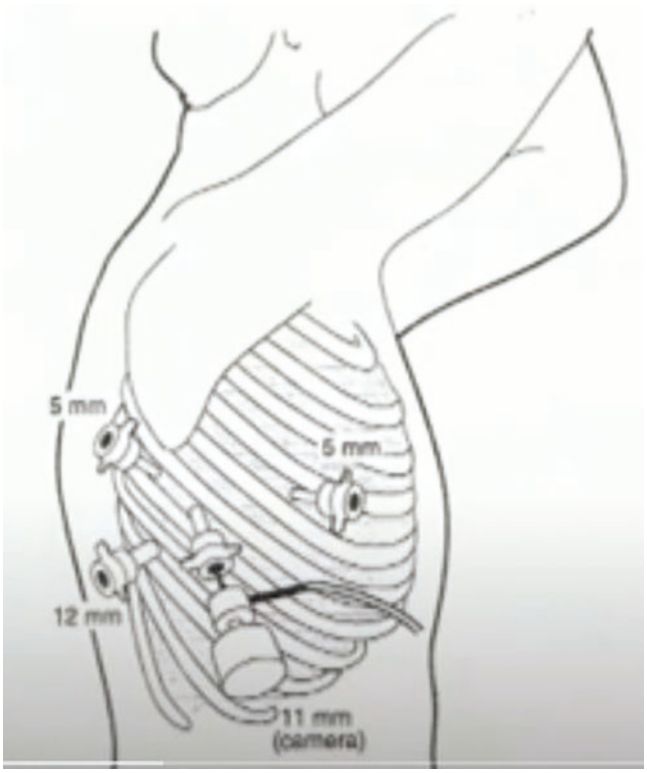

Image 50.5 Port placement for Ivor Lewis

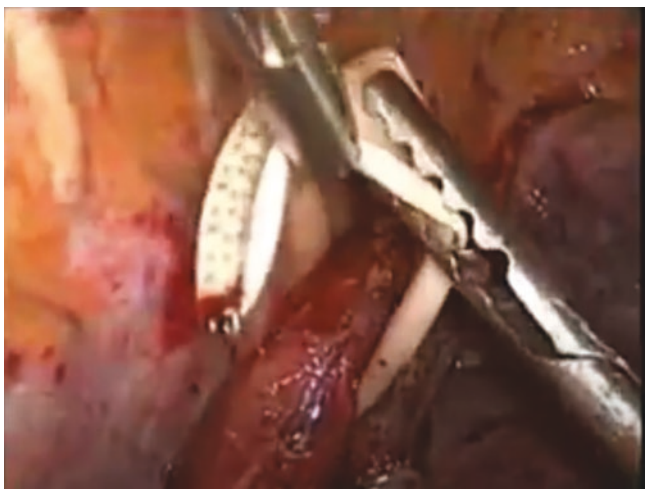

Image 50.6 Penrose placement around esophagus

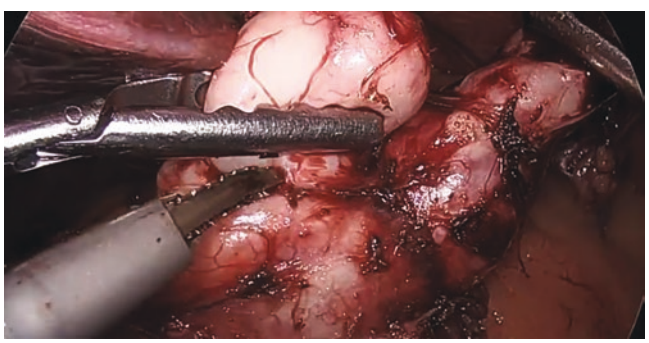

Image 50.7 Blunt and sharp dissection of gastric GIST

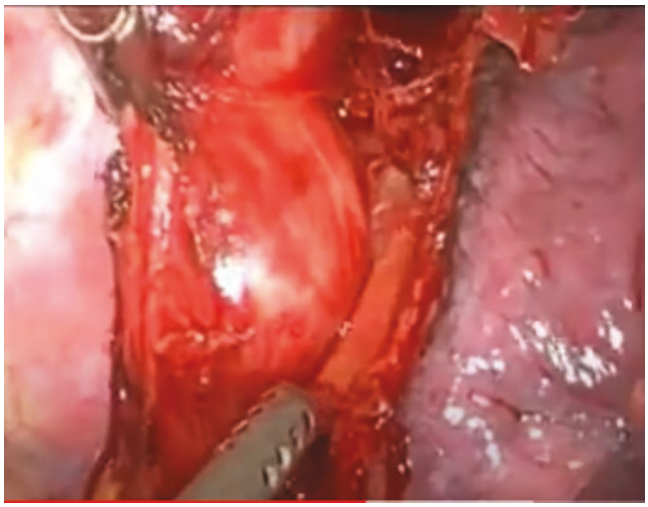

Image 50.8 Esophageal SMT prior to dissection

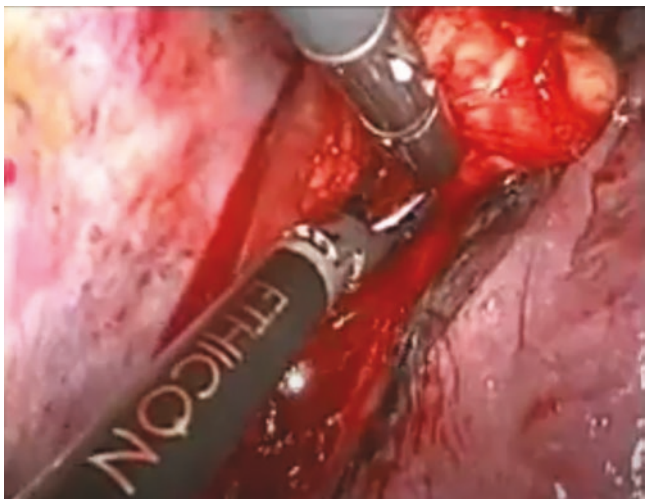

Image 50.9 Esophageal mass exposed

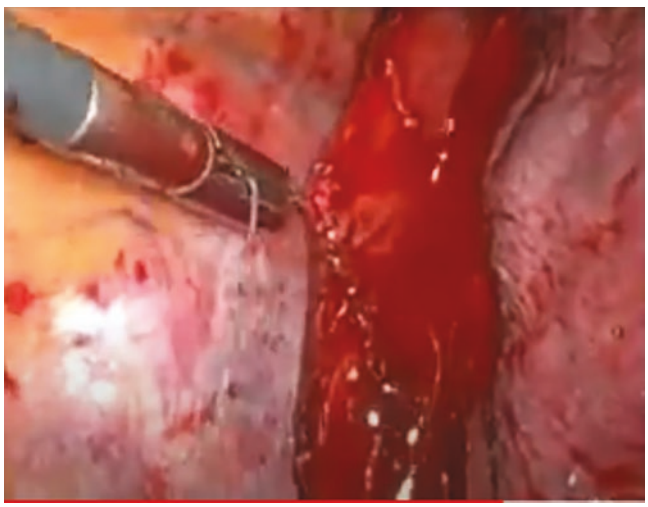

Image 50.10 Double-layer closure of esophageal muscle fibers

Pneumoperitoneum is established, and all trocars are placed under laparoscopic visualization in the usual position for surgical procedures requiring hiatal dissection. After dissection of the phrenoesophageal ligament, a Penrose drain is placed around the esophagus to aid in esophageal retraction. The esophagus is then circumferentially dissected high into the posterior mediastinum to allow for adequate mobilization of the esophagus and exposure to SMTs. Usually, through this approach, lesions located up to 3–4 cm proximal to the GEJ can be accessed. If the lesions are not appropriate for enucleation due to size and/or extension, we use combined laparoscopic/thoracoscopic Ivor Lewis esophagectomy for resection of mass and reconstruction if a total gastrectomy cannot be used.

Stomach

Room Step-Up and Port Placement

Patient is placed in supine position with footboard or split-leg position. Monitors are over each shoulder of the patient. Port placement is typical foregut port placement with four ports and a liver retractor. The patient is placed in steep reverse Trendelenburg position to allow for adequate visualization of the hiatus (Image 50.11).

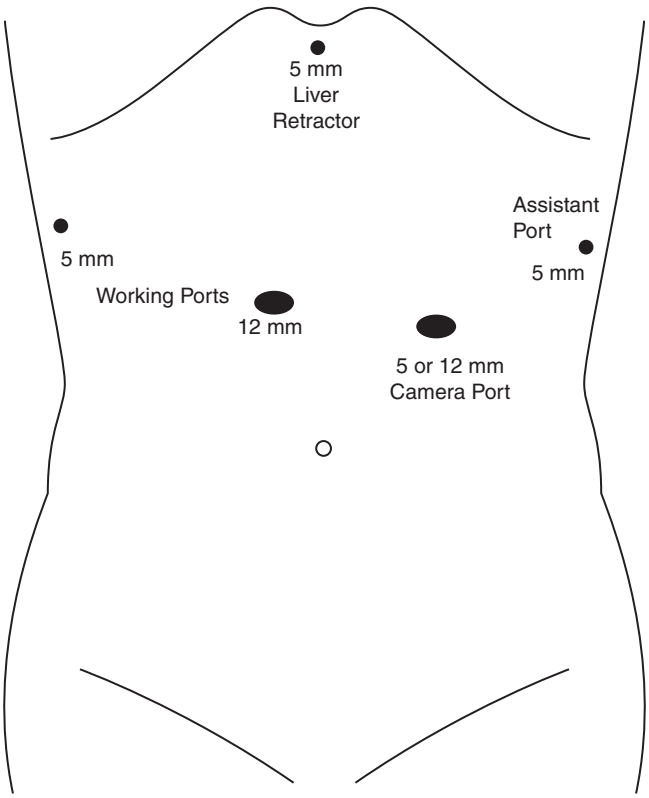

Image 50.11 Port placement for gastric GIST

Gastric Fundus and Greater Curvature Tumors

When tumors are localized to the fundus and greater curvature of the stomach, laparoscopic resection can be performed. In tumors that are endophytic, intraoperative endoscopy is used to localize them. Once the tumor and margins are confirmed, a laparoscopic gastric wedge resection is performed using a laparoscopic linear stapler with or without staple line reinforcement. In order to ensure negative margins, a generous wedge resection is performed (Images 50.12 and 50.13).

Lesser Gastric Curve and Pre-pyloric Tumors

When pre-pyloric or lesser curvature tumors are present, a distal or subtotal gastrectomy is often needed. Such cases often are not amendable to gastric wedge resection due to the risk of narrowing or devascularizing a significant portion of the stomach. For these tumors, the distal stomach and first portion of duodenum are mobilized. The duodenum and distal stomach are transected using a laparoscopic linear stapler, ensuring the tumor is within the resection margins. A Roux-en-Y or Billroth II reconstruction is then performed. For the Roux-en-Y reconstruction, we aim for a 30–40 cm biliopancreatic limb and at least 60 cm Roux limb to avoid alkaline reflux and unneeded malabsorption.

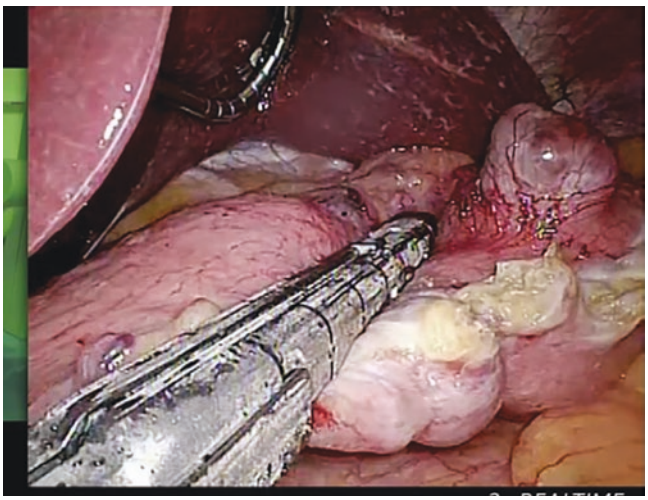

Image 50.12 Laparoscopic resection of gastric GIST

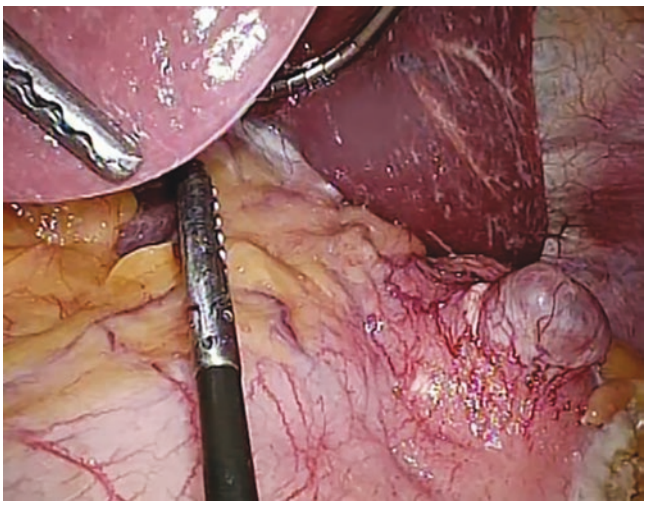

Image 50.13 Laparoscopic view of gastric GIST

Gastric Cardia-Exophytic GEJ Tumors

When exophytic tumors of the gastric cardia or gastroesophageal junction are confirmed and a wedge resection is not possible due to concern for narrowing of GEJ, a laparoscopic enucleation is performed. Typical laparoscopic access and foregut port placement are used. An incision is made in the gastric serosa adjacent to the tumor until the submucosal mass is exposed. The tumor is mobilized from the surrounding gastric tissue with a combination of blunt and ultrasonic dissection while taking precautions to preserve the integrity of gastric mucosa. After complete enucleation of the tumor, the gastric muscularis propria is closed with interrupted sutures. If the gastric mucosa is violated, the area should be closed with full-thickness running or interrupted sutures.

Gastric Cardia-Endophytic GEJ Tumors Without Esophageal Extension

When endophytic tumors of the gastric cardia or esophageal junction are confirmed and there is a significant risk of narrowing the GEJ with resection, or to avoid a total gastrectomy in smaller tumors, a laparoscopic assisted transgastric enucleation is considered. Typical laparoscopic access and foregut port placement are used. Endoscopy is used to identify the lesion and can be used as camera to perform the enucleation. Three balloon trocars are inserted transgastric. A fourth port can be inserted if more retraction is needed or the endoscopic view was not adequate for safe enucleation. The mass is freed using a combination of blunt and ultrasonic dissection while taking precautions to preserve the integrity of gastric serosa. If a full-thickness gastrotomy is made, repair is performed using suture in a running fashion. The gastrotomies are either sutured or stapled closed upon completion of the enucleation. Repeat endoscopy is performed confirming hemostasis, and a leak test is performed.

Esophageal Outcomes

Comparative analysis of open thoracotomy vs VATS surgery for esophageal leiomyomas.

Author	Year	Lap	Open	Conversion (%)	Recurrence	Comment
Xu et al.	2018	16	40	0	NR	No statistical difference in operative time, blood loss, chest tube duration, or the length of postoperative stay
Zhao et al.	2012	55	1	1	0	Less bleeding with VATs
Zhang et al.	2013	83	1	1	0	No cases of dysphagia
Choi et al.	2011	18	45	3	NR	VATs with earlier discharge
von Rahden et al.	2004	13	12	0	NR	Minimally invasive approach reduced pulmonary complications, hospital stay, and postoperative wound-related pain

Gastric Outcomes

Comparative analysis of open vs laparoscopic surgery.

Author	Region	Year	Lap	Open	Conversion (%)	Recurrence Lap	Recurrence Open
Goh et al.	Singapore	2010	14	39	7.1	0	2
Karakousis et al.	USA	2011	40	40	22.5	1	1
Dai et al.	China	2011	18	30	NR	2	3
De Vogelaere et al.	Belgium	2012	37	16	NR	0	6
Melstrom et al.	USA	2012	17	29	5.9	0	4
Lee et al.	Korea	2011	50	50	2	0	0
Wan et al.	China	2012	68	88	NR	3	4
Pucci et al.	USA	2012	57	47	1.8	NR	NR
Kim et al.	Korea	2012	24	14	NR	1	3
Shu et al.	China	2013	15	21	NR	NR	NR
Lee et al.	Taiwan	2013	30	32	NR	NR	NR
Kasetsermwiriya et al.	Japan	2014	23	10	NR	0	1
Lin et al.	China	2014	23	23	4.3	2	3
Takahashi et al.	Japan	2014	12	15	25	1	2

Postoperative Considerations

In cases where reconstruction is needed or there is a risk of narrowing, an upper gastrointestinal series is performed on postoperative day 1, and patients are started on a liquid diet. There are no current generalized guidelines for follow-up of patients who have undergone resection of an esophageal or gastric submucosal tumor. Current practice is based on clinician's preference while taking into account histology, the tumor site, size, and mitotic index. If pathology confirms GIST, low-tumor-risk patients can be followed with CT scan every 6 months for 5 years. Intermediate- to high-tumor-risk patients should be closely followed up with CT scan every 3–4 months for 3 years, then every 6 months for 5 years, and then yearly. PET/CT is more sensitive than CT in detecting response, resistance, and recurrence following TKI therapy when it is used for neoadjuvant, adjuvant, or definitive therapy.

Conclusion

Submucosal tumors are well-circumscribed mesenchymal tumors originating from the muscular layer of the gastrointestinal tract. Most tumors are located in the stomach but can be found in any part of the gastrointestinal tract. They are generally asymptomatic; however, benign lesions can create mass effect and lead to symptoms, while GISTs can undergo malignant degeneration and can also metastasize. Imaging modalities for diagnosis and surveillance include CT, MRI, PET/CT, and endoscopy. Surgery is the treatment of choice for any symptomatic leiomyoma and any potentially resectable GIST, whether in the esophagus or stomach.

Tumor location is the most significant factor in planning the surgical approach for SMT of the esophagus and stomach. Approach can be hybrid (endoscopy/laparoscopy), minimally invasive, or open. Esophageal lesions can be removed by enucleation and avoidance of a major esophagogastric resection and the associated significant perioperative risks, nutritional deficiencies, and reflux complications associated with a major anatomic resection. However, if the esophageal lesion extends to the GEJ or a GEJ lesion extends into the esophagus, esophagectomy may be required.

For tumors located in the fundus, the gastric body, and along the greater curvature, a gastric wedge resection can be performed as long as there is no narrowing of the gastric lumen. When the location of the tumor causes an increased risk of gastric luminal narrowing or gastric emptying issues with a wedge resection, most commonly, with tumors in the

cardia or along the lesser curvature or antrum, a laparoscopic enucleation or transgastric enucleation should be considered. When neither approach is appropriate without significant risk of gastric narrowing, then formal resection will be required. Formal resection is most common needed for prepyloric gastric tumors or tumors along the distal lesser curvature, particularly at the incisura. A second significant factor in operative approach is dictated by the characteristics of the tumor, particularly whether the tumor is exophytic or endophytic. Tumors that are largely endophytic and not amenable to a gastric wedge resection and do not require a formal gastrectomy may be appropriately approached with a transgastric resection or enucleation. More recently, there has been movement toward endoscopic resections (band ligation, snare, endoscopic submucosal dissection) of small SMTs that are less than 2 cm, regardless of location. Robotics has also gained acceptance in treatment of SMTs of the esophagus and stomach and may lead to further adoption of minimally invasive techniques for resection SMTs, as it offers improved visualization and wristed instruments with a potentially shorter learning curve.

Questions

1. With regard to gastrointestinal stromal tumors (GISTs), which of the following statements is correct?
   A. After the small intestine, the stomach is the second most common location for GISTs, followed by the colon and rectum.
   B. The majority of GISTs have an activating mutation in the *PD1* oncogene.
   C. GISTs are usually responsive to conventional chemotherapy and radiation therapy.
   D. Complete surgical resection is the standard of treatment.

Answer: D. Complete surgical resection is the treatment of choice for GIST, with laparoscopic approach being favored as long as negative margins can be achieved.

2. A 35-year-old woman is evaluated for dysphagia and chest pain. A barium esophagogram shows a 2 cm smooth filling defect in the distal end of the esophagus. Which of the following is true?
   A. Lesion often shows hemorrhage and ulceration and has malignant degeneration potential.
   B. Endoscopic ultrasound (EUS) will show a hypoechoic mass in the submucosa.
   C. Endoscopic biopsy should be performed.
   D. Esophagectomy is recommended for lesions larger than 2 cm.

Answer: B. Leiomyomas have a characteristic smooth filling defect on barium esophagogram and are described as a hypoechoic mass within the submucosa or muscularis propria on EUS. Biopsies are not indicated and can lead to risk of perforation.

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Peptic Ulcer Disease

51

Jordan Shapiro, Dan Lister, and David Y. Graham

Objectives

1. To review the epidemiology of PUD.
2. To review classic presentations and management of uncomplicated and complicated PUD.
3. To understand the pathophysiology of PUD.
4. To highlight non-*H. pylori*/non-NSAID etiologies for PUD.
5. To review treatment strategies for *H. pylori*.

Introduction

A peptic ulcer is defined histologically as a mucosal break that penetrates the muscularis mucosa of the gastrointestinal tract exposed to acid and pepsin. Mucosal breaks superficial to the muscularis mucosa are defined as erosions. Endoscopically and radiographically, both size and depth are used to separate ulcers from erosions. Ulcers are defined as mucosal breaks ≥5 mm with apparent depth; smaller and more superficial lesions are called erosions. Based on the requirement for the presence of acid, the most common ulcer locations are the distal esophagus, stomach, and duodenum. However, ectopic acid-secreting parietal cells can also occur elsewhere in the digestive tract resulting in ulcers in ectopic locations, most often in the proximal esophagus (inlet patch) and within a Meckel's diverticulum in the ileum. Typical duodenal ulcers occur in the proximal duodenum, but with excessive acid secretion (e.g., Zollinger-Ellison syndrome), ulcers occur from the duodenal bulb to the jejunum. The most common causes of ulcers are use of nonsteroidal anti-inflammatory drugs (NSAIDs) and infection with *Helicobacter pylori* (*H. pylori*). *H. pylori* infection causes traditional peptic ulcer disease (PUD) which is a chronic condition with gastric and/or duodenal ulcers recurring over many decades (i.e., the dictum "once and ulcer, always an ulcer").

Epidemiology

The lifetime risk for developing PUD in patients with *H. pylori* infection is about 17%. A recent systematic review of 31 studies reported the pooled incidence rates per 1000 person-years as 0.90 (95% C.I. = 0.78–1.04) for uncomplicated PUD, 0.57 (0.49–0.65) for peptic ulcer bleeding, 0.10 (0.08–0.13) for perforated ulcers, and 3.18 (2.05–4.92) for nonspecific PUD. However, *H. pylori* has been losing its place as the most common cause of ulcer to NSAIDs as the prevalence of *H. pylori* infections has declined. NSAID use results in a fourfold increase in ulcer risk and a doubling of risk in individuals with *H. pylori*. The discovery of that the most common cause of a PUD was *H. pylori* (i.e., a treatable infection) resulted in *H. pylori*-associated PUD becoming both preventable and, with treatment, a one-off condition. The continued decline in prevalence of *H. pylori* infections and increase in life expectancy in many parts of the world has led to an increased relative proportion of ulcers being either NSAID-induced or idiopathic (non-*H. pylori*/non-NSAIDs) ulcers.

Pathophysiology

Gastro-duodenal ulceration can be caused by any mechanism that directly or indirectly damages the gastric mucosa (e.g., drugs, ischemia, trauma, etc.) (Table 51.1; Fig. 51.1). Acid and pepsin play important roles in chronic *H. pylori*-induced PUD (e.g., Schwarz's dictum "no acid—no ulcer"). In the early twentieth century, peptic ulcers had been identified as being related to poor wound healing based on the observation that similar sized wounds produced adjacent to a

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Table 51.1 Non-*H. pylori*/non-NSAID causes of PUD

Non-NSAID medications/drugs with ulcerogenic potential
Bisphosphonates
Glucocorticoids
Iron supplements
Potassium (especially wax matrix formulations)
Sirolimus
Spironolactone
Chemotherapy (e.g., 5-fluorouracil)
Molecular targeted therapy (e.g., erlotinib)
Localized radiation therapy (e.g., Y-90)
Cocaine
Non-H. pylori infections with ulcerogenic potential
Herpes simplex virus type I (HSV-I)
Cytomegalovirus (CMV)
Rare infections (e.g., candidiasis, mucomycosis, syphilis, tuberculosis, Epstein Barr virus)
Mechanical causes of ulcers
Obstruction (e.g., annular pancreas)
Foreign body
Post-surgical (e.g., marginal ulcer after Roux-en-Y gastric bypass, antral exclusion)
Acid hypersecretory states
Gastrinoma (including in the setting of multiple endocrine neoplasia type 1, MEN 1)
Systemic mastocytosis
Myeloproliferative disorders
Antral G-cell hyperfunction
Ischemic causes of ulcers
Arterial/venous diseases
Non-occlusive ischemia
Inflammatory and infiltrating disease
Sarcoidosis
Crohn's disease
Other gastroenteritides (e.g., eosinophilic gastroenteritis)
Other
Idiopathic hypersecretory duodenal ulcer
Stress ulcers in the intensive care unit

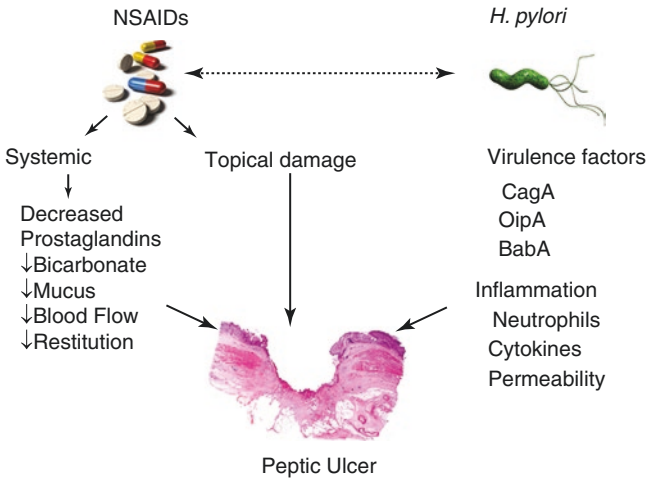

Fig. 51.1 *Helicobacter pylori* and NSAIDs are the most common causes of gastric and duodenal ulcers. (From: Yamada's Atlas of Gastroenterology. 4th ed. Hoboken: Wiley-Blackwell, 2008:237–250, with permission)

chronic ulcer healed rapidly, whereas the ulcer did not. Ulcers and gastric cancer had long been known to be tightly associated with gastritis. The breakthrough came in the 1980s when *H. pylori* infection was identified as the cause of ulcer and gastric cancer-associated gastritis.

The most common site of a gastric ulcer due to *H. pylori* is on the lesser curve near the gastric angle. The ulcer site moves proximally at, or just ahead of, the *H. pylori*-associated inflammatory front that advances proximally from the antrum (Fig. 51.2). Gastric ulcers occurring at the greater curvature of the antrum are often due to gastrotoxic medications which when swallowed fall to this most dependent portion of the stomach.

H. pylori-induced gastric inflammation results in defective downregulation of acid secretion associated with antral acidification or distention. The average *H. pylori* duodenal ulcer is associated with an increase in duodenal acid load related to the increased parietal cell mass and *H. pylori*-related dysregulation in acid secretion resulting in an average pH in the duodenal bulb of below 4. The duodenum is normally protected against *H. pylori* infection because bile, which is normally present, inhibits growth of the bacterium. However, the high duodenal acid load precipitates glycine conjugated bile acids allowing *H. pylori* to colonize ectopic gastric cells in the duodenum (Fig. 51.3). Duodenal inflammation, acid secretion by gastric metaplasia/heterotopia, and the small deformed duodenal bulb with abnormal duodenal bulb motility together with smoking which both increases acid secretion and inhibits duodenal and pancreatic bicarbonate secretion combine to produce the perfect storm resulting in chronic duodenal ulcer disease. The presence of post-bulbar ulcers should raise suspicion of a non-*H. pylori* etiology such as a hypersecretory state (e.g., Zollinger-Ellison syndrome, systemic macrocytosis), drug-induced ulcers, Crohn's disease, etc. (Table 51.1).

H. pylori

Approximately, half of the world's population is currently infected with *H. pylori*. The prevalence varies greatly from as low as <20% in affluent young North American adults to >80% in rural Africa. The populations most at risk are characterized as disadvantaged with low socioeconomic status, poor sanitation, lack of running water, overcrowding, bed sharing as children, poor household hygiene, etc. Most often the infections are acquired in childhood and are lifelong. *H. pylori* infection is the most common cause of peptic ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) tumors.

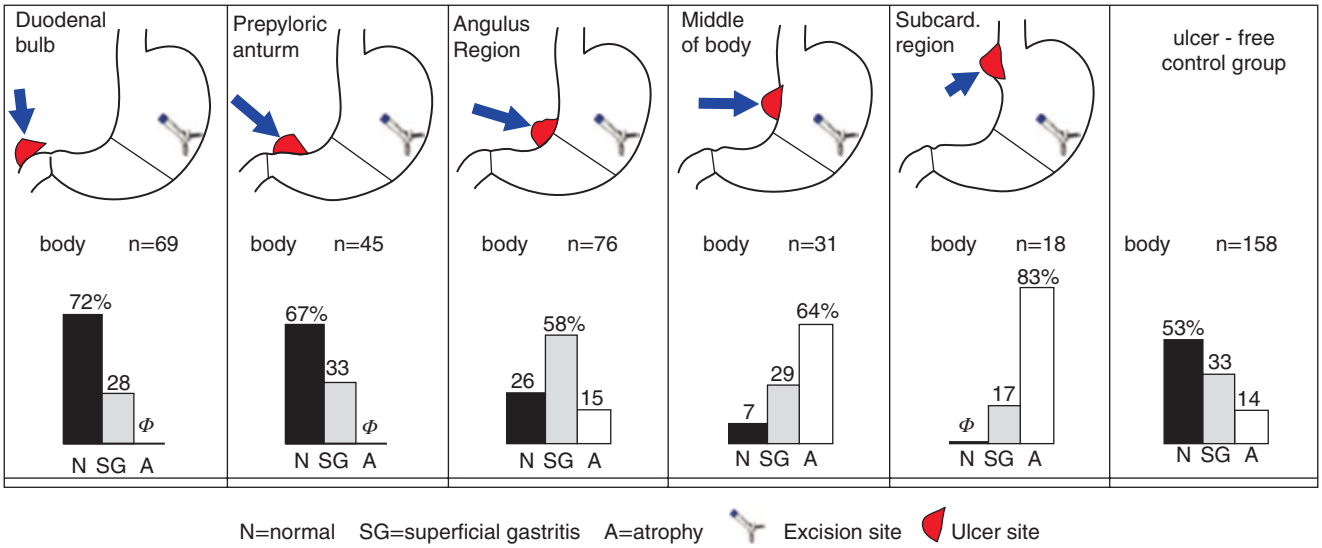

Fig. 51.2 The ulcer site moves proximally at, or just ahead of, the *H. pylori*-associated inflammatory front that advances proximally from the antrum. (From World J Gastroenterol. 2014;20(18):5191–204, with permission)

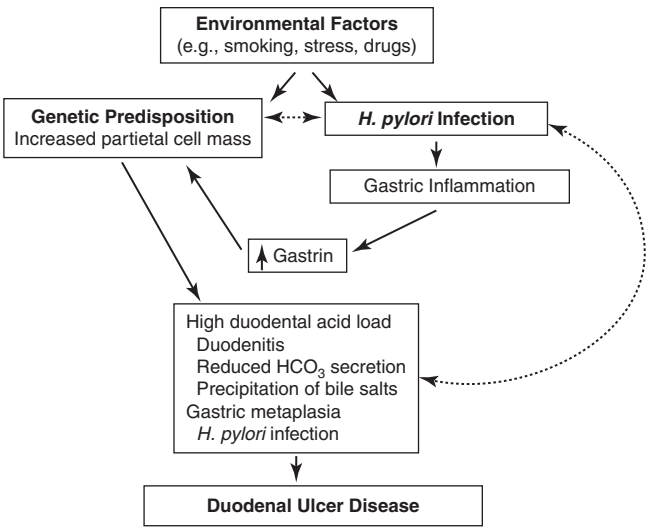

Fig. 51.3 The high duodenal acid load precipitates glycine conjugated bile acids allowing *H. pylori* to colonize ectopic gastric cells in the duodenum. (From: Yamada's Atlas of Gastroenterology. 4th ed. Hoboken: Wiley-Blackwell, 2008:237–250, with permission)

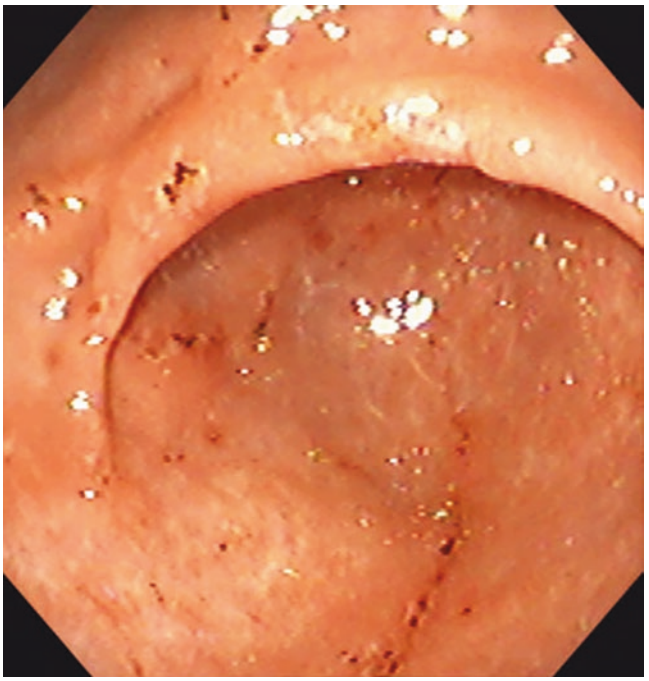

Fig. 51.4 Photograph of the distal stomach after aspirin ingestion showing multiple small erosion and red dots characteristic of acute NSAID injury

NSAIDs

NSAIDs inhibit prostaglandin synthesis which is critical in maintaining the normal protective mucosal barrier. NSAIDs decrease mucosal production of bicarbonate and glutathione as well as mucosal blood flow. The risk of developing an NSAID ulcer depends in part on the specific NSAID, the dose, and the duration of therapy (Fig. 51.4). When given at full anti-inflammatory doses, the NSAIDs with highest risk for PUD are ketorolac (adjusted RR 14.4, 95% CI 5.2–39.9) and piroxicam (RR 12.6, 95% CI 7.8–20.3). Naproxen (RR 7.3, 95% CI 4.7–11.4), ibuprofen (RR 4.1, 95% CI 3.1–5.3), and diclofenac (RR 3.1, 95% CI 2.3–4.2) have moderate risk. Long-term studies have confirmed that the selective COX-2 inhibitor, celecoxib, has a low to moderate risk when full anti-inflammatory doses are needed. When NSAIDs are primarily used for analgesia, low-dose ibuprofen (200 mg) or

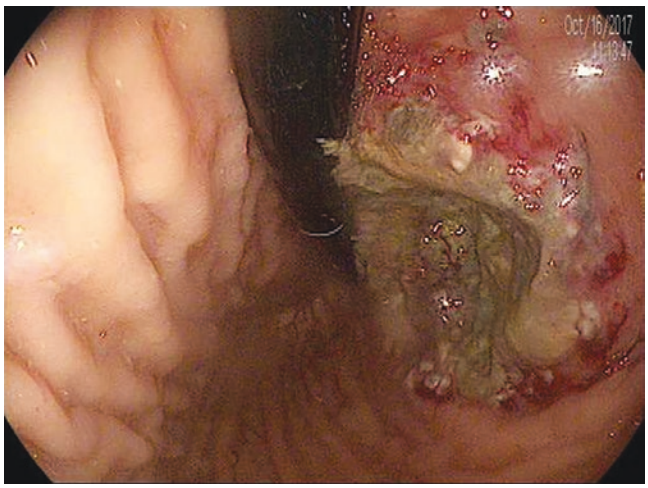

Fig. 51.5 A case of giant deep gastric ulcer due to mucormycosis in a patient status-post lung transplant for cystic fibrosis

naproxen OTC (224 mg) provides near near-maximum analgesia with low ulcer risk. Because of its widespread use for cardiovascular prophylaxis, aspirin is overall probably the most common cause of ulcers.

Non-*H. pylori*/Non-NSAID Causes of PUD

Although there are many non-*H. pylori*/non-NSAID causes of PUD (Table 51.1), false-negative testing for *H. pylori* and failure to solicit a history or denial of NSAIDs or gastrotoxic drugs remain common reasons for inappropriately reaching the conclusion of non-*H. pylori*/non-NSAIDs PUD. In addition, rare causes of ulcers (e.g., diffuse B-cell lymphoma and mucormycosis) may appear in immunocompromised patients (Fig. 51.5). Nonetheless, the relative frequency of idiopathic ulcers has increased in parallel with the decline in previously more common causes.

Clinical Manifestations

Although gastric and duodenal ulcers, especially among NSAID users, may remain asymptomatic until discovered at endoscopy or presentation as a complication, classic *H. pylori* peptic ulcer disease generally is associated with symptoms. The most common symptom, present in roughly 80% of patients with endoscopically evident PUD, is epigastric pain. Ulcer pain is typically located in the epigastrium (sometimes to the left or right), is described as "burning" pain, and is occasionally associated with radiation to the back, especially with posterior penetration of ulcers. Classically, *H. pylori* ulcer pain relates to the acid cycle: it is generally absent upon waking, appears 2–3 h after breakfast when meal-stimulated gastric acid exceeds the buffering capacity of the meal, and is relieved by food (i.e., food, milk, or antacids provide reliable, temporary relief). If a late-night snack is taken, pain may awaken the patient when the circadian pattern increases acid secretion (i.e., 11 PM to 2 AM). Symptoms are often periodic in that they resolve only to reappear again. Ulcer-like pain is a type of dyspepsia that is present in 21% (range of 1.8–57%) of adults, with greater prevalence in women, smokers, NSAIDs users, and those with *H. pylori*. Although most patients with dyspepsia do not have PUD, it is recommended that all those with dyspepsia get tested for *H. pylori*, and if present, the infection should be cured.

Complications of Peptic Ulcer Disease

The incidence of complicated PUD (i.e., bleeding, perforation, or hospitalizations) has fallen along with the decline in *H. pylori*; however, familiarity with the complications of PUD is critical to aid in prompt recognition and potentially life-saving treatments. The strongest risk factors for complicated PUD are history of PUD complications or concomitant use of aspirin or other NSAIDs in the setting of *H. pylori*.

Hemorrhage

Acute upper GI hemorrhage presenting clinically as hematemesis, coffee ground emesis, melena, and occasionally hematochezia is the most common complication of PUD, accounting for approximately 70% of PUD complications. The annual incidence of hemorrhage from PUD ranges from 19 to 57 cases per 100,000 individuals. NSAID-induced ulcers are more likely to bleed, especially in the presence of coexisting *H. pylori* infection. In addition, use of concomitant antiplatelet therapies (e.g., clopidogrel) and steroids increases risk of bleeding PUD with NSAIDs, whereas anticoagulation does not. Odd ratios for bleeding peptic ulcers associated with *H. pylori* and NSAIDs are 1.8 and 4.8, respectively, and increase to 6.1 in individuals with both risk factors.

Perforation

Perforation occurs in 2–10% of patients with PUD, with an annual incidence of perforation ranging from 4% to 14% per 100,000 individuals. Perforation typically presents as sudden, severe, diffuse abdominal pain, tachycardia, and rigid abdomen. Most perforations occur in the prepyloric stomach; the second most common site is the duodenal bulb.

Gastric Outlet Obstruction

Gastric outlet obstruction accounts for up to 3% of PUD complications. Ulcers in the pyloric channel or duodenum can cause gastric outlet obstruction with associated symptoms of early satiety, bloating, epigastric pain shortly after eating, and weight loss. With the decline in *H. pylori*-induced PUD, gastric malignancies are becoming a more common cause of gastric outlet obstruction.

Penetrating/Fistulizing PUD

Peptic ulcers may penetrate through the wall of the stomach/duodenum and into adjacent organs. Clues to presence of a penetrating ulcer include the pain becoming more severe, lasting longer, referred to new locations (typically the back), and failure to be relieved by food or antacids. Penetration of ulcers into adjacent structures may cause a wide variety of signs and symptoms depending on involved structures: gastro-duodenocolic with halitosis, feculent vomiting, and post-prandial diarrhea; vascular structures such as the aorta or cystic artery may present with exsanguination, biliary tree with choledochoduodenal fistula and extrahepatic biliary obstruction, and pancreatic duct with mild hyperamylasemia and rarely pancreatitis.

Diagnostic Testing

The choice of diagnostic test depends on the presentation, the patient's age, prior history of PUD, family history, physical exam, review of drugs used, and routine laboratory (especially anemia). For an otherwise healthy patient with dyspepsia, the first question might be "Does this patient have an *H. pylori* infection?" The Houston consensus for *H. pylori* testing recommends a proactive approach to *H. pylori* testing and treating all who are positive (Table 51.2). Testing options include non-invasive urea breath test, stool antigen test, or endoscopy with gastric biopsies. For a young healthy person (e.g., <60), non-invasive testing would be the best initial choice as cure of *H. pylori* in a patient with uncomplicated peptic ulcer will also cure the ulcer disease. However, in an older patient, one might consider early endoscopy with gastric biopsies to exclude gastric cancer and to examine the health of the gastric mucosa (e.g., atrophic vs. non-atrophic). For complicated disease, endoscopy would generally be the first choice. Indications for endoscopy first in patients <60 include significant weight loss (>5% usual weight over 6–12 months), overt GI bleeding, and >1 alarm feature (unintentional weight loss, dysphagia, odynophagia, unexplained iron deficiency anemia, persistent vomiting, palpable mass or lymphadenopathy, or family history of upper GI cancer).

Endoscopic Evaluation of Ulcers

The endoscopy report should include a description (round, smooth base vs. nodular, deep, overhanging irregular margins, protruding mass, etc.). The folds surrounding a gastric ulcer crater should be examined in terms of nodularity, fusion, clubbed, or stop short of the ulcer margin and (when overhanging, irregular, thickened ulcer margins appear, etc.) location along with high-quality photographs. The appearance of the gastric mucosa should also be described (e.g., atrophic vs. normal, smooth vs. nodular, fold size, and thickness). For gastric ulcers, all four quadrants and the base should be biopsied. For both gastric and duodenal ulcers, high-quality photography should be done (Fig. 51.6). The mucosa surrounding the ulcer should also be examined for scars or evidence of prior ulcers. In both gastric and duodenal ulcers, gastric biopsies of the antrum and corpus should be taken for *H. pylori* using the Sydney protocol (Fig. 51.7).

Table 51.2 Recommendations to test for *H. pylori* infection

Risk factor
With suspected *H. pylori* infection (e.g., active DU)
With current or past gastric or duodenal ulcers
With uninvestigated dyspepsia
With gastric mucosa-associated lymphoid tissue lymphoma
Family members residing in same household of patients with proven active *H. pylori* infections
Family history of peptic ulcer disease
With family history of gastric cancer
First-generation immigrants from high prevalence areas
High-risk groups (e.g., in the United States: Latino and African American racial or other ethnic groups)

Based on Clin Gastroenterol Hepatol. 2018;16(7):992–1002.e6

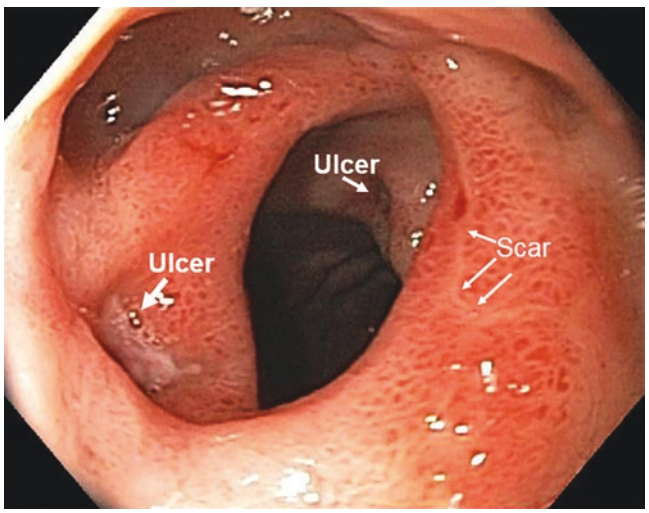

Fig. 51.6 Photograph of a very scarred duodenal bulb with active duodenal ulcers, scars from prior healed ulcers, and inflamed mucosa with lack of a villus pattern

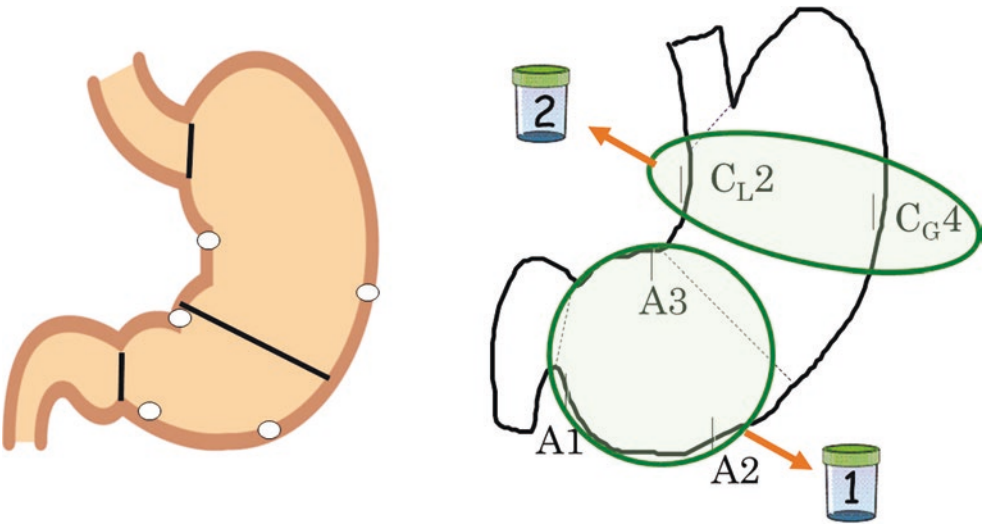

Fig. 51.7 To identify *H. pylori* and map the stomach to determine the extent and severity of damage, gastric biopsies of both the antrum and corpus should be taken for *H. pylori* using the Sydney protocol. Illustration of the biopsy sites for using the Sydney system to assess the status of the gastric mucosal and search for the presence of *H. pylori*. The figure also shows that all antral biopsies should be combined into one jar of formalin and the corpus biopsies in a separate bottle

Diagnostic Tests for *H. pylori* Infection

A wide variety of tests are available including serologic testing for *H. pylori* antibodies, stool antigen tests, the urea breath test, histology with special stains, culture, and molecular tests for the *H. pylori* genes. Serology is no longer recommended for initial testing because it has relatively poor specificity and sensitivity. A positive anti-*H. pylori* serology alone should not be the sole criteria for treatment as it may remain positive for months to years after successful *H. pylori* treatment. Treatment should be based on the results of a test for active infection such as the urea breath or stool antigen test. False-positive tests for active infection are rare when using tests that require a high density of *H. pylori* such as the rapid urease test, urea breath test, stool antigen test, or gastric mucosal biopsy. However, false-negative results with these tests may occur if there has been exposure to antibiotics with activity against *H. pylori* within 4 weeks or use of PPIs or bismuth-containing compounds within 2 weeks of testing as these may lower *H. pylori* density below levels necessary for detection. While upper gastrointestinal bleeding does not impact the yield of gastric biopsies for *H. pylori*, PPI use in the setting of bleeding may reduce *H. pylori* numbers and potential to limit diagnostic stigmata of *H. pylori* infection to the presence of mucosal inflammation.

Treatment of *H. pylori* Infection

Recently, susceptibility testing for *H. pylori* has become universally available in the USA using culture of gastric biopsies, next generation sequencing of gastric biopsies (fresh or formalin-fixed paraffin blocks) or stools (American Molecular Laboratories), or by polymerase chain reaction performed on stools for clarithromycin at Mayo Clinical Laboratories [21]. The universal availability of susceptibility testing eliminates empiric use of clarithromycin, levofloxacin, and metronidazole triple therapies. Therapies are now divided into those regimens that can be used empirically—provided they reliably achieve high cure rates—and those that should only be given as susceptibility-based regimens. Susceptibility testing should be considered for all treatment failures in order to evaluate why treatments failed. If the infection remains susceptible to the antibiotic used, consider issues with adherence or duration of therapy. When resistance has emerged during treatment—often due to heteroresistance meaning that subset of bacterial cells present was resistant to a treatment—the next therapy can be chosen rationally based on the results of susceptibility testing. The alternative for failures following susceptibility-based therapy is to choose another antibiotic from the original susceptibility test and forgo repeating the susceptibility testing to identify why treatment failed. In mid-2022, the potassium competitive acid blocker (P-CAB) vonoprazan was approved for treatment of *H. pylori* infections in the USA. However, the cure rates were unexpectedly and unacceptably low for both P-CAB-containing regimens—vonoprazan, amoxicillin, and clarithromycin triple therapy and vonoprazan with high dose amoxicillin dual therapy—as well as for the lansoprazole clarithromycin triple therapy control group, even with susceptible infections. These results are unprecedented and vonoprazan-containing regimens should not be used until they are optimized to reliably achieve acceptable cure rates. Of note, more than 90% of the clarithromycin in the vonoprazan triple therapy was unnecessary as the cure rates with resistant and susceptible strains were remarkably similar such that the clarithromycin was primarily only contributing to global antibiotic resistance, is another reason not to prescribe it. Current treatment regimens for *H. pylori* are shown in Table 51.3.

Table 51.3 Recommended *H. pylori* therapies

Empiric therapies	
Bismuth quadruple therapy Bismuth subsalicylate q.i.d. 14 days	Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d. 30 min before meals, tetracycline HCl 500 mg and metronidazole 500 mg 30 min after meals q.i.d. plus a PPI, 30 min b.i.d. before meals and bedtime (see PPP below)
Bismuth quadruple therapy Bismuth subsalicylate b.i.d. 14 days	Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d, 30 min before meals, tetracycline HCl 500 mg b.i.d. and metronidazole 500 mg, 30 min after meals q.i.d. plus a PPI, b.i.d. 30 min before morning and evening meals (see PPP below)
Bismuth quadruple therapy Pylera® formulation (bismuth citrate) 14-days	Give combination tablets with means plus a PPI, q.i.d. 30 min before meals and bedtime (see PPP below) (see text for specific details). 14-day therapy recommended with metronidazole resistance likely.
Rifabutin triple therapy. 14-days	Rifabutin 150 mg b.i.d., amoxicillin 1 g t.i.d. plus 40 mg of esomeprazole or rabeprazole 30 min before meals b.i.d. (see PPP below) (see text for specific details)
Talicia® formulation of rifabutin triple therapy. 14-days	As directed by package insert
Therapies only effective as susceptibility-based therapy *Do not use empirically unless proven to cure >90% locally*	
Clarithromycin triple therapy. 14-days	Clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d., 30 min before meals, (see PPP below)
Metronidazole triple therapy. 14-days	Metronidazole 500 mg b.i.d., amoxicillin 1 g b.i.d., 30 min before meals, (see PPP below)
Levofloxacin triple therapy. 14-days[a]	Levofloxacin 500 mg in a.m., amoxicillin 1 g b.i.d., 30 min before meals, (see PPP below)
PPI dose should at a minimum be 40 mg of omeprazole or equivalent b.i.d. We recommend 40 mg of rabeprazole or esomeprazole b.i.d.	
Therapies that remain to be optimized for effective local use	
PPI or P-CAB-amoxicillin dual therapies	In western societies dual therapies are generally ineffective and remain to be optimized before the can be recommended
Therapies that contain unneeded antibiotics and should not be used	
All include at least one antibiotic that offers no therapeutic benefit and only serves to increase global antimicrobial resistance: concomitant, hybrid, reverse hybrid, sequential therapies, vonoprazan clarithromycin triple therapy.	

[a]The FDA recommends fluoroquinolones be used as a last choice because of the risk of serious side effects (adapted from ref. [21])

Screen for and Stop NSAIDs in Patients with PUD

Cessation of NSAIDs or other gastrotoxic drugs is critical to healing and preventing recurrence of PUD. It is possible to stop the PPI after ulcer healing of an uncomplicated ulcer in someone requiring aspirin for cardiovascular prophylaxis. For NSAID users with an uncomplicated ulcer, it is possible to restart the NSAID at the lowest effective dose or switch to celecoxib 200 mg or less per day along with a PPI, at least 30 mg of omeprazole equivalent daily (e.g., 20 mg of esomeprazole or rabeprazole). For complicated ulcers (e.g., GI bleeding), NSAIDs of all types should be avoided in the future.

Acid Suppressive Therapy

If an uncomplicated *H. pylori* PUD is detected and *H. pylori* is treated, PPI use is not indicated beyond the 14-day *H. pylori* treatment. For complicated PUD, antisecretory therapy should not be stopped until cure of the *H. pylori* infection has been proven. If non-invasive testing is planned, it is best to switch to a histamine-2-receptor antagonist for the 2 weeks prior to testing. Large duodenal and gastric ulcers, especially those due to NSAIDs, may a need longer duration of PPI therapy. Idiopathic ulcers require continued long-term PPI therapy possibly even for decades.

Other Suggestions to Promote Ulcer Healing

Smoking cessation and possibly limiting alcohol intake to one drink per day may help promote ulcer healing. However, dietary therapies and stress management have not been shown to impact ulcer healing and may require clarification for patients who may perceive that these contributed to their PUD.

Evaluation for Suspected Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome (ZES) should be suspected in patients with multiple or refractory peptic ulcers, ulcers distal to the duodenal bulb, PUD with diarrhea, steatorrhea, enlarged gastric folds, MEN1, family history of PUD or MEN1, or diarrhea responsive to PPIs (Fig. 51.8). When ZES is suspected, a fasting serum gastrin concentration and gastric pH should be measured. Fasting serum gastrin levels >1000 pg/mL in the

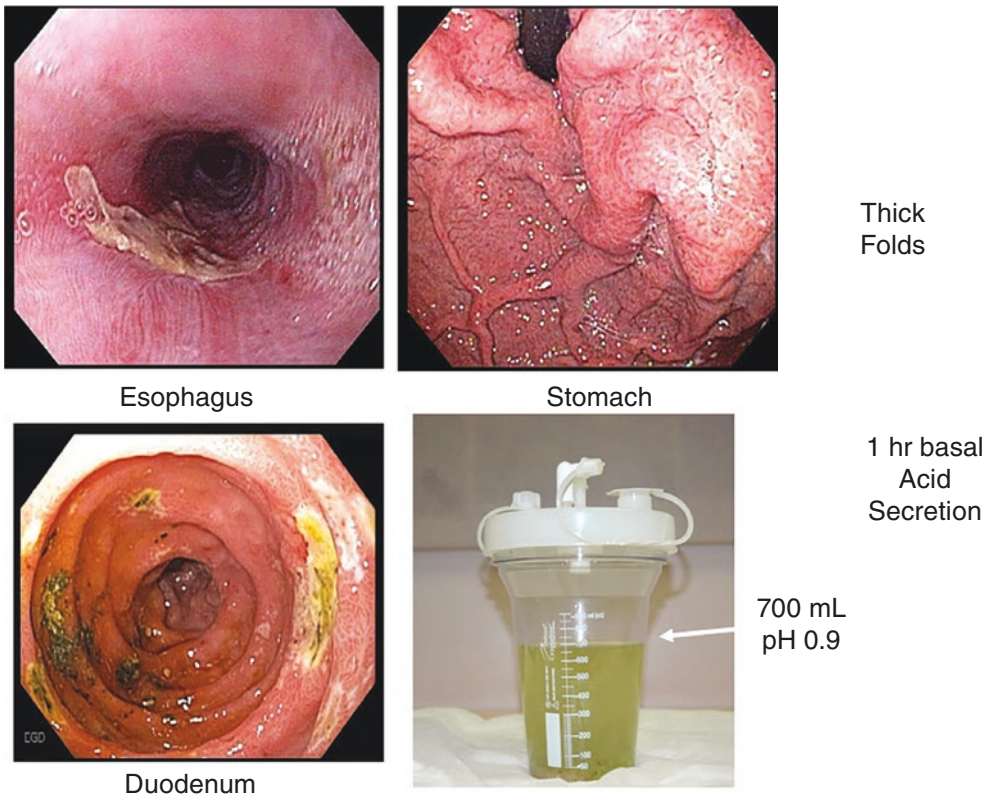

Fig. 51.8 A collage showing the spectrum of findings in Zollinger-Ellison syndrome with endoscopic findings of esophagitis, large gastric folds, extensive duodenal damage, and a very large volume of highly acidic gastric fluid obtained in 1 h of basal acid secretion. (Image courtesy of Dr. Clark Hair. Michael E. DeBakey VA Medical Center)

presence of gastric pH <2 is diagnostic of ZES. However, two-thirds of patients with ZES have fasting gastrin levels <1000 pg/mL; if the pH is <2, then a secretin stimulation test should be performed. Secretin stimulation testing requires changing from PPIs to H2RAs 1 week prior to testing, two fasting serum gastrin levels, and infusion of secretin, and repeat gastrin levels at 2, 5, and 10 min later. Positive testing is defined as an increase in gastrin levels >120 pg/mL over basal fasting levels (sensitivity 94% and specificity 100%). Secretin testing should not be done in patients with severe abdominal pain, vomiting, diarrhea, or multiple ulcers as these patients are at risk for life-threatening consequences of stopping acid suppression. Tumor localization studies (e.g., EGD/EUS, Gallium-68 DOTATATE PET imaging) are used to search for gastrinomas. Secondary hypergastrinemia is typically due to achlorhydria (e.g., atrophic gastritis, pangastritis-associated *H. pylori*, renal failure, post-vagotomy, and with use of PPIs) which can be differentiated from hypersecretory states by measuring fasting gastric pH.

Stress Ulcers

Stress ulcers are defined as acute mucosal injury and disruption of the mucosal barrier due to critical illness, classically burns (Curling's ulcer) and intracranial injuries (Cushing's ulcer). Stress ulcers are often asymptomatic and found during endoscopy for other reasons (e.g., percutaneous endoscopic gastrostomy tube placement). Bleeding is the most common presentation and occurs in <1% to 17% of stress ulcers depending in part on use of stress ulcer prophylaxis. The greatest risk factors for the development of stress ulcers are respiratory failure requiring mechanical ventilation for >48 h and coagulopathy. Other risk factors include sepsis, shock/use of vasopressors, corticosteroids, severe burns (>35% of the body surface area), recent history of gastrointestinal bleeding, head/spinal cord injuries, intensive care unit stays >1 week, and hepatic, renal, or multi-organ failure.

Measures for preventing stress ulcers include both non-pharmacologic (early enteral nutrition, oro-/nasogastric feeding tube placement without unnecessary suctioning, resuscitation with fluid and blood as needed, and correction of coagulopathy) and pharmacologic therapy such as antacids, HRAs, prostaglandins, or PPIs. Stress ulcer prophylaxis, although standard of care in some ICUs, is not necessary in lower-risk populations such as general medicine patients. Although stress ulcer prophylaxis with PPIs may be superior to HRAs for prevention of clinically significant bleeding, PPIs may not add significant benefit beyond early enteral nutrition. Lastly, in many patients the use of PPIs is inappropriately continued after discharge from hospital.

Endoscopic, Interventional Radiology, and Surgical Treatments for Complicated PUD

Most of this section will focus on management of hemorrhage due to PUD. Penetrating PUD may be identified at the time of endoscopy or on cross-sectional imaging and typically responds rapidly to antisecretory therapy and eradication of *H. pylori*.

Management of Hemorrhage Due to PUD

PUD bleeding stops spontaneously in approximately 75% of patients. The management strategy consists of stopping ongoing bleeding and preventing rebleeding. Medical management of bleeding PUD includes resuscitation with intravenous fluids and blood transfusion to a hemoglobin goal of 7–9 g/dL, endoscopy to identify the cause and apply treatment if appropriate, and PPI therapy to stop acid-induced damage and promote ulcer healing. Nasogastric tube lavage is no longer recommended, but prokinetic agents prior to endoscopy may improve gastric visualization.

Early endoscopy allows one to diagnose the cause of bleeding, to stratify the risk for rebleeding, and, when appropriate, to endoscopically intervene. The Forrest classification (Fig. 51.9) divides untreated peptic ulcers into low and high risk of rebleeding. Any lesion other than those with flat pigmented spots (class IIc) or clean base ulcers (class III) are considered higher risk for rebleeding and should receive endoscopic therapy as well as intravenous PPI therapy (80 mg push then 8 mg/h) for at least 24 h preferably for 72 h followed by oral PPI therapy with 40 mg of esomeprazole or rabeprazole. Low risk lesions (class IIc and III) that do not require endoscopic therapy and can be treated with 24 h of IV continuous PPI therapy followed by oral PPI therapy (e.g., 40 mg of esomeprazole or rabeprazole b.i.d.). PPIs require 3–4 days to reach maximum effectiveness when given orally or by intermittent injection. Whether given orally, intravenously, or intramuscularly the effects on acid secretion are the same for an individual PPI. The time the pH remains above 3 or 4 (to inhibit pepsin) differs among PPIs and dosages. It is lowest with pan-

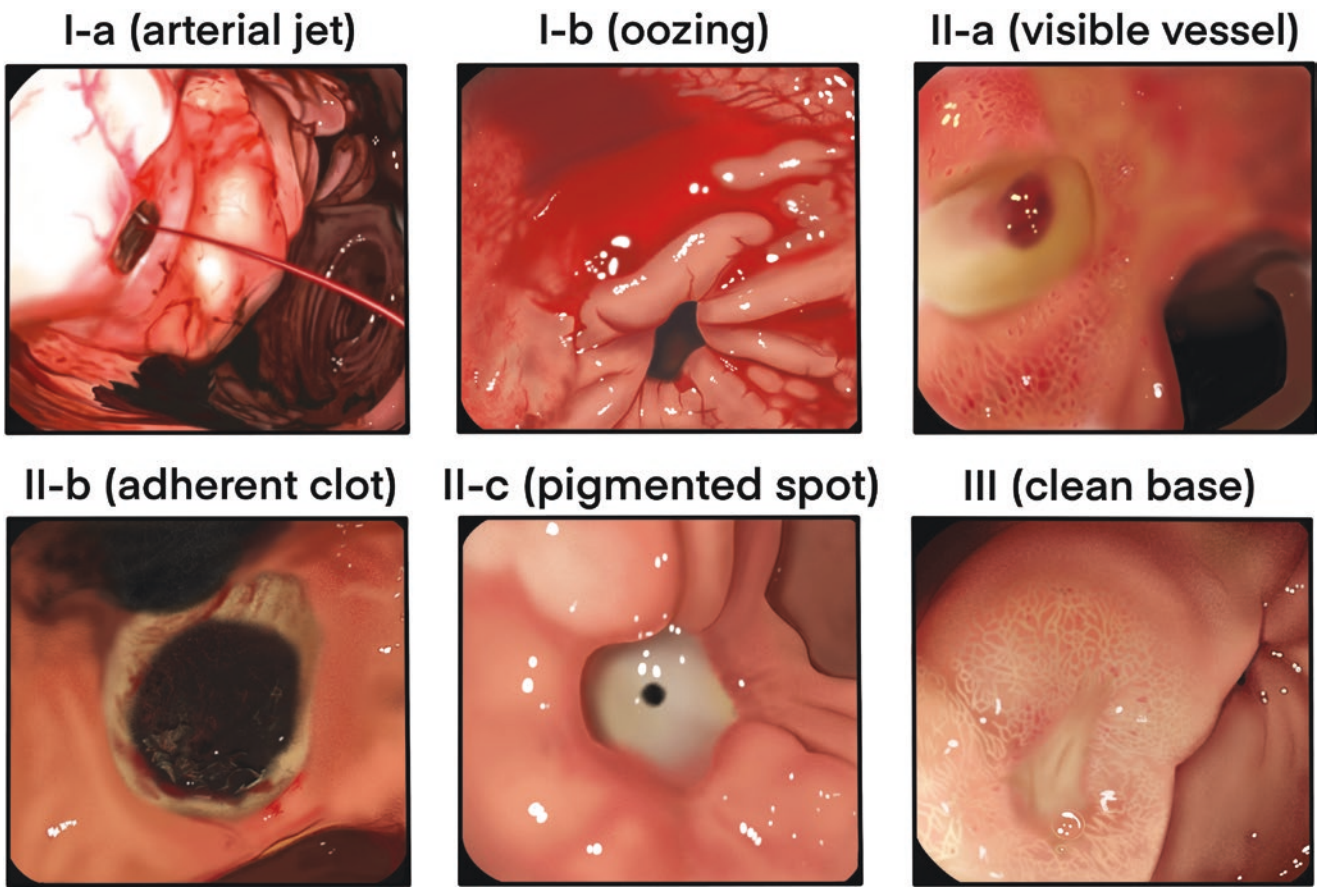

Fig. 51.9 The Forrest classification divides untreated peptic ulcers into low and high risks of rebleeding

Table 51.4 Potency of PPIs based on omeprazole equivalents (OE)

Drug at lowest available dosage	OE (mg)
Pantoprazole 20 mg	4.5
Lansoprazole 15 mg	13.5
Omeprazole 20 mg	20
Esomeprazole 20 mg	32
Rabeprazole 20 mg	36

From: Clin Gastroenterol Hepatol. 2018;16(6):800–8.e7

toprazole and higher with 40 mg of esomeprazole or rabeprazole [22] (Table 51.4).

The relative potency of pantoprazole is such that 20 mg of pantoprazole is equivalent to 4.5 mg of omeprazole; thus, the most commonly used dose of pantoprazole, 40 mg, is equal to 9 mg of omeprazole. The most effective acid control is obtained by continuous infusion of a PPI.

For high-risk ulcers, thermal coagulation or hemoclips combined with injection of epinephrine is recommended. Hemostatic nanopowder spray (Hemospray) may be used as a temporizing measure when other endoscopic techniques fail to stop the bleeding. Monotherapy with epinephrine or nanopowder is associated with rebleeding in up to 50% of patients and is not recommended.

Angiography with embolization by interventional radiology and surgical management should be considered for bleeding PUD when endoscopic management fails. Success rates for IR embolization for acutely bleeding PUD range from 52% to 98% with recurrent bleeding occurring in 10–20% of cases. The interventional radiology approach is less invasive than surgery and is preferred for hemorrhage into the biliary tree or pancreatic duct. Compared to surgical approaches, angiography is associated with lower mortality and greater risk of rebleeding and further interventions. Studies differ on whether or not there is a greater risk of complications from IR angiography.

Surgery for bleeding PUD may include oversewing of the ulcer (to ligate the bleeding artery) with truncal vagotomy (to reduce acid secretion) and pyloroplasty, antrectomy with gastrojejunostomy (Billroth II procedure), or selective vagotomy. Emergency surgery for PUD bleeding carries a mortality risk of over 30% and is becoming increasingly uncommon.

Management of Other Complications of PUD

Patients with perforations due to PUD require intravenous fluids, correction of electrolyte abnormalities, broad-spectrum antibiotics, and high-dose iv PPI, and most require surgery (open or laparoscopic). The most common surgery for perforated PUD is oversewing of the ulcer with a Graham patch. Perforations at the pylorus may be treated with a pyloroplasty which incorporates the ulcer in the closure and truncal vagotomy either done laparoscopically or with open laparotomy. Patients with contained perforations and/or development of gastrointestinal fistulae maybe managed conservatively without surgery.

Patients with partial gastric outlet obstruction should be treated with high-dose intravenous PPI, avoidance of NSAIDs, and eradication of *H. pylori*. Endoscopic dilation and surgery should be considered in those patients with complete gastric outlet obstruction and/or those failing more conservative measures.

Conclusion

PUD is a classic disease with a new, emerging look that includes an increased prevalence of non-*H. pylori* causes of PUD, overall less complicated disease, and generally treatable ulcers given the advent of evidence-based management strategies (i.e., optimization of PPI use, eradication of *H. pylori*, and endoscopic techniques for hemostasis). Today's clinician is certain to encounter new challenges such as identifying etiologies of non-*H. pylori*/non-NSAID PUD, using antibiotic stewardship principles to mitigate increasing antibiotic resistance, and providing value-based care in an increasingly complex healthcare ecosystem.

Questions

1. A 60-year-old man was brought to the hospital because of sudden onset of severe abdominal pain. For several years he has experienced recurrent non-radiating epigastric pain typically relieved by food. He also smokes one pack of cigarettes and drinks two beers daily. He was in his usual state of health until early this morning when he was awakened from sleep by severe sharp mid-epigastric pain that has spread to include his entire abdomen. He appears in acute distress lying very still and taking shallow breaths. Vital signs are as follows: T 100.2 °F; respirations 29 per min and shallow; pulse 104 per min; BP 128/70; he refused to sit up; and PO_2 saturation was 99%. Physical examination showed him to be in acute distress, lying on his back. Examination showed exquisite abdominal tenderness to light percussion and no bowel sounds. The liver and spleen were not felt. The remainder of the examination was normal. Laboratory shows a normal hemoglobin and elevated WBC count of 13,000 with 94% PMNs. Electrolytes, BUN, liver function tests, and urinalysis were normal.

   What is your most likely diagnosis?

   A. Perforated peptic ulcer
   B. Acute pancreatitis
   C. Acute cholecystitis
   D. Inflammatory bowel disease
   E. Intestinal obstruction

   Answer: A.

2. A 70-year-old man came to see you because of recurrent abdominal pain and diarrhea. He had been diagnosed with duodenal ulcer disease about 5 years ago and had been treated for *H. pylori* infection. He also has a long history of heartburn and was told he had erosive gastroesophageal reflux disease. He relates that he has loose stools approximately 5 times daily for 21 years. Since treatment for *H. pylori*, he has taken 20 mg of omeprazole daily. One year ago he experienced hematemesis and melena, was hospitalized for 3 days, and received blood transfusions. Upper gastrointestinal endoscopy showed a normal appearing mucosa with an ulcer in the duodenal bulb and another in the third portion of his duodenum. Gastric biopsy showed no *H. pylori*. He was told increase the omeprazole to twice a day. His heartburn, abdominal pain, and loose stools decreased. His vital signs, physical examination, and routine laboratory tests are normal.

   What is your most likely diagnosis?

   A. Crohn's disease
   B. Irritable bowel syndrome
   C. Functional bowel disease
   D. Zollinger-Ellison syndrome
   E. Food intolerance

Answer: D.

3. Which of the following medications does *not* need to be held prior to testing for *Helicobacter pylori* via endoscopic biopsy, stool antigen, or urea breath test?

   A. Bismuth-containing medications
   B. Histamine-2 receptor antagonists
   C. Antibiotics with activity against *H. pylori*
   D. Proton pump inhibitors

Answer: B. Histamine-2 receptor antagonists can be taken up until the day prior to *H. pylori* testing. Proton pump inhibitors should be discontinued 2 weeks or more, and antibiotics and bismuth-containing medications for 4 weeks or more before testing for *H. pylori*.

4. What is the omeprazole equivalent dose of pantoprazole 40 mg?

   A. 4.5 mg
   B. 9 mg
   C. 15 mg
   D. 30 mg

Answer: B. Pantoprazole 40 mg is equal to 9 mg of omeprazole. Dose equivalents should be considered when using proton pump inhibitor therapy to heal ulcers given that differences in potency of medications in the class may impact treatment outcomes.

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Potential Conflicts Dr. Graham is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *H. pylori* therapies and has received research support for culture of *Helicobacter pylori*. He is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease and a consultant for Otsuka, Japan, regarding novel breath tests.

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Primary Gastric Lymphoma

52

Daniel Tseng, Spencer Shao, and Tris Arscott

Introduction

Non-Hodgkin lymphoma (NHL) represents the seventh most common cancer discovered in the United States in 2020 [1]. The American Cancer Society estimates that 777,240 people will be diagnosed with NHL and 19,940 people will ultimately succumb from this [2]. Of the non-Hodgkin lymphomas (NHL), 85% are mature B-cell type, while the remaining 15% are mature T-cell and NK-cell. While diffuse large B-cell lymphoma represents the most common type of NHL, marginal zone lymphomas account for 5–10% of all lymphomas. Extranodal NHL sites primarily include the central nervous system and intestinal and cutaneous regions. However, the most common site is the stomach which ranges between 30% and 40% of all extranodal NHL and 55–65% of all gastrointestinal lymphomas [3]. Of the primary gastric neoplasms, approximately 5% are primary gastric lymphomas (PGL). While B-cell type represents the overwhelming majority of PGL tumors, T-cell and Hodgkin lymphoma occasionally occur within the stomach (Table 52.1).

Table 52.1 Histologic subtypes in primary gastric lymphoma [4]

Subtype	Frequency (%)
Diffuse large B-cell	49
MALT	38
Diffuse large B-cell with small-cell component	11
T-cell	1.2
Mantle cell	0.7

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Gastric MALT

Extranodal marginal zone lymphoma is more commonly known as mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphomas may present in organs such as the lung, thyroid, and salivary gland but most commonly occur in the stomach.

Isaacson and Wright in 1983 first theorized the histiogenesis of MALT in relationship to the normal maturation sequences of gut-associated lymphoid tissue (GALT). It has been proposed that lumenal antigens stimulate the follicular cell centers (FCC) of GALT to migrate into the lymphatics and follow the systemic circulation via mesenteric lymph nodes and thoracic duct. These FCCs migrate to the lamina propria of the intestine from which they arose and transform to plasma cells [5]. This lymphoid infiltration results in the destruction of normal gastric glands resulting in lymphoepithelial lesions that are pathognomonic for lymphoma [6].

Coincidentally, it was about that same time when the discovery of the relationship between MALT and *Helicobacter pylori* (*H. pylori*) was reported. Warren et al. in 1983 first editorialized the presence of an unidentified curved bacilli growing between the cells of the epithelium present of biopsy specimens of active chronic gastritis [7]. However it was not until 1991 when the first study linked *H. pylori* with gastric MALT lymphoma was published. They discovered that the majority of gastric MALT lymphoma were superinfected with *H. pylori* [8]. Continuous gastric inflammation is triggered by host immune response to the bacteria with the recruitment of neutrophils, T and B lymphocytes, plasma cells, and macrophages that damage the native epithelium resulting in chronic gastritis. Release of proinflammatory cytokine IL-10, IFN-γ, TNF-α, and IL-1β along with cytokine imbalance by varying cytokine alleles likely contributes to heterogeneous outcomes from the infection [9]. IL-1β is upregulated in the presence of *H. pylori* which is known to inhibit gastric acid secretion. The resulting hypochlorhydria favors the colonization of *H. pylori* and promotes the development of MALT.

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H. pylori stimulation of MALT lymphoma B-cells does not occur by direct stimulation due to the inability of MALT surface immunoglobulins to recognize *H. pylori* antigens. However, *H. pylori* antigens stimulate helper T-cells to produce differentiation signals such as CD 40 and cytokines that stimulate B-cell growth. In patients with chronic gastritis, *H. pylori*-induced upregulation of B-cell differentiation is autoregulated by a negative feedback mechanism that results in cytolytic destruction of B-cells. However, in MALT lymphoma, T-cells are unable to induce apoptosis necessary for downregulation in B-cell differentiation, thus allowing for ongoing proliferation [10]. Interestingly 5–10% of gastric MALT lymphomas do not demonstrate evidence of *H. pylori* infection. The pathogenesis of this occurrence remains unclear, although genetic alterations (t(11;18)) and other pathways have been theorized.

Gastric Diffuse Large B-Cell Lymphoma

The spectrum of malignancy begins with low-grade MALT lymphomas and progresses to high-grade diffuse large B-cell lymphomas (DLBCL). The increase in the presence of large cells in sheet-like proliferation suggests a transformation of low-grade MALT into high-grade DLBCL tumors. It remains a mystery whether all gastric DLBCL tumors arise from low-grade MALT or occur de novo. Evidence of a transformation pathway includes upregulation of chemokine receptors CXCR7 and loss of CXCR4 in DLBCL tumors compared with MALT lymphoma specimens. These data suggest that there is some degree of autocrine signaling in development of DLBCL tumors [11]. Ubiquitous in all DLBCL somatic mutations include TP53, B2M, CD30, CD58, and BCL6 [12]. Similar to MALT lymphomas, *H. pylori* plays a significant role.

Clinical Presentation

Common foregut complaints such as abdominal pain, nausea, vomiting, fullness, and indigestion are often the initial presentation but are nonspecific and thus can lead to a significant delay in diagnosis. Physical exam findings—splenomegaly, hepatomegaly, palpable epigastric mass, and lymphadenopathy—are present in only approximately 50% of cases [13]. The typical lymphoma-like presenting symptoms of weakness, night sweats, jaundice, and fever occur much less frequently. Due to a delay in diagnosis, progression toward late-stage disease can result in dysphagia, gastric outlet obstruction, perforation, splenomegaly, and lymphadenopathy with approximately 20–30% of patients reporting hematemesis and/or melena [14]. It has been reported that the "alarm symptoms" of persistent vomiting, anemia, melena, hematemesis, and weight loss were more suggestive of high-grade lymphoma versus low-grade [15] (Table 52.2).

Table 52.2 Frequency of presenting symptoms [16]

Symptom	%
Epigastric pain	93
Weight loss	56
Anorexia	31
Vomiting	27
Melena	20
Hematemesis	16
Anemia	13
Backache	9
Nausea	7

PGL occurs in all ages at a mean over 50 years with a slight favoritism toward males over females (1.27:1) [17].

Diagnosis

Clinical and radiographic imaging is unable to definitively distinguish PGL from other gastric malignancies. Therefore, the diagnosis of PGL must be established by histologic examination of tissue specimens. Upper endoscopy with biopsy is the least invasive method to obtain sufficient tissue specimens for pathologic diagnosis.

These lesions are commonly located more distally on the body and antral regions rather than proximally. Endoscopic features include erosions, ulcerations, whitish granularity, cobblestone appearance, thickened gastric folds, abnormal vascularization, and destruction of gastric epithelial structure [18]. There are four primary endoscopic classifications: ulcerative, polypoid, granulonodular, and infiltrative. Ulcerative type of lesions has been most consistently associated with gastric lymphoma. However, these endoscopic findings are also characteristic of other gastric pathologies, and thus the diagnostic sensitivity of endoscopy for PGL has been shown to be only 21% indicating the endoscopic appearance alone has little value to determining the presence of PGL [19] (Fig. 52.1).

In order to obtain sufficient tissue for histologic examination, it is recommended that up to ten biopsies of the suspicious area are performed. The mucosal appearance of PGL may be subtle; therefore, it is important to perform stomach mapping from the antrum to fundus from four quadrants to properly evaluate and understand the extent of the disease [20].

The addition of endoscopic ultrasound (EUS) to aid in the diagnosis has been helpful since PGL may only have very subtle or no mucosal irregularities. Early studies demon-

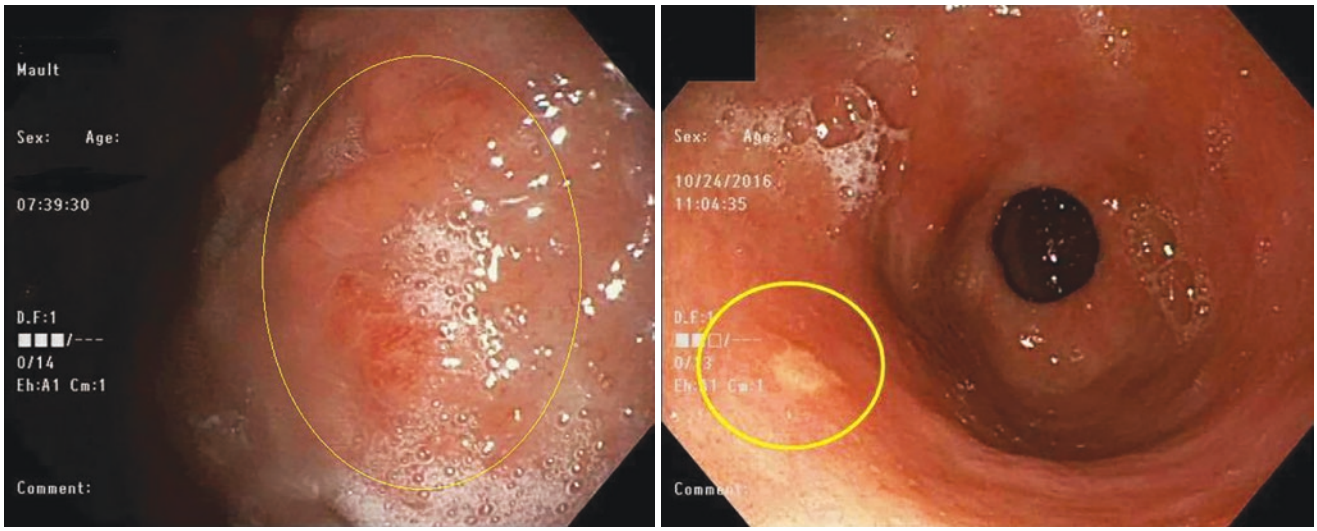

Fig. 52.1 Endoscopic appearance of gastric MALT

strated that EUS had a sensitivity of 93% and specificity of 98% for PGL [21]. Endosonographic features may include thickening layers of the wall with or without preservation of the five-layer structure [22]. EUS has the added value of superior sensitivity when compared to CT scan for staging of PGL since EUS can detect subtle differences in the gastric wall as well as detect lymph node involvement [23].

A new method of obtaining high-resolution real-time mucosal histology that may be helpful in the identification of PGL is performing confocal laser endomicroscopy (CLE). A specially designed endoscope integrates a miniaturized laser scanning confocal microscope into the tip which allows endoscopy and microscopy to be performed simultaneously. Injection of 1% IV fluorescein distributes into the vasculature, lamina propria, and intracellular spaces of the tissue. The CLE catheter is placed through the working channel and illuminates the tissue with a low power laser, and the fluorescent light reflected from the tissue is detected. Since the laser is focused for a specific depth, only the light detected from that tissue plane is detected. The depth may be adjusted to help see deeper structures. The focused area is scanned both in a horizontal and vertical plane, and the image is reconstructed. The images are classified into eight types with unique gastric pit patterns A to $G_{1,2}$ [24]. These characteristics have been shown to assist detection of MALT lymphoma with higher sensitivity and specificity than endoscopic ultrasound or traditional white light endoscopy with a sensitivity of 93% and specificity of 100% [25] (Table 52.3).

Table 52.3 Gastric pit categorization by confocal endomicroscopy

Category	Description	Pathology
A	Round pits with round opening	Normal mucosa
B	Non-continuous short rod-like pits with short thread-like opening	Corporal mucosa with chronic inflammation
C	Continuous short rod-like pits with slit-like opening	Normal mucosa with pyloric gland
D	Elongated and tortuous branch-like pits	Antral mucosa with chronic inflammation
E	Number of pits decreasing and pits prominently dilated	Chronic atrophic gastritis (sens 84%, spec 99%)
F	Villous appearance, interstitium in the middle and goblet cells	Intestinal metaplasia mucosa
G	Normal pits disappeared, appearance of diffusely atypical cells	Cancer (sens 90%, spec 99%)

Staging

Determining the extent of disease can be performed by appropriate diagnostic testing. Critical features in gastrointestinal lymphoma evaluation are depth of invasion, localization of lymphadenopathy, and hematogenous spread. In order to accomplish this investigation, a multimodal approach is applied with the use of imaging as well as biopsies to properly and fully stage the disease.

Already mentioned previously is the use of EUS to determine the depth of the lesion and assess invasion into other

structures as well as to identify the presence of locoregional gastric lymphadenopathy. Studies have demonstrated that EUS is superior to CT scan with higher sensitivity in detecting more subtle differences in gastric wall thickness and invasion into adjacent structures. Another added benefit is the EUS identification of suspicious lymph node involvement by tumor using established features such as rounded hypoechoic structure, sharp borders, and size >1 cm [26]. Unfortunately EUS has been shown to correctly classify lymphoma in only 53% of patients with sensitivity ranging between 67% and 83% for early-stage disease.

In order to improve PGL staging, additional radiographic modalities have been utilized. The most frequently utilized is a CT scan of the chest, abdomen, and pelvis. Particular attention is paid to the presence and location of lymphadenopathy with lymph nodes >1 cm likely harboring tumor. Suspicious areas of local tumor invasion into adjacent structures are characterized by thickening of the gastric wall, loss of natural tissue and fat planes, and stranding of the perigastric fat.

PGL tumors are metabolically active and thus demonstrate a strong avidity for FDG found during ^{18}F-FDG PET/CT imaging scans. Approximately 90% of primary gastric lymphomas demonstrate FDG uptake with a higher proportion of diffuse large B-cell (100%) versus MALT (71%) type [27]. In fact, higher SUVmax values have been associated with higher stage and overall worse survival on multivariate analysis [28]. Since the sensitivity is high, it can be helpful to detect submucosal disease that may not be appreciable on endoscopic evaluation and even biopsy. Thicker gastric wall lesions with high SUV values are more suggestive of lymphoma compared with gastric cancer. The addition of the ^{18}F-FDG PET beyond CT alone has improved accuracy of staging and can be found to help upstage or downstage. The pattern of gastric wall lesions characterized by ^{18}F-FDG PET/CT imaging can be classified into three types (Table 52.4). The majority of PGL are Type 1 and 2 (91%), whereas Type III is less common (10%) [29] (Table 52.5).

Table 52.4 ^{18}F-FDG PET/CT imaging gastric wall lesions

Type	Findings
I	Diffuse thickening of the gastric wall with increased FDG uptake involving more than 1/3 of stomach
II	Segmental thickening of gastric wall with less than 1/3 of stomach
III	Local thickening of gastric wall with focal FDG uptake

Table 52.5 Staging system of primary gastric lymphoma (Lugano, modified Ann Arbor, and TNM) comparison [30]

Lugano staging system for gastrointestinal lymphomas		Lugano modified Ann Arbor staging system for primary nodal lymphomas	TNM	Lymphoma extension
Stage I (limited to GI tract only)	I_1 mucosa, submucosa	I_E	T1N0M01	Mucosa, submucosa
	I_2 muscularis propria, serosa	I_E	T2N0M0 T3N0M0	Muscularis propria Serosa
Stage II (extending into abdomen)	II_1 local nodes	II_E	T_{1-3}N1M0	Perigastric lymph nodes
	II_2 distant nodes (below diaphragm)	II_E	T_{1-3}N2M0	Distant regional nodes
Stage IIE (involvement of adjacent organs)	II_E	II_E	T_4N0M0	Local invasion into other organs
Stage IV (hematogenous spread)	IV	IV	T1-4N3M0 T1-4N3M1	Lymph nodes on both sides of diaphragm Bone marrow or extranodal sites

Treatment

Prior to the development of affective chemotherapeutic regimens, surgery was the mainstay of treatment for all forms of primary gastric lymphoma. However, these tumors were discovered to be highly sensitive to the effects of radiation and chemotherapy, thus altering the paradigm in the role of surgery. A landmark controlled clinical trial was published in 2004 that compared several arms: surgery, surgery + radiation, surgery + chemotherapy, and chemotherapy alone (Fig. 52.2) [31].

The evidence has clearly demonstrated that medical therapy is the primary modality for treatment in uncomplicated primary gastric lymphoma. Surgery is typically reserved for complications related to advanced tumors that result in bleeding or perforation or for those patients who have residual disease despite chemotherapy and radiation therapy. Due to the strong association with *H. pylori* in particular MALT lymphoma, eradication of this bacteria is the first-line treatment when encountered regardless of stage. Antibiotic eradication of *H. pylori* is successful in up to 70% of patients [32]. Typical triple-therapy regimens combine a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole for 10–14 days. Urea breath test is used to check for eradication, and if necessary second-line treatment should be instituted with alternative regimens. While 70–90% of MALT lymphoma are *H. pylori* positive, the remaining 10–30% can still be treated with a trial of *H. pylori* eradication regimens but are certainly far less effective. It is theorized that these *H. pylori*-negative MALT are a result of a different bacterial infection with organisms such as *Helicobacter heilmannii* or *Helicobacter felis* and thus may be responsive to antibiotic therapy [33]. Those with t(11;18)(q21;q21) tumors have been found to have only a 5% response to antibiotic treatment, and therefore consideration can be made to treat with radiation [34]. The following table summarizes treatment based upon NCCN guidelines (Fig. 52.3).

Repeat evaluation by endoscopy with biopsy is necessary 3 months after completion of therapy unless symptoms of recurrent disease develop sooner. If *H. pylori* remains present in subsequent endoscopic evaluation, second-line antibi-

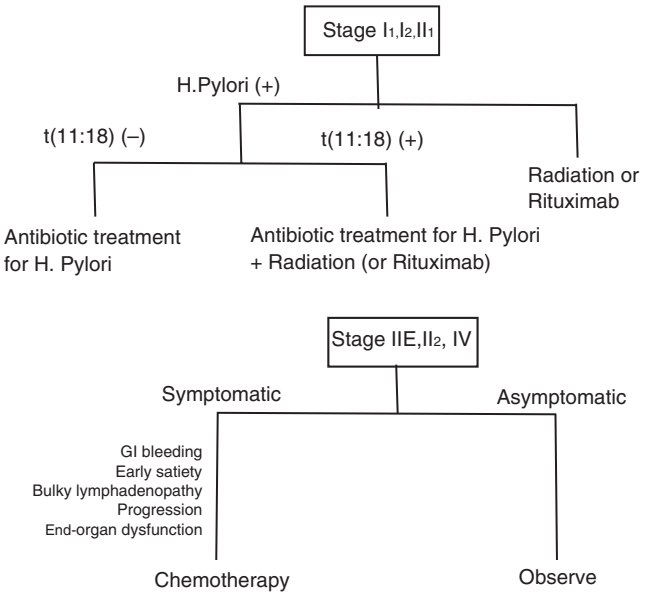

Fig. 52.3 NCCN 4.2021 guidelines for the treatment of gastric MALT lymphoma

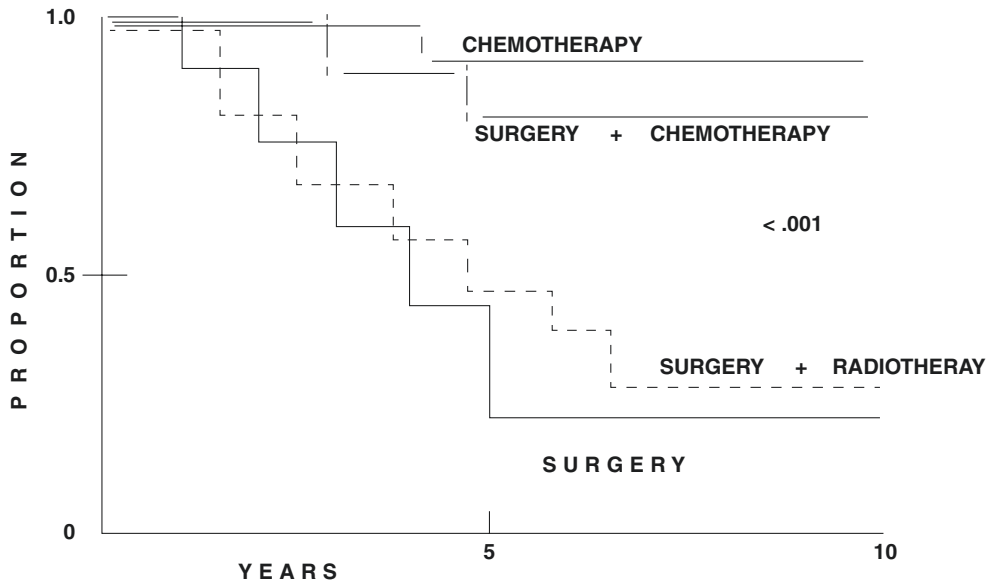

Fig. 52.2 Kaplan-Meier actuarial curves based upon treatment arms [32]

otic regimens are recommended. The presence of residual lymphoma warrants consideration of radiation therapy. Non-responsive tumors to both antibiotic and radiation therapy are amenable to treatment with chemotherapeutic regimens.

Chemotherapy

For patients with early-stage gastric MALT lymphoma related to *Helicobacter pylori*, appropriate antibiotic treatment with or without radiation would be the treatment of choice [35]. Rituxan as a single agent can be considered if radiation is contraindicated. An overall response rate of 77% including a complete remission rate of 44% can be achieved with 54% of the study population being disease free at a median follow-up of 28 months according to a small study of 26 patients with gastric marginal zone lymphoma [36].

For advanced stage disease, conventional treatment will not provide a cure. Therefore, patients are often observed if they are relatively asymptomatic. Chemotherapy treatment is directed toward symptoms. Indications for treatment would include GI bleed, threatened end-organ function, bulky disease or rapidly progressive disease, or other patient-reported symptoms. The principles of chemotherapy would be similar to that for other types of marginal zone lymphoma. The choice of chemotherapy treatment is highly individualized requiring consideration of many factors, including patient characteristics, comorbid conditions, and plans for subsequent treatment.

Prior to initiating systemic treatment, prophylaxis for tumor lysis syndrome should be implemented. Screening for hepatitis B is needed, and entecavir treatment initiated if positive, prior to treatment with anti-CD20 antibodies [37, 38].

First-Line Chemotherapy for Advanced Stage Disease

The preferred first-line treatment choices would include BR (bendamustine and rituximab), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone).

BR has been shown to provide a non-inferior progression-free survival when compared to R-CHOP or R-CVP in previously untreated indolent lymphoma according to the randomized phase III StiL NHL1 [39] and BRIGHT [40] trials. Toxicity from this treatment would include bone marrow suppression, skin rash, nausea, and vomiting. Smaller trials specifically studying marginal zone lymphoma also demonstrated the efficacy of BR. The phase II MALT2008-01 trial enrolled 60 patients with previously untreated MALT lymphoma, including 20 patients with gastric MALT lymphoma [41]. The overall response and complete response rates were 100% and 98%, respectively. The 7-year event-free survival was 88% for all patients.

In a phase II study of 40 patients with previously untreated advanced marginal zone lymphoma, R-CVP demonstrated an overall response rate of 88%, including 60% complete remission [42]. Progression-free survival and overall survival at 3 years were 59% and 95%, respectively.

As a consolidation or maintenance strategy once maximum response is achieved with rituximab-based immunochemotherapy, extended treatment with rituximab one dose every 8–12 weeks for up to 2 years can be considered [43].

Efforts to identify an ideal anti-CD20 antibody in combination with chemotherapy have been the subject of clinical investigation. In a randomized trial comparing obinutuzumab with rituximab in combination with chemotherapy (bendamustine, CHOP, or CVP) in 198 previously untreated patients with advanced stage marginal zone lymphoma, no meaningful differences in overall response rate or progression-free survival were observed after a median follow-up of 38 months [44]. Adverse events were higher in the obinutuzumab arm, such as bone marrow suppression and infections. Therefore, immunochemotherapy containing obinutuzumab is not recommended as first-line treatment for patients with marginal zone lymphoma.

Other treatment options would include the ibritumomab tiuxetan radioimmunotherapy which targets CD20 with radioactivity. In a phase II study with 16 untreated marginal zone lymphoma patients, this treatment program resulted in an overall response rate of 88% including 50% complete remission [45]. The median progression-free survival was 48 months, and the median overall survival was not reached after 66 months of follow-up. The 5-year progression-free survival and overall survival were 40% and 72%, respectively. Bilateral bone marrow sampling was recommended prior to treatment with ibritumomab tiuxetan due to the increased risk of subsequent myelodysplastic syndrome.

Another reasonable option in the first-line setting is lenalidomide and rituximab. The multicenter AGMT MALT-2 phase II trial enrolled 46 patients with gastric and non-gastric MALT lymphoma [46]. It demonstrated an overall response rate of 80%, including 54% complete response.

Second and Subsequent Lines of Chemotherapy

For patients with relapsed and refractory disease, treatment options will include immunochemotherapy regimens (see previous section) not yet used in the first-line setting, as well as BTK and PI3K inhibitors.

Although not generally favored in the treatment-naïve patient population, obinutuzumab is efficacious in the second-line setting. The 413-patient GADOLIN study compared bendamustine and obinutuzumab combination versus bendamustine alone [47]. The trial included 47 patients with marginal zone lymphoma who were not previously exposed

to bendamustine. After a median follow-up of 32 months, the median progression-free survival was 26 versus 14 months in favor of the combination group. Once maximum response is reached, consolidation or maintenance with extended obinutuzumab can be considered [48].

The BTK inhibitor ibrutinib was studied in a multicenter phase II study including 60 patients with relapsed and refractory marginal zone lymphoma [49]. Toxicities of ibrutinib would include diarrhea, fatigue, and anemia. Bleeding events and new-onset atrial fibrillation have been reported with this treatment. Overall response rate was 48% with a median progression-free survival of 14 months after a median follow-up of 19 months. An overall survival of 81% was reported at 18 months.

The PI3K inhibitors idelalisib, copanlisib, duvelisib, and umbralisib have been shown to be active in the relapsed and refractory setting. Unusual toxicities such as hepatitis, colitis, pneumonitis, dermatitis, and opportunistic infections have been reported with these treatments. Idelalisib was reported to produce an overall response rate of 47% in a subgroup of 15 patients with relapsed marginal zone lymphoma in a phase II study [50]. Copanlisib was studied in a phase II trial including 23 patients with relapsed or refractory marginal zone lymphoma [51]. The objective response rate was 70% including 9% complete response. The phase II DYNAMO trial studied duvelisib in indolent lymphoma patients who have received prior treatment with both rituximab and chemotherapy or radioimmunotherapy [52]. The overall response rate was 39% in the marginal zone lymphoma subgroup. The progression-free survival for the study population was around 10 months. A 208-patient phase IIb trial studied the dual PI3Kδ/CK1ε inhibitor umbralisib in patients with relapsed or refractory indolent lymphoma [53]. Among 69 patients with marginal zone lymphoma, the overall response rate was 49% including 16% complete response. The median progression-free survival was not reached after a median follow-up of 28 months.

Similarly, the radioimmunotherapy agent ibritumomab tiuxetan has been shown to be an active treatment option [54].

Treatment Options for Elderly or Infirm Patients

Rituximab as a single agent is the preferred first-line or subsequent treatment for elderly or infirm patients. Rituximab plus chlorambucil can also be considered a reasonable option. This treatment is well tolerated with low levels of adverse events. In the randomized IELSG-19 trial, this combination provided significantly better event-free survival compared to either rituximab or chlorambucil alone [21, 55]. After a median follow-up of 7 years, the 5-year event-free survival was 68% for the combination group, compared to 51% and 50% for either chlorambucil or rituximab alone, respectively. Second and subsequent treatment options for the elderly or infirm patients would include ibrutinib [49], lenalidomide plus rituximab [46], or umbralisib [53].

Histologically Transformed or High-Grade Lymphoma

Histological transformation of marginal zone lymphoma into a higher-grade lymphoma occurs at a rate of 3–5% per year. It is invariably associated with a poor clinical outcome. Risk factors for histological transformation include high international prognostic index (IPI) score, high LDH, multiple sites of disease, and failure to achieve complete remission after initial therapy [56]. The optimal treatment strategy is unknown since these patients are often excluded from randomized trials.

Diffuse large B-cell lymphoma can coexist with gastric MALT lymphoma, or it can involve the stomach primarily. Chemotherapy treatment is typically similar to that for early-stage nodal diffuse large B-cell lymphoma. In addition to prophylaxis for tumor lysis syndrome and screening and treatment for hepatitis B if positive, assessment of cardiac function with either echocardiogram of MUGA is needed in anticipation of doxorubicin-based chemotherapy. Upfront treatment is typically R-CHOP for three cycles followed by involved site radiation [57, 58]. R-miniCHOP (reduced chemotherapy dose with conventional rituximab dose) can be considered for elderly and frail patients [59].

For patients with refractory or relapsed disease, numerous salvage chemotherapy treatment options are available depending on goals of treatment and plans for subsequent treatment, including high-dose chemotherapy with autologous stem cell rescue, allogeneic hematopoietic cell transplant, and anti-CD19 CAR T-cell therapy. Available trial results are not specific for gastric lymphoma, and a detailed discussion would be beyond the scope of this chapter.

Radiation Therapy

While medical management is generally the first treatment modality for *H. pylori*-associated gastric lymphomas, radiotherapy remains an effective second-line therapy. Sixty-eight percent of gastric MALTs are cleared after eradication of the bacterium. For those refractory to eradication or independent of *H. pylori* infection, involved-field radiotherapy (IFRT) treating the entire stomach/gastric mucosa to 30 Gy has become the current standard of care in gastric MALT for over two decades, reserving partial or total gastrectomy as a later salvage approach. A 2021 single institutional review of 178 patients treated with radiotherapy in this manner demon-

strated 95% complete response rate and <10% local recurrence rate [60]. A smaller investigation in the same year evaluated 41 patients treated with radiotherapy for gastric MALT, with 16 receiving reduced dose (mean 24 Gy) [61]. Though the patient numbers are small, complete response and freedom from treatment failure were numerically greater in the reduced dose group compared to conventional dose (30–36 Gy in this study; 94% vs. 81% and 100% vs. 92%, respectively), though there was no significant difference between groups. Organs at risk for radiation injury (notably, liver and heart) received less radiation dose in the reduced dose group. Thus, there may be an opportunity for dose reduction to minimize acute and long-term toxicities. Similarly, other lower-grade NHL which can occur in the stomach though are less common, such as low-grade follicular lymphomas, are curable with 24 Gy, whereas palliation can be achieved with as little as 4 Gy.

Diffuse large B-cell lymphomas make up the greatest portion of gastric lymphomas, and while systemic therapies previously discussed are the mainstay of treatment, radiotherapy remains an excellent salvage option for treatment of refractory disease or in cases where full-course chemotherapy cannot be delivered. Doses of 30 Gy are generally effective, with higher doses considered for refractory disease (36 Gy). The ability to escalate dose further in this setting is limited due to poor tolerance of the gastric mucosa to higher doses of radiation.

Radiation doses used to treat gastric lymphomas are generally well tolerated, though modern radiotherapy techniques have an opportunity to further improve tolerance to therapy. 4D computed tomography imaging (4DCT), which evaluates motion during simulation for treatment planning, allows for reduced treatment volumes as motion is individually assessed and accounted for with each patient. In addition, intensity-modulated radiotherapy (IMRT) allows for high-dose conformity while limiting dose to surrounding organs sensitive to radiation. These techniques allow for personalized treatment plans that further improve the tolerability and safety of radiation treatments. While serious side effects from radiotherapy are rare, acute nausea may occur with irradiation of the gastric mucosa even at low doses and can be managed with common antiemetics administered prior treatment (e.g., ondansetron or prochlorperazine). Patients are routinely prescribed a proton pump inhibitor for daily use during radiotherapy to reduce risk of gastritis and reflux-like symptoms.

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Part VII

Obesity and Metabolic Disease

Laparoscopic and Robotic Sleeve Gastrectomy

53

Collin E. M. Brathwaite, Raelina S. Howell, Jun Levine, Maxime Lapointe-Gagner, and Michel Gagner

Objectives

1. Describe the mechanism and indications for sleeve gastrectomy.
2. Discuss the preoperative and postoperative care of patients who undergo sleeve gastrectomy.
3. Detail the operative technique for laparoscopic and robotic sleeve gastrectomy.
4. Review common postoperative complications of sleeve gastrectomy.
5. Give an overview of performing a sleeve gastrectomy in special patient populations.

Introduction, Definition, Incidence/Prevalence

Epidemiology, Pathophysiology/Mechanism

Laparoscopic sleeve gastrectomy (SG) as a bariatric procedure was initially described in 1999 as part of a laparoscopic duodenal switch and then performed as a two-stage procedure for high-risk patients, the initial stage of a duodenal switch in 2000. SG was approved by the ASMBS as a standalone bariatric procedure in 2008 and has since gained popularity and frequency over the years become the most performed bariatric/metabolic intervention worldwide, with >75% of all primary procedures in USA, due to its positive effect on excess weight loss and resolution of comorbidities. SG is a restrictive and hormonal modification procedure that transforms the stomach into a tubular conduit, lessens the patient's caloric intake, and decreases serum ghrelin and raises GLP-1 and PYY 3-36. Weight loss is also achieved due to early satiety triggered by vagally mediated proximal gastric stretch receptors. In comparison to other bariatric procedures, SG is a technically simpler procedure that preserves the pylorus (reduces dumping syndrome) and may alter the microbiome. While it is irreversible, it reserves the ability to be converted to another bariatric procedure should the need arise. SG has been shown to have fewer mortality and complications with comparable EWL of >50% at 3–5 years as Roux-en-Y gastric bypass.

Indications and Patient Selection

The National Institute of Health and a recent International Consensus Conference listed the following indications for SG: patients with a body mass index (BMI) 30–34 with type 2 diabetes that is difficult to control with medical therapy and lifestyle modification, BMI 35–39 with serious comorbidities (e.g., heart disease, sleep apnea, type 2 diabetes), BMI >40, morbidly obese patients with metabolic syndrome, elderly patients with morbid obesity, adolescents, transplantation recipients and donors, and patients with inflammatory bowel disease. Relative contraindications included Barrett's esophagus, large hiatal hernias, and severe gastroesophageal reflux disease. However, these ASMBS-IFSO endorsed guidelines have recently changed to include individuals with a body mass index(BMI) of 35kg/m^2, regardless of presence,

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absence, or severity of co-morbidities. Sleeve gastrectomy should be considered for individuals with metabolic disease (not just type-2 diabetes) with a BMI of 30–34.9 kg/m^2. BMI thresholds should be adjusted in the Asian population such that a BMI >25 kg/m^2 suggests clinical obesity, and individuals with BMI >27.5 kg/m^2 should be offered sleeve gastrectomy.

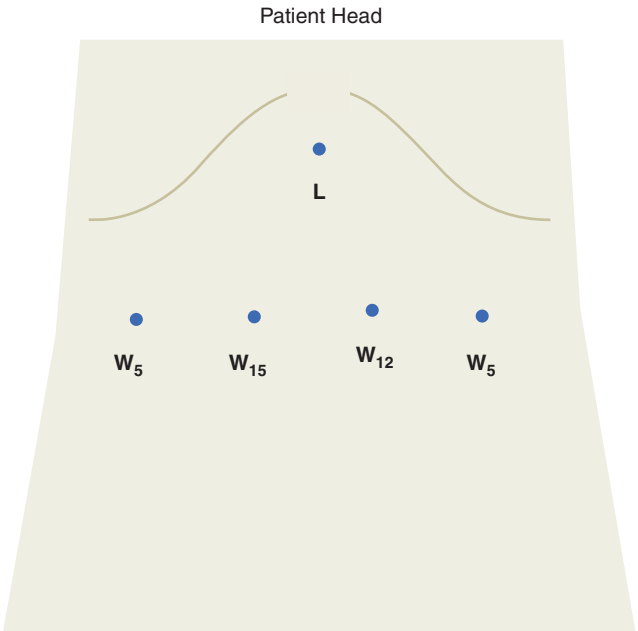
Preoperative Evaluation

Extensive preoperative assessments should be performed, including nutritional and psychological evaluations. Smoking cessation is recommended for a minimum of 6 weeks prior to bariatric procedures, and confirmatory testing can be performed using carboxyhemoglobin and nicotine levels. Oral contraceptive pills were held 1 month prior to and 1 month following surgery. Females of child-bearing age should avoid pregnancy for a minimum of 18 months postoperatively. Patients with a known hyper-coagulable state should be referred to a hematologist for evaluation prior to surgery. In patients with diabetes, insulin secretagogues can be held, and injectable insulin given accordingly. Prophylaxis against deep vein thrombosis (DVT) includes preoperative use of one dose of 5000 units of low-molecular-weight heparin injected subcutaneously in combination with external, bilateral lower-extremity intermittent pneumatic compression. Postoperatively, daily enoxaparin sodium injections should be used along with early and frequent ambulation. Consideration should be given to continued DVT prophylaxis following discharge in patients with a BMI >50 kg/m^2.

Technical Considerations

Laparoscopic Technique

Patients are placed supine and secured to the operating table with arms tucked and appropriately padded. Sequential pneumatic compression stockings are placed on the bilateral lower extremities, and a supporting footboard is attached in anticipation of the reverse Trendelenburg position. Alternatively, patients may be placed on the split leg table with the surgeon standing between the legs. After induction of general anesthesia and sterile draping of the abdomen, local anesthesia with 0.25% bupivacaine and 1% lidocaine in 50:50 mixture is injected prior to all incisions. Pneumoperitoneum is established to a pressure of 15 mmHg either using a Veress needle in the left upper quadrant at Palmer's point (3 cm below the costal margin in the midclavicular line) or with an optical 12-mm trocar placed one-third the distance between the xiphoid and the umbilicus to the left of the midline or with an open technique in the umbilicus (safest technique). An open epigastric substernal transverse incision may be used in patients who had multiple upper abdominal open operations, to insert the first trocar under direct vision. A bilateral transversus abdominis plane (TAP) block is frequently performed under laparoscopic visualization using 30 cc of 0.5% bupivacaine mixed with saline. Under direct visualization, four other trocars are placed: a 5-mm trocar subxiphoid, right and left upper quadrants, and a 15-mm trocar in the right upper quadrant. Trocar placement for laparoscopic sleeve gastrectomy is shown in Fig. 53.1. In an open umbilical trocar technique used, the 15-mm trocar is positioned there.



L · Liver retraction port, 5 mm
W_5: Working trochar port, 5 mm
W_{10}: Working trochar port, 10 mm
W_{12}: Working trochar port, 12 mm

Fig. 53.1 Laparoscopic port placement for sleeve gastrectomy

The patient is then placed in a steep reverse Trendelenburg position with the surgeon standing on the patient's right side. The left lobe of the liver is retracted cephalad with a self-sustaining liver retractor. Alternatively, if there is not a very large left lobe of the liver, a 5-mm grasper may be placed via the subxiphoid port under the liver and attached to the superior aspect of the right crus of the diaphragm to facilitate exposure of the stomach and the GE junction. After visualizing the angle of His and fat of Belsey, the hiatus is inspected for the presence of a hiatal hernia. A calibrating 40-French bougie or orogastric tube is placed and directed along the lesser curvature. A calibration tube is inserted prior to staple firing to avoid an overly narrow sleeve, to ensure adequate distance from the incisura angularis, and to assist in mobilization of the gastric fundus. Larger calibration sizes (median 36-French) are being used to avoid strictures and their associated staple line leaks. Full mobilization of the greater curvature of the stomach is achieved by dividing the omentum and short gastric vessels with 5-mm ultrasonic shears or bipolar energy device starting 4 cm proximal to the pylorus and progressing all the way up to the angle of His. Care is taken to avoid avulsion or injury to the spleen or major splenic vessels. Titanium clips should be used liberally for larger short gastric vessels, especially near the upper splenic hilum. Bleeding branches from the gastro-epiploic arcade may need suturing with an absorbable monofilament 3-0, on the arcade itself. The stomach is then divided beginning with one or two applications of the thick-tissue black load stapler with some form of buttress material (Peri-strips Dry® with Veritas®, Baxter Healthcare Corporation, or GORE® SEAMGUARD® Bioabsorbable Staple Line Reinforcement or Endo GIA™ Reinforced Reload with Tri-Staple™ Technology, Medtronic, or ECHELON ENDOPATHTM Staple Line Reinforcement) for reinforcement, which is introduced into the 15-mm right upper quadrant trocar. Next, the medium-tissue blue (or purple) load stapler with buttress material reinforcement is inserted into the 12-mm left upper quadrant trocar, parallel to the calibration tube, and repeated firings are used to complete the creation of a longitudinal calibrated sleeve. The stapling may also be continued via the 15-mm trocar with the use of articulation. Care is taken to place the staple line adequately away from the calibration tube to avoid narrowing the stomach or having the bougie get caught between the staple jaws compromising the stapling. The surgeon should also insure that the staple line is straight with equal amounts of stomach anteriorly. Varying staple heights along the sleeve are now being addressed with a movement toward using taller staples with buttress reinforcement along the antrum and when thicker gastric tissue is encountered. The calibration tube is then withdrawn to above the gastroesophageal junction; a leak test is performed by instilling methylene blue at a high pressure to facilitate full distention of the stomach with close inspection of the staple line. Distention with air or visualization with intra-operative endoscopy is also an option for testing for leaks. Bleeders on the staple line from lesser curvature visible branches are oversewn with an absorbable monofilament 3-0. The resected portion of the stomach is then placed in a 15-cm bag and retrieved under direct visualization from the 15-mm right upper quadrant trocar. The 15-mm trocar site is closed with trans-fascial absorbable suture using a suture passing device under direct visualization, and the abdomen is inspected a final time to ensure hemostasis.

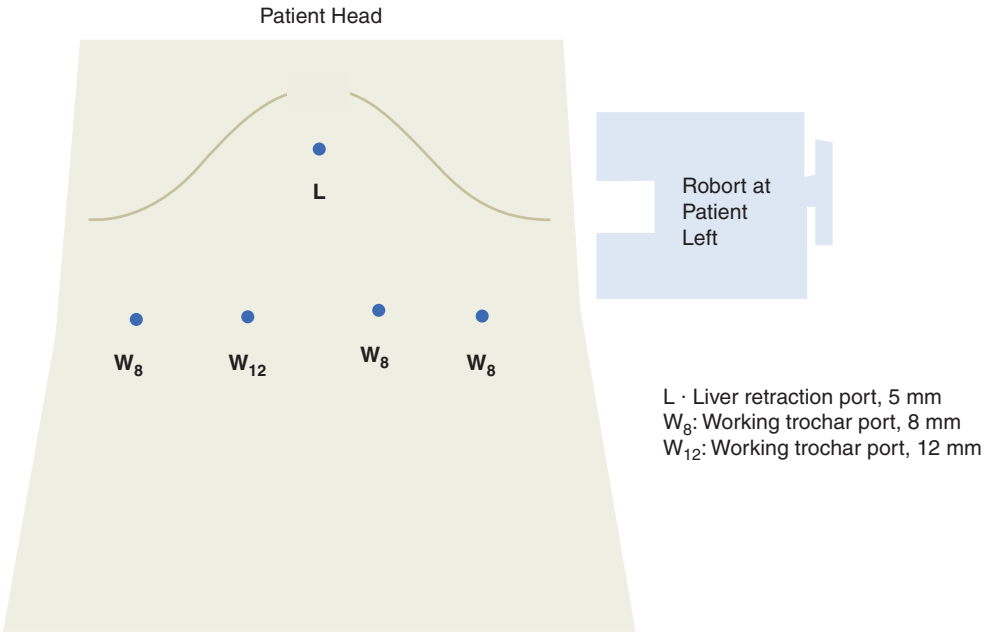


Fig. 53.2 Trocar placement for robot-assisted sleeve gastrectomy using the da Vinci Xi Robot

Robotic

The patient is placed supine similar to the laparoscopic positioning described above; however, the arms are placed abducted on arm boards and secured in a neutral position. Access to the abdomen and insufflation are performed as above. Trocar entry to the abdominal cavity is obtained through an 8-mm incision in the left mid-clavicular line in the epigastrium via an optical trocar under direct visualization. Pneumoperitoneum is achieved to a pressure of 15 mmHg, and a bilateral TAP block performed. Three additional ports are then introduced into the peritoneal cavity, one 12 and two 8 mm in the upper abdomen in a linear fashion. Trocar and robot placement is depicted in Fig. 53.2.

Once the trocars and liver retractor are placed, the da Vinci Xi robot was docked as per institution protocol, and upper abdominal anatomy was targeted. Dissection and mobilization of the stomach are performed in a similar fashion as above. One of the robotic arms may also be used for liver retraction. The greater curvature of the stomach is then divided with black, green, or blue 60-mm robotic stapler reinforced with buttressing material. The specimen is retrieved using a laparoscopic bag and removed via the 12-mm port site, which can be dilated. The 12-mm port site fascia is closed using a suture passer under direct visualization, and the abdomen is inspected a final time to ensure hemostasis.

Concomitant Hiatal Hernia Repair

After visualizing the angle of His and fat of Belsey, the hiatus is inspected for the presence of a hiatal hernia. The pars flaccida is divided and the right crus of the diaphragm is dissected free from attachments using a combination of blunt and sharp dissection while avoiding injury to the esophagus, stomach, and surrounding structures. This maneuver is repeated on the left crus as well. It is often easier to perform the division of the greater curvature vessels and short gastric vessels completely freeing up the left crus prior to moving to the right side. The hiatus is circumferentially dissected free from all the attachments so that the two crus of the diaphragm are skeletonized. The anterior and posterior vagus nerves are identified and preserved. Injury to the aorta is also avoided. The esophagus is gently dissected free from the mediastinum circumferentially so that 4–5 cm of the esophagus is mobilized intra-abdominally and without tension. The hernia sac is reduced with the stomach. The left and right crus are approximated posteriorly with the 40-French calibrating tube in place, using barbed, nonabsorbable suture in a running fashion. Permanent sutures with pledgets attached may also be utilized. Upon completion of the hiatal hernia repair, the hiatus is inspected for easy mobility of the esophagus.

Conversion to Sleeve Gastrectomy

When performing laparoscopic conversion from gastric band to sleeve gastrectomy, ports are placed as shown in Fig. 53.1. Adhesiolysis of the gastric band is performed using ultrasonic shears, followed by band unbuckling and extraction, along with removal of the tubing. The gastric fundoplication is then divided using sharp dissection with careful use of an energy device or with a stapler and articulating dissector if the stomach appears thickened. A calibrating 40-French tube is positioned along the lesser curvature. Ultrasonic shears are then used to divide the gastro-colic omentum and short gastric vessels up to the angle of His, and the stomach is divided using a thick-tissue black load stapler with buttress material reinforcement. A thick-tissue black load was used for the first two staple firings in the antrum, followed by a green load up to the angle of His, crossing the staple lines to reduce the incidence of leak. Conversion procedures include key steps in an effort to decrease morbidity: staple lines are oversewn and/or reinforced with buttress material in high-risk patients, and precaution is taken to avoid stapling or anastomosing into gastric band-induced scar capsule tissue. Attention is made to staple away from the area of scarring due to the relative ischemia of the fibrotic tissue. For robotic cases, 8-mm robotic trocars are used in place of 5-mm laparoscopic ports.

Outcomes

Postoperative Considerations

Postoperatively, the patients are started on a low-sugar, clear liquid diet with supplemental crushed or liquid medications as necessary. Even though many institutions have moved away from the use of routine postoperative upper gastrointestinal swallow studies following uncomplicated, primary bariatric procedures, they are still used for patients undergoing bariatric conversions due to the complexity and morbidity associated with the operation.

Complications include staple line leak, bleeding, and stricture. Tachycardia is a cardinal sign that alone may herald a complication, but particularly when seen in conjunction with fever and leukocytosis. Staple line leaks have been attributed to smaller bougie sizes resulting in higher sleeve pressures and tend to occur in the proximal one-third of the stomach. Leaks are divided into acute (<7 days) and chronic. Management of acute leaks includes nil per os, total parenteral nutrition, antibiotics, endoscopic double pigtails drain insertion in the opening, stenting, over the scope metal clip and percutaneous drain placement, and/or laparoscopic drainage and feeding jejunostomy. Chronic leaks are often managed with conversion to gastric bypass; however,

options include re-sleeve, total gastrectomy, and Roux-en-Y fistulojejunostomy. Stricturing or stenosis, typically at the incisura angularis, secondary to a twist or too aggressive stapling, may be treated with endoscopic dilatation (sometimes repetitive) with an achalasia balloon at controlled pressure and/or stenting. De novo development of GERD following sleeve gastrectomy has also been extensively studied. Early data suggested that SG may worsen pre-existing GERD, and Roux-en-Y gastric bypass may be performed as a salvage procedure; however, newer data may suggest that rates of both de novo and worsening GERD following SG may be low. Patients should be well informed of the risks of postoperative symptoms, especially in those with pre-existing GERD, and further study is needed due to conflicting data to date.

SG has been consistently shown to result in improvement of weight-related comorbidities. Postoperatively, patients experience improved glycemic control and renal function, weight loss, higher quality of life scores, and reduction of medication use for type 2 diabetes, hypertension, obstructive sleep apnea, and dyslipidemia, with many studies showing sustained results at 5-year follow-up. Disadvantages of SG, the fact that it is a non-reversible procedure, include a potential for long-term vitamin deficiencies and higher early complication rate than gastric banding. SG may require conversion to RNY, SADI (single anastomosis duodeno-ileostomy), or full DS, if patients achieve insufficient weight loss.

Postoperative pain control is imperative in the bariatric population. Many institutions have implemented enhanced recovery after surgery protocols that focus on multimodal, reduced opioid therapy. Patients are encouraged to ambulate early and frequently with aggressive incentive spirometry to decrease pulmonary complications. Patients are typically stable for discharge within 1–2 days postoperatively and follow-up in the surgeon's office in 1–2 weeks. Subsequent visits are scheduled at 6 weeks, 3 months, 6 months, and 1 year.

Healthcare Costs

Reducing weight loss surgery care costs is important since more than 300,000 patients undergo these interventions annually in the USA and more than half a million worldwide (8000,000 pre Covid in 2019). A recent study by Murtha JA et al. comparing laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass from 2012 to 2017 identified costs incurred from the time of entering the preoperative unit until exiting the postanesthesia care unit. They studied 546 bariatric surgery patients with a mean age of 49.7 years and BMI of 45.9 kg/m^2, respectively. There were no significant differences in median perioperative costs between sleeve and bypass ($14,942 versus $15,016; $P = 0.80$). The surgical disposable stapler was the largest cost contributor for both operations, accounting for 27.7% and 29.2% of costs for sleeve and bypass, accordingly. In multivariable analyses, preoperative patient variables and BMI were not linked with higher cost.

However, the costs differ after leaving the acute care facility, and Callaway K et al. have used a national insurance claims database to identify adults undergoing sleeve gastrectomy and gastric bypass between 2008 and 2016. The matched cohort included 4263 sleeve gastrectomy and 4520 gastric bypass patients. SG patients had slightly lower risk of emergency department visits and hospitalizations, especially for events associated with biliary and gastrointestinal ailments. SG patients also had lower odds of high emergency department and high total acute costs, but this difference would lesser toward the fourth year and may decreased further over time.

Specific Considerations

Super super obese patients (BMI >60) pose a challenge to management and represent the patient population who most require surgical intervention. High-volume bariatric surgery centers have reported better outcomes in managing super super obese patient population when compared to centers that perform these procedures infrequently. This population may benefit from an aggressive preoperative diet over several weeks and use of GLP-1 receptor agonists, to decrease 10–15% of their initial weight. It has been shown that SG is most appropriate to be performed first and avoid intestinal surgery, when the anastomosis maybe under tension from a large mesentery.

Revisions and conversions have now become a significant part of bariatric surgery. Revisional bariatric surgery is a recreation of the original procedure, and conversion is a change from one procedure to another (e.g., gastric band to sleeve). Bariatric revision procedures are indicated for patients with inadequate weight loss, defined as less than 50% of excess weight loss at 18 months, or for patients with weight regain, comorbidity recurrence, or procedure-associated morbidities. Conversion from a failed gastric band to a SG can be performed in one- or two-stage procedure; however, there is currently no consensus in the literature regarding the optimal choice. Complications of conversions have been reported as high as 46%. Conversion from gastric band to SG has been associated with a lower complication rate than conversion to RNY, which is thought to be due to the decreased procedural complexity, fewer anastomoses, and less intra-abdominal manipulation. Overall, conversion can be performed safely, but careful consideration must be given in high-risk patients.

Dietary and exercise limitations of congestive heart failure (CHF) increase the difficulty of treating morbid obesity. Cardiac remodeling following bariatric surgery and subsequent weight loss has been well documented, and most studies show that bariatric surgery is safe and efficacious in patients with CHF and cardiac disease. Benefits include a reduced risk of cardiovascular events, improved symptomatology, increased left ventricular function and diastolic filling, and decreased left ventricular mass. Sleeve gastrectomy is particularly favored in patients with CHF due to the lower complication rate compared to Roux-en-Y gastric bypass; however, risks and benefits must be carefully weighed prior to operation.

Pulmonary embolism (PE) remains a leading cause of death after bariatric surgery. While there are clear guidelines from the American Society for Metabolic and Bariatric Surgery on the issue and need for DVT prophylaxis, no universally accepted protocol exists for the peri-operative management of patients undergoing bariatric surgery, particularly in those with a history of DVT or PE. Recent large study of over 500,000 bariatric patients showed a VTE rate of 2.2%, with a PE and DVT rate of 0.9% and 1.3%, respectively. This shows that the problem is large, but the exact solution is not clear.

The prevalence of morbid obesity is increasing among adolescent patients, and a strong predictive correlation exists between adolescent and adult obesity. Bariatric surgery in the adolescent population has been shown to be safe and effective with a mean EWL of 26–28% over 3 years. However, long-term follow-up is highly recommended due to the risk of developing nutritional and vitamin deficiencies. Most surgeons recommend performing the operation after the patient's growth spurt. Long-term data is needed to delineate which, if any, procedure is associated with higher efficacy in this population. Conversely, morbid obesity among the elderly population (age >65) is also rising. Overall, bariatric surgery has been shown to be safe and effective in older adults. Preoperative evaluation should focus on the functional status, life expectancy, and physiologic reserve.

Conclusions

The sleeve gastrectomy is an established safe and effective primary bariatric procedure. Its popularity has risen exponentially to the extent that it is used as a metabolic procedure in type 2 diabetes patients and can be converted to other intestinal procedures for additional efficacy. Although SG is technically less complex than RNY, there are several points of technique which should be adhered to in every patient, like paying attention to the compression time of the stapler, the first and the last stapler firings should prevent excessive narrowing, avoid twisting, and including too much tissue into the stapler. Emphatically, the hiatus should be inspected purposefully, and if present, hiatal hernia should be repaired immediately.

Questions

1. All the following characteristics are true regarding sleeve gastrectomy *except*:
   A. It is a restrictive and metabolic bariatric procedure
   B. Weight loss is in part achieved by vagally mediated gastric stretch receptors
   C. It is a reversible procedure
   D. It can be safely performed in adolescents

Answer: C. Sleeve gastrectomy is an irreversible, restrictive bariatric procedure.

2. Which of the following is not an indication for sleeve gastrectomy?
   A. BMI <30
   B. Metabolic syndrome and obesity
   C. BMI >40
   D. Failure to achieve adequate weight loss after gastric banding

Answer: A. Sleeve gastrectomy should be considered in patients with a body mass index (BMI) 30–34 with type 2 diabetes that is difficult to control with medical therapy and lifestyle modification, and recommended for individual with BMI 35–39 with comorbidities (e.g., heart disease, sleep apnea, type 2 diabetes), BMI >40, morbidly obese patients with metabolic syndrome, elderly patients with morbid obesity, adolescents, transplantation recipients and donors, and patients with inflammatory bowel disease.

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Laparoscopic and Robot-Assisted Roux-en-Y Gastric Bypass

54

Kelly Andrew Lara, Esther Wu, and Yong Choi

Objectives

1. Understand mechanisms and pathophysiology of morbid obesity.
2. Understand the comorbidities associated with obesity and their consequences.
3. Understand indications and key contraindications to bariatric surgery and specifically to the Roux-en-y gastric bypass (RNYGB).
4. Understands pros and cons to RNYGB.
5. Know the key steps RNYGB via a minimally invasive approach.
6. Understanding, identifying, and approaching short- and long-term complications of this surgery.

Introduction

Epidemiology

Morbid obesity has become one of the most important disease processes in the modern era. As a society, both nationally and globally, we are amid a medical crisis in which the incidence and prevalence of morbid obesity continue to rise. Consequently, sequelae of obesity and comorbid conditions continue to increase as well. Obesity plays a central role in a multitude of metabolic conditions such as hypertension, dyslipidemia, sleep apnea, diabetes mellitus, and many more. There are more than 40 distinct medical conditions linked to obesity. These comorbidities further cause damage through dramatic dysfunction of almost every organ system.

The World Health Organization classifies obesity as a function of the body mass index (BMI—kg/m^2) (Fig. 54.1).

In 2018, the Centers for Disease Control and Prevention reported the overall prevalence of obesity to be 42.4% in the United States. They also reported a gradual, but significant, linear increase in incidence over the last 20 years (Fig. 54.2).

In recent years, this has been somewhat under scrutiny, as there can be a substantial variation in BMI in healthy individuals. For instance, BMI does not apply well to individuals with large muscle mass. However, once in the morbid obesity category, especially in conjunction with obesity-related comorbidities, the benefit of bariatric surgery is undeniable.

WHO BMI classification	
Underweight	< 18.5
Normal range	18.5–25
Overweight	≥ 25
Obese	≥ 30
Class 1 obese	30–34.9
Class 2 obese	35–39.9
Class 3 obese	≥ 40

Fig. 54.1 Classification of obesity by the World Health Organization

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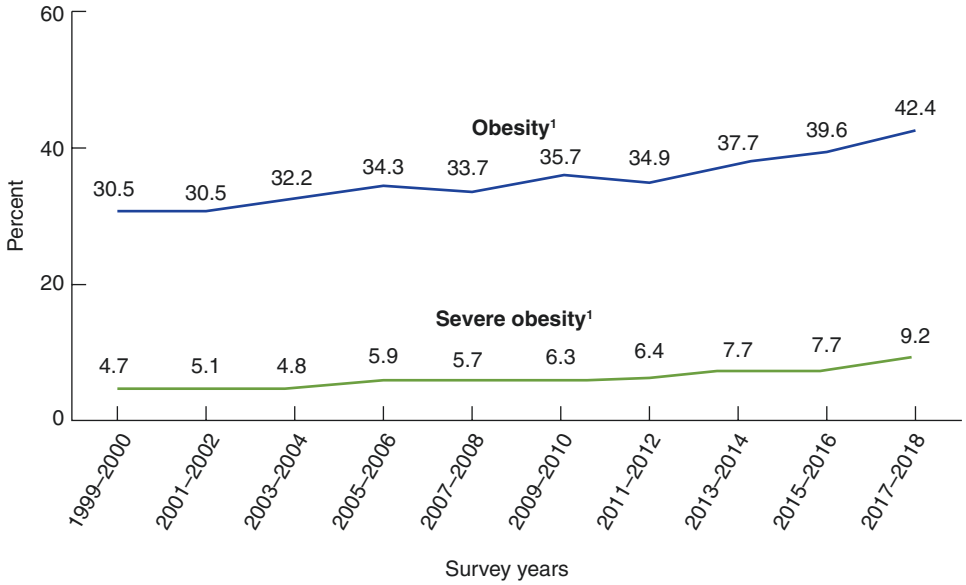

Fig. 54.2 Increasing incidence of obesity and severe obesity in the United States from 1999 to 2018. (Source NCHS, National Health and Nutrition Examination Survey [1])

Pathophysiology

A thorough discussion of the evolution of our current understanding of the pathophysiology of morbid obesity is out of the scope of this discussion. It is a complex interaction of environmental, behavioral, genetic, and epigenetic factors that can be influenced by both voluntary and involuntary input.

The primary center of regulation of this complex system is the hypothalamic feeding center (HFC). The HFC is regulated by a multitude of adipokines, gut hormones, and cytokine which fluctuate in response to alternative states of fasting and feasting. The first of these to be well described and studied was leptin.

Leptin is categorized as an adipokine and is rightfully produced primarily by adipocytes. When the body is in a feasting state, it sends positive signals through first-order and second-order neurons in the HFC to induce an anorexigenic state, catabolism, and satiety. It simultaneously downregulates orexigenic and anabolic signals [2].

Conversely, leptin's well-known counterpart ghrelin has an opposing effect. Known commonly as the *hunger hormone*, it is secreted primarily from the gastric fundus to induce hunger signaling pathways and, thus, an orexigenic/anabolic state in the body.

These hormones are only a couple of examples of more than 25 known mediators of hunger, satiety, and energy expenditure. In concert, these mediators regulate to an intrinsic set point of adiposity in the body referred to as the *adipostat*. This signaling pathway is so strong that individuals who achieve weight loss through dieting alone can lower resting metabolic rates below those whom are already at a similar weight. This relative metabolic insufficiency can last for years after dieting, making it easier to regain the weight [3].

Through bariatric surgery, we can physically alter these mechanisms and help to lower the adipostat while paradoxically increasing metabolic expenditures. In combination with behavioral and sometimes environmental modification, we can help to drive long-lasting weight loss and metabolic changes and improve upon comorbid conditions for years or even decades after surgery.

Indications and Patient Selection

Indications

Well-established qualifying criteria for bariatric surgery include the following:

1. Any surgically fit individual with BMI greater than or equal to 40 kg/m^2 or 100 lb overweight.
2. An individual of BMI of at least 35 kg/m^2 with obesity-related comorbidities.
   (a) There are more than 40 comorbidities that qualify, including but not limited to hypertension, diabetes mellitus type 2, sleep apnea, non-alcoholic fatty liver disease, and heart disease.

Patient Selection

Patients should be screened for certain factors which would dramatically decrease their chances for success or increase risk for certain complications. The surgeon must ensure the patient does not have underlying psychiatric conditions. These conditions could prohibit the patient from successfully completing the bariatric program or adhering to nutritional and exercise guidelines. Well-controlled depression,

anxiety, bipolar, or even schizophrenia should not solely dissuade the surgeon from recommending surgery.

We must also consider if the patient is on non-negotiable medications which may not be absorbed well after bariatric surgery (specifically after gastric bypass), the most common example being current or future transplant patients who will require lifelong immunosuppression. It is our practice to recommend sleeve gastrectomy in these situations.

Patient selection and screening are a complex endeavor. All major surgical and bariatric societies agree that bariatric surgery should be conducted by a board-certified bariatric surgeon at a bariatric center of excellence with a well-established multidisciplinary team. Teams should include a nutritionist, exercise physiologist, a mental health professional, and additional ancillary staff for coordination.

Contraindications

There are no well-established absolute contraindications to RNY gastric bypass. However, few relative contraindications do exist. These may include impaired mobility, Crohn's disease, active drug and alcohol dependence, iron deficiency anemia, end-stage lung disease, and/or end-stage heart failure.

In the case of end-stage heart failure, recent evidence and practice have made this an indication for bariatric surgery. Many heart transplant programs require the patient to be under a BMI of 35 kg/m^2. Established bariatric programs can work in conjunction with heart transplantation centers to help get these patients to an acceptable weight and to bridge morbidly obese patients to transplantation surgery. There is some limited data that also suggest certain patients have improvement of cardiac function in the interval, and some may even obviate the need for cardiac transplantation. As noted above, patients considered for transplantation may actually benefit more from sleeve gastrectomy, as there is less risk of malabsorption of medications and the surgery itself exhibits less cardiopulmonary stress.

Preoperative Evaluation

Multidisciplinary Evaluation and Education

Historically, outcomes from bariatric surgery were surgeon and center dependent due to inconsistent pre- and postoperative care. As the field evolved, a multidisciplinary approach has been recommended and undertaken which has consistently improved outcomes. It is now the recommendation from major bariatric groups that bariatric surgery be performed at a center of excellence with the appropriate multidisciplinary evaluation, education, and follow-up.

Psychiatric Evaluation

As part of this multidisciplinary approach, patients require an initial psychiatric assessment that should be done by psychiatrist or psychologist who specializes in bariatrics, eating disorders, or related fields.

Medically Supervised Weight Loss

Medically supervised weight loss and education are a key aspect of preoperative assessment and preparation. The required timeline for this is variable and somewhat dependent on insurance provided requirements and individualization to the patient's needs. It can typically be conducted for 3–12 months prior to bariatric surgery approval.

During this phase, the patient will periodically meet with a medical specialist for weight loss therapies. The patient is educated on specific diet routine, exercise routine, and exercise goals. The patient will have appropriate follow-up to ensure goals are optimally attained.

Upper Endoscopy

The role of routine preoperative upper endoscopy for bariatric patients remains a topic for debate and is under active research. Recommendation and completion of such depend on individual practice [4].

Patient Education

This is perhaps the most understated aspect of the preoperative phase. Patient education and understanding with periodic reinforcement are critical to the success of bariatric surgery. It is our practice to routinely educate from different perspectives to reinforce key principles. For instance, patients will learn about pre- and postoperative bariatric diets from the surgeon, the nutritionist, educational videos, support group, and online forums. Patients are invited to an online social media group which allows for community education. Within this group, our bariatric coordinator can also answer questions directly. Postoperatively, prior to discharge home, the patient is re-educated by the surgeon or nurse practitioner as well as the inpatient nutritionist. It is through these redundant efforts that we can minimize patient confusion and optimize compliance to improve outcomes.

Technical Consideration

Laparoscopic Roux-en-Y Gastric Bypass

The following is the technical description of performing a laparoscopic Roux-en-Y gastric bypass. It is broken down into steps with pitfalls as needed.

Patient Positioning

For best access during laparoscopic surgery, the patient can be placed in split leg or supine position with arms out at 90°. Exposure often requires steep reverse Trendelenburg position, often upward of 30° or more. The patient must be secured to tolerate these angles. We prefer an anti-slip pink pad on the bed and padded straps under the axilla and over the chest with additional straps or tape at thigh and shin levels. Some may prefer footboards as well for added security. Appropriate padding at all pressure points is crucial to avoid nerve or soft tissue injury.

Trocar Placement

With the patient in reverse Trendelenburg position, the Veress needle is inserted in the left upper quadrant of the abdomen at Palmer's point. Saline meniscus/drop test is performed to verify proper needle position prior to insufflation. The abdomen is insufflated to a pressure of 15 mmHg.

For our laparoscopic approach, we use two 5 mm and two 12 mm trocars, placed in a common configuration as seen in Fig. 54.3. The initial 12 mm port is placed with trocar over the camera about 15 cm inferior to the xiphoid process, slightly right of midline.

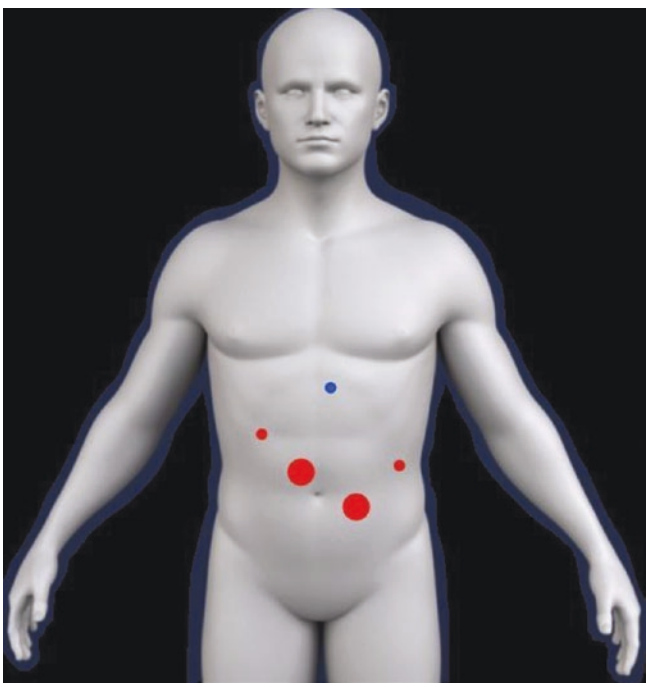

Fig. 54.3 Trocar placement

Biliopancreatic Limb

The omentum is divided with energy sealing device from mid transverse colon aiming toward the greater curvature of the stomach. This creates a track for the Roux limb which will reduce undue tension on the gastrojejunostomy.

From here, the colon is lifted and retracted cephalad. The mesocolon is followed to its base to identify the ligament of Treitz. The jejunum is followed distally from the ligament for 45 cm and is divided with a 60 mm linear stapler. For all our bowel/gastric transection, we use a staple line reinforcement material. We routinely mark the Roux limb at this point with a suture to ensure orientation is not lost.

Pitfall *Losing orientation may result in inappropriate reconnection of bowel. This may lead to the dreaded Roux-en-O configuration. The surgeon also must ensure no inadvertent twisting of the limb which may lead to obstructive symptoms. Diligence in this regard throughout the surgery is paramount to avoid these complications.*

Note that there is some variation in the length of this biliopancreatic (BP) limb ranging from 30 to 60 cm in the literature.

Pitfall *The optimal length of the BP limb is somewhat unclear. Research in the past tended to focus on alimentary limb length in terms of weight loss benefit and diabetes control. There is no clear body of evidence to dictate the best BP limb length. A paper by Luiz F. Zorrila-Nunez and colleagues conducted a systematic review of 13 articles that evaluated this in various ways. They concluded that a long BP limb yielded more bariatric and metabolic benefit. This still comes with some controversy.*

Alimentary Limb

The alimentary limb (or Roux limb) length can be quite variable. There have been attempts to quantify the length of the Roux limb and correlate with weight loss and metabolic benefit. Some practices vary the length based on the preoperative BMI, creating longer bypasses for those with higher BMI. Modern literature suggests there is no clear benefit to a longer Roux limb and can lead to shortening of the common channel and complications related to excessively long Roux limbs. It is important to have a limb of at least 60 cm to prevent bile reflux to the gastric pouch. Acceptable length varies from 60 cm up to 150 cm.

It is our practice to measure 125 cm of jejunum for our Roux limb. We also routinely create, and subsequently resect, a candy cane portion to optimize the low tension on the gastrojejunostomy. This additional length is taken into account

when measuring the Roux limb from the point of initial jejunal transection.

Jejunojejunostomy

The jejunojejunostomy (JJ) can be created in a few different methods. We conduct a side-to-side anastomosis using a 60 mm laparoscopic stapling device. The common enterotomy is closed in two layers of absorbable suture. We regularly close the mesenteric defect with running non-absorbable barbed suture.

Other options may include firing two 45 mm staplers; one retrograde and one antegrade form enterotomy. This effectively creates a wide, 90 mm enteroenterostomy. The common enterotomy may be closed with suture or a transverse deployment of another 45 mm stapler (this is sometimes termed the *triple staple technique*).

Pitfall *The important point that has been clearly elucidated in the literature is that a smaller (45 mm) anastomosis is insufficient. It is associated with higher rate of early edema, stricture, and kinking which may cause transient or permanent obstruction at this site. In a comparison of a unidirectional 45 mm stapler versus bidirectional firing of two 45 mm staplers, the early postoperative JJ obstruction rate dropped from 1.75% to 0% (p = 0.0012)* [5].

The mesenteric defect created at JJ anastomosis is closed with a running suture. We typically apply a barbed permanent monofilament suture for this closure. The stitch is started as an anti-obstruction stitch taking seromuscular bites on either side of the anastomosis and running to close the mesenteric defect.

Pitfall *There is much variation in specifics of practice regarding routine closure of the mesenteric defects. It is clear, however, that leaving these defects open during laparoscopic RYBG has been associated with nearly twofold increased risk in internal hernia formation, from about 0.78% to 1.66% overall* [6].

Gastric Pouch Creation

Attention is then turned toward creating the gastric pouch. The patient is placed in steep reverse Trendelenburg position. The liver retractor is placed at this time.

About 5 cm distal from the gastroesophageal junction along the lesser curvature of the stomach, a peri-gastric blunt dissection is conducted to tunnel posterior to the stomach without injury to adjacent vasculature or nerves. Using a 45 mm linear stapler with staple line reinforcement material, a 25–30 mL gastric pouch is created. Gastric sizing balloons are available for this purpose. Some surgeons estimate the volume based on length and width of the pouch after transection.

Some recent literature suggests that a long narrow pouch is equally efficacious as the traditional 25 mL pouch. It appears the important aspect of pouch creation is complete transection of the fundus from the gastric pouch.

Gastrojejunostomy

The gastrojejunostomy (GJ) can be created using a linear stapler, a circular stapler, or a completely hand-sewn technique. This is up to the discretion of the operating surgeon and institution. We routinely use a circular-stapler technique similar to that described initially by de la Torre and colleagues in 1999 [7].

After the firing of the first horizontal stapler from the lesser curvature, a gastrotomy is created in the region of the gastric remnant. A 25 mm circular stapler anvil is placed through the gastrotomy and into the region of the gastric pouch. The gastrotomy is closed in two layers with absorbable suture, and gastric pouch creation is completed with additional 45 mm linear stapler loads as described above.

Pitfall *Techniques have been described where the anvil was introduced trans-orally, exiting at the site of the gastric pouch anastomosis. This technique has the added risk of oral and esophageal trauma. It contaminates the operative field with oropharyngeal flora and may be associated with higher rates of surgical site infections.*

Pitfall *Using a circular stapler smaller than 25 mm is associated with GJ stenosis and obstruction at the gastric level. The rate of stricture with a 21 mm device is estimated to be about three times as high compared to a 25 mm device* [8]. *On the contrary, increasing the size of the stapler is not inconsequential. This would require a larger abdominal wall defect to introduce the anvil and stapler via a transgastric approach, size may be limited by the diameter of the small bowel, and a larger connection may increase risk of dumping syndrome.*

To complete the gastrojejunostomy, the Roux limb is then brought up into position, ensuring no twisting of the small bowel or mesentery. A site is chosen where a tension-free anastomosis with the stomach can be created. An enterotomy is then created in the *candy cane* portion of the Roux limb. A 25 mm circular stapler is inserted through this enterotomy, and a 25 mm circular gastrojejunal anastomosis is created. The mesentery of the candy cane portion of the Roux limb is then transected with an energy device. A 60 mm linear stapler is used to close the opening in the Roux limb (or transect the excess candy cane limb).

Pitfall *It is important that the entire excess Roux limb is resected. Excessive bowel here can lead to "candy cane syndrome" in which food retainment and bacterial overgrowth can lead to bloating, abdominal pain, nausea, and emesis. The surgeon must also ensure there is no encroachment on the anastomosis or its blood supply. Careful visualization of the vessels supplying the anastomosis is crucial.*

The small bowel specimen and circular stapler are then placed in a laparoscopic retrieval bag and removed. This is the only port site that we regularly close with absorbable suture using a percutaneous suture passer.

We typically place medial and lateral absorbable sutures on each side of the gastrojejunal anastomosis to relieve any undue tension.

Intraoperative upper endoscopy is then performed to confirm patent gastrojejunal anastomosis, good hemostasis, and a negative intraoperative air leak test. We then apply fibrin-based biological sealant along the staple line of the gastrojejunal anastomosis, gastric pouch, gastric remnant, and Roux limb to complete the procedure. This is optional and left up to the surgeon's discretion.

Robot-Assisted Roux-en-Y Gastric Bypass

Key steps when performing a robot-assisted Roux-en-Y gastric bypass are similar to the laparoscopic procedure. There are some distinct considerations and modifications that can be made.

The patient positioning and port placement are crucial. These are difficult to modify mid-procedure and must be precise and consistent.

Port placement will triangulate to the left mid and upper abdominal regions. If using the da Vinci Si or X system (Intuitive Surgical, Sunnyvale, CA), this means that the robot must be docked either directly over the head of the patient or side-docked parallel to the head of the bed. Side docking does limit the degrees of freedom of the arm furthest from the base. But, it does free up the head of the patient for easier access during intraoperative upper endoscopy. Of note, this positioning will typically require the bed to be turned 120–180° to allow for the robot to dock. If utilizing the da Vinci Xi with an extending and rotating boom, no rotation of the bed is required. You may park the robot base perpendicular and midway of the side of the bed. This simplifies the logistics for both the anesthesiologist (who can remain at the head of the bed) and the surgeon, who has easy access for upper endoscopy.

The jejunojejunostomy can be fashioned with linear cutting staplers in a similar fashion as described in the section "Laparoscopic Roux-en-Y Gastric Bypass" above.

When utilizing the surgical robot, we conduct a linear stapled gastrojejunostomy. A 45 mm stapler is positioned to create a 25 mm gastroenterostomy. The common enterotomy is again closed in two layers. This is logistically easier than using the circular stapler in this setting. It also supplies variant surgical technique in our training program without compromising patient outcomes.

Example Video of Laparoscopic Roux-en-Y Gastric Bypass

See Video 54.1.

Postoperative Care

Postoperative care is well protocolized to reduce risk of variation between patients and improve overall care and outcomes. Patients are started on a clear liquid diet 6 h after completion of surgery. They are coached to trial small volumes (10–15 mL) by mouth every 10–15 min while awake with the goal of 240 mL by mouth per 12-h shift prior to discharge. Intravenous fluids are given to supplement until goals are achieved. At the time of discharge, our patients will transition to a full liquid diet after formal education with a dietician. Patients will continue with 2-week interval dietary advancements from full liquids to puree, to soft, to regular diet over the next 6 or more weeks.

Patients are started on a multimodal pain regimen that consists of scheduled oral liquid acetaminophen as well as non-narcotic adjuncts. After screening for contraindications to each, adjuncts may include ketorolac, methocarbamol, and gabapentin. In addition, a minimal amount of narcotic medication is allowed for breakthrough pain only.

Nursing staff is diligent to ensure the patient conducts early ambulation. They are instructed to get out of bed and into a chair and ambulate as often as possible during daytime hours.

Forty-eight hours after discharge from the hospital, all patients receive a call to ensure proper oral intake and pain control have been attained. If concerns arise, early adjustment and potential outpatient intravenous hydration may minimize hospital readmissions.

At 2 weeks from the day of the surgery, all patients have a scheduled visit with a surgeon and with a nutritionist.

Then, the patient has a 6-week follow-up with our bariatric nurse practitioner. This coordinated multi-disciplinary postoperative care approach is crucial to optimize the patient's recovery and minimize complications.

Each practice may differ somewhat in the postoperative care and follow-up. However, what is important is the multidisciplinary education the patients receive and the proper, close follow-ups after surgery.

Outcomes

The 2-year benchmark after bariatric surgery has been well established as a key point in the timeline to review the success or the failure of the procedure. There is much literature on this topic and all bariatric surgeries are compared at this point. The laparoscopic RYGB has been shown to provide 57–67% excess body weight (EBW) reduction at 2 years [9]. This is in conjunction with significant reduction of all comorbid conditions that are typically measured during trials.

More recently, long-term data has been published evaluating 10-year outcomes. Studies are consistently showing sustained benefits of gastric bypass with a 57% EBW at 10 years after surgery. Rates of improvement of comorbidities were 83%, 87%, 67%, and 76% for diabetes mellitus type 2, hypertension dyslipidemia, and obstructive sleep apnea, respectively [10].

Healthcare Costs and Considerations

The cost of performing a laparoscopic Roux-en-Y gastric bypass (LARYGB) is highly variable. A commonly quoted figure is $23,000 on average. With such a substantial initial investment in an individual's health, one must wonder if the benefit of this surgery is worth its cost.

Several studies have concluded that the RNY gastric bypass is, in fact, cost-effective long-term. Several model predictions based on variable factors of comorbidities, age, BMI, and gender have shown that in most scenarios, there is a financial benefit of bariatric surgery over medical management [11]. In one study, it was determined that LRYGB was the most cost-effective when compared to laparoscopic sleeve gastrectomy and laparoscopic adjustable gastric banding [12].

Conclusion

Laparoscopic Roux-en-Y gastric bypass has become the gold standard by which all bariatric surgeries are now compared. It is a highly effective procedure that can be used as a powerful tool against the chronic condition of morbid obesity. The proceedings which revolve around this procedure are highly specialized and specific. A surgeon cannot approach these patients or this surgery lightly. It should be conducted in the hands of a surgeon with advance training in bariatric surgery in conjunction with a specialized multi-disciplinary team. When done properly in this fashion, this surgery can be conducted safely and effectively to change the lives of bariatric patients for the better.

Questions

1. A 45-year-old female with a BMI of 45 is interested in bariatric surgery. She is trying to decide which type of surgery to pursue. She was confused with what she found on the Internet. During the initial consultation, she is told that laparoscopic Roux-en-Y gastric bypass is associated with what percentage of excess body weight loss at 2 years from surgery?
   A. 30–42%
   B. 45–53%
   C. 57–67%
   D. 72–81%

Answer: C. Explanation: There is expected variability of success weight loss after bariatric surgery. A meta-analysis in 2004 identified that on average patients lost 56.7–66.5% of excess body weight by the 2-year follow-up after gastric bypass.

Buchwald H, Avidor Y, Braunwald E, et al. Bariatric Surgery: A Systematic Review and Meta-analysis. JAMA. 2004;292(14):1724–1737. doi:10.1001/jama.292.14.1724.

2. A patient attends a weight loss seminar. During the presentation, he is wondering if certain patients do better with one type of surgery versus the other. Which of the following patients is the best candidate for laparoscopic Roux-en-Y gastric bypass?
   A. A 43-year-old with BMI 34 kg/m^2 and type 1 diabetes mellitus.
   B. A 54-year-old female with BMI 36 kg/m^2, type 2 diabetes mellitus, and obstructive sleep apnea.
   C. A 36-year-old female with BMI 41 kg/m^2, chronic iron deficiency anemia, and obstructive sleeve apnea.
   D. A 28-year-old male with BMI 54, type 2 diabetes mellitus, obstructive sleep apnea, and osteoarthritis who has been bed bound for the last 8 months.

Answer: B. Explanation: Bariatric surgery is indicated in patients with BMI of 35 kg/m^2 or more with comorbidities related to morbid obesity or any patient with BMI of 40 kg/m^2 or more. This rules out answer "A." Although there are few well-established absolute contraindications of RYGB, some are commonly accepted. Iron deficiency anemia can be exacerbated by a gastric bypass. A sleeve gastrectomy (or other procedure with less risk of malabsorption) may be considered in these patients (rules out answer "C"). Immobility is a commonly accept contraindication to bariatric surgery as the risk of DVT, PE, and other complication is elevated and the risks begin to outweigh the benefits (rules out answer "D").

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Endoscopic Gastric Remodeling for Weight Loss

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Introduction

Obesity is a growing worldwide epidemic with massive implications for individual health as well as public healthcare costs. In the United States, the prevalence of obesity continues to increase affecting 42.4% of individuals older than 20 years, and 9.2% meet criteria for severe obesity [1]. Obesity is traditionally defined as having a higher-than-normal weight adjusted for height (body mass index, BMI) and can be further categorized as class I obesity (BMI 30.0–34.9 kg/m^2), class II (BMI 35.0–39.9 kg/m^2), and class III or severe obesity (BMI ≥40.0 kg/m^2). In overweight individuals (BMI 25–29.9 kg/m^2), waist circumference can also be used to indicate central obesity. Obesity is a chronic disease and significant contributor to heart disease, stroke, diabetes, and cancer. It can also affect the gastrointestinal tract and is commonly associated with gastroesophageal reflux disease (GERD) and esophageal motility disorders, small bowel changes in absorption and bacterial overgrowth, diverticular disease, colon polyps and cancer, non-alcoholic fatty liver disease, and benign biliary disease [2].

The initial approach to combating obesity consists of lifestyle modifications, dietary interventions, and pharmacotherapy. Given the limited durability of these interventions, bariatric surgery has become the cornerstone of therapy for motivated patients with BMI ≥40 or ≥35 with at least one comorbidity. In parallel to rapidly rising rates of obesity in the United States, there has been a significant increase in utilization of bariatric surgery with a 10.8% increase from 2017 to 2018 alone [3]. The most robust and preferred surgery for patients with concomitant metabolic disease or GERD is Roux-en-Y gastric bypass (RYGB), and the most common operation is laparoscopic sleeve gastrectomy (LSG) where the greater curvature and fundus are removed and a sleeve is created along the lesser curvature. The major drawbacks of surgery are acute and long-term complications as well as nutritional deficiencies. A multidisciplinary, team-based approach may include a bariatric surgeon, endocrinologist, registered dietician, obesity medicine specialist, psychologist, and health/behavior coach.

Bariatric Endoscopy

The emerging field of bariatric endoscopy provides an endoscopic alternative to weight loss surgery through a variety of different procedures targeting the stomach and small bowel. The current FDA-approved therapies include intragastric balloons, gastric aspiration therapy, and the transpyloric shuttle which are primarily weight loss-inducing interventions through alterations in gastric motility with secondary improvements of obesity-related complications. Duodenal mucosal resurfacing interventions have direct metabolic effects and are currently under study. The focus of this chapter will be gastric remodeling procedures that utilize full-thickness gastric tissue plication and work by restricting the size of the gastric reservoir and altering gastric motility to affect appetite. These primary approaches include endoscopic sleeve gastroplasty (ESG) and primary obesity surgery endoluminal (POSE), as well as revisional procedures after prior surgical or endoscopic bariatric interventions.

Candidates for ESG and POSE

ESG and POSE are the two major endobariatric procedures that can be thought of as gastric remodeling interventions. These are mainly considered in patients with BMI of 30–40 kg/m^2 (but can be an option for individuals with higher BMI >40 kg/m^2 and represent an alternative for those who

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either do not qualify for bariatric surgery or who do not want bariatric surgery due to risk for potential complications). Patients who are overweight (BMI 27–30) with comorbid illness may be considered in some centers, especially if refractory to pharmacotherapy. Potential candidates should undergo a thorough medical, psychological, and lifestyle evaluation to ensure that there are no underlying comorbid conditions that would prevent them from being able to adhere to the post-procedure lifestyle and dietary guidelines. Individuals undergoing ESG or POSE should have good functional status (ideally be able to exercise), as well as motivation to comply with all follow-up recommendations and visits. Providers should take a thorough history of weights at specific time points including highest and lowest, previous weight loss attempts and successes through diet or exercise, a detailed review of medications that may contribute to both weight gain and loss, an evaluation of eating patterns including a diet recall or food log, and assessment of physical activity. Contraindications may include prior bariatric surgical intervention or anatomic alterations such as prior gastric or esophageal surgery.

Preoperative Evaluation

Preoperative evaluation typically includes an upper endoscopy to assess anatomy and exclude patients with a large hiatal hernia as well as biopsies to rule out *Helicobacter pylori* infection and treatment if confirmed positive. Although not a contraindication, caution should be taken in patients with significant intestinal metaplasia or a strong family history of gastric cancer as the plications may preclude complete mucosal evaluation in the future. An upper GI series is not mandatory but can be helpful, especially for comparison after the procedure. There are no standardized protocols for perioperative care for endobariatric procedures, and recommendations are largely center dependent. Our practice is to instruct patients to start a proton pump inhibitor 1 week prior to the procedure, avoid all non-steroidal anti-inflammatory medications, and discontinue antiplatelet or anticoagulant medications as appropriate. We typically prescribe a scopolamine patch to begin the evening prior to the procedure. Other antiemetics such as aprepitant or ondansetron can be provided in advance at home or in the preoperative area. Some providers will even prescribe a limited bowel preparation to prevent post-procedure discomfort due to constipation.

Intraprocedural and Postoperative Protocol

Intraprocedural considerations may include use of total intravenous anesthesia to limit postoperative nausea and vomiting or IV dexamethasone. If an over-tube or large diameter plication device is being used, upfront paralytics may be helpful. A dose of prophylactic antibiotics is given as well as continuous intravenous fluids. Our practice is to prescribe a 5-day post-procedure course of prophylactic antibiotics (amoxicillin/clavulanic acid or ciprofloxacin if there is penicillin allergy) for these full-thickness interventions, but there is no formal guidance in this area, and other centers may only prescribe an extended course of antibiotics if there is substantial pneumoperitoneum. Patients are monitored in the hospital post procedure for a 23-h observation with nothing by mouth until an upper GI series the following day confirms there is no leak or perforation. Antiemetics and pain medications are provided intravenously during this time. It is also reasonable to perform these procedures on an outpatient basis where patients recover post procedure for 1–2 h and are discharged home. Prior to hospital discharge, it is critical that patients receive dietary instructions and continue to work with a dietitian to help maintain their post-procedure regimen. The post ESG/POSE diet consists of 1 day of non-caloric, non-carbonated, and non-caffeinated clear liquids (2–4 ounces per hour), followed by 30 days of full liquids (calorie restricted, high in protein, and low in fat), followed by 14 days of semi-solid and pureed food and, finally at week 6, solid food with calorie restriction of 1200 kcal/day. During this time, it is critical to have regular follow-up visits with the patient to ensure that they can adhere to dietary restrictions as well as to encourage regular aerobic activity at least three times a week for over 30 min. For those who have no other limiting health restrictions, we encourage everyone to choose their preferred form of aerobic exercise that is readily accessible (preferably in the home, such as stationary bike) with the goal of gradually getting their heart rate above 120 bpm, up to 45 min per day, 5 days per week. We find these simple and easy to remember guiding principles (120 bpm, 1200 kcal/day) help patients to stay on track.

Weight loss pharmacotherapy should be considered around 3 months if the patient has not achieved at least 10% total body weight loss (TBWL) or starts to show signs of weight regain. Several medications with different mechanism of action are FDA approved for obesity treatment including phentermine (enhanced norepinephrine release) or combination phentermine/topiramate (with Gaba receptor modulation), orlistat (pancreatic lipase inhibitor), naltrexone/bupropion (opiate antagonist with a norepinephrine and dopamine reuptake inhibitor), and liraglutide (GLP-1 receptor agonist). Metformin is also commonly used in clinical practice and decreases hepatic glucose production. Medication can be initiated prior to the procedure or can be added after to augment weight loss by either the bariatric endoscopist or a physician with specialized training in obesity medicine.

Endoscopic Sleeve Gastroplasty

Endoscopic sleeve gastroplasty (ESG) utilizes full-thickness suturing along the greater curvature to create a semi-tubular stomach that mimics a surgical sleeve but preserves the fundus. ESG is performed using the OverStitch endoscopic suturing system (Apollo Endosurgery, Austin TX) which was FDA approved in July 2022 for ESG and endoscopic bariatric revision in patients with BMI 30–50 kg/m^2. Weight loss with ESG is primarily achieved through gastric volume reduction, though additional physiologic improvements have been demonstrated such as suppression of ghrelin, impaired gastric accommodation, and delayed emptying that leads to early and prolonged satiety [4].

Technical Aspects and Procedural Considerations

Argon plasma coagulation (APC) is used to mark the sites for suturing from the distal gastric body extending backward in two linear arrays placed along the anterior and posterior wall. The OverStitch device is loaded on the double-channel gastroscope which allows for passage of additional instruments through the second channel. The tissue helix is advanced forward into the gastric mucosa and turned clockwise to catch tissue and retracted backward to capture a full-thickness bite, and then the suturing device is closed which drives the curved needle through the folded mucosa. Tension is then applied to tighten the suture and the cinch is deployed to lock it in place. To maximize the full-thickness bite, suction is applied (and even the CO_2 insufflator is often turned off) to allow for tension-free retraction of tissue into the "jaws" of the needle driver.

The basic approach is to continue to take bites moving from the anterior wall, greater curvature, then posterior wall, and work your way proximally. Several iterations of suture patterns have been described with the goal to both shorten and narrow the stomach, but there is no evidence that any one pattern has superior outcomes. The most common pattern is the U shape comprised of six to nine bites taken close to one another, often followed by a second reinforcing layer. Our modified pattern utilizes a U alternating with an I-shaped suture given the strength of this single interrupted suture. We start with a simple interrupted suture at the level of the incisura and add additional sutures to reinforce and narrow this area to create an outlet that mimics a pylorus, thereby establishing a smaller gastric reservoir to promote satiety (Fig. 55.1).

Outcomes

ESG has been performed around the world, and results from the Middle East, South America, Europe, and the United States demonstrate a consistent improvement in TBWL of 15–20%. The largest meta-analysis to date includes 1772 patients who underwent ESG and achieved a mean TBWL at 6, 12, and 18–24 months of 15.1% (95% CI 14.3–16.0), 16.5% (95% CI 15.2–17.8), and 17.2% (95% CI 14.6–19.7) [5]. ESG appears durable with longer-term follow-up data by Sharaiha et al. demonstrating mean TBWL of 15.9% at 5 years [6]. ESG has also yielded improvements in metabolic parameters including hemoglobin A1c, liver enzymes, serum triglyceride, and systolic blood pressure [7]. Several predictors of success with ESG have been identified including younger age, male gender, higher baseline BMI, higher TBWL at 1 month, and compliance with scheduled visits [6]. Data suggests that most individuals who achieve short-term success (>10% TBWL at 3–6 months) will likely have durable outcomes at 2 years. A recent study from Brazil showed that combination ESG with liraglutide added at 5 months had higher TBWL at 7 months (24.72% vs. 20.51%, $p < 0.001$) and greater reduction in body fat at 12 months (7.85% vs. 10.54%, $p < 0.001$) compared to ESG alone [8].

ESG has never been compared to LSG in head-to-head trials, though pooled results of observational data including 2188 patients showed greater excess weight loss (EWL) with LSG over ESG (absolute difference in EWL 18.12%) [9]. Comparative studies are needed to determine efficacy, long-term durability, and patient characteristics to optimize results from a surgical versus endoscopic approach to a gastric sleeve.

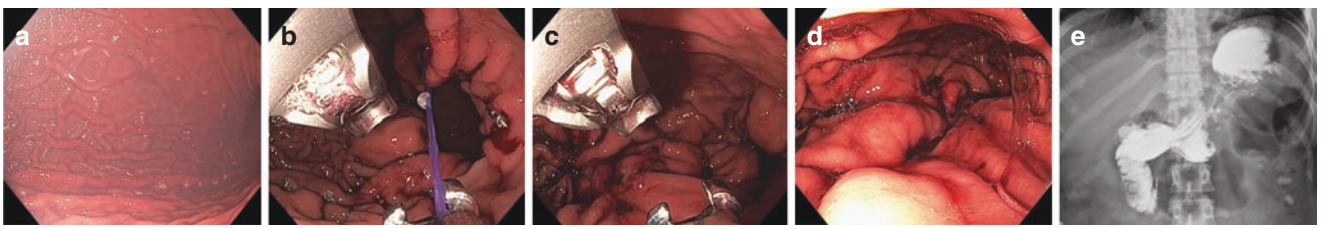

Fig. 55.1 Endoscopic sleeve gastroplasty. (**a**) Stomach, long view, at baseline. (**b**, **c**) Endoscopic suturing is performed at the level of the gastric incisura along the lesser curvature to create a neo-pylorus. (**d**) Stomach, long view, after ESG. (**e**) Post-procedure upper GI series demonstrates delayed contrast movement through the new gastric sleeve

Safety

ESG is overall safe with a pooled adverse event (AE) rate of 2.2% (95% CI 1.6–3.1) that includes severe pain or nausea, requiring hospitalization (1.08%), gastrointestinal bleeding (0.56%), and peri-gastric leak or fluid collection (0.48%) [5]. Intraprocedural AEs are usually related to the suturing device malfunctioning or getting stuck on tissue. Occasionally the needle may hit a vessel and cause an expanding submucosal hematoma, which may impact the location of the next suture and force early cinching, though this typically takes care of the bleeding. Inadvertent or superficial mucosal tears are unlikely to cause issues. Common post-procedure complaints include nausea, epigastric pain and tightness, sore throat, or shoulder discomfort. Patients should avoid retching and use of positive airway pressure therapy for the first 1–2 weeks post procedure as this could cause suture disruption. If there is ongoing difficulty tolerating liquids or progressing to solid food after very aggressive suturing, there may be a stenosis near the incisura that requires dilation. Although data is limited on new-onset GERD after ESG, rates appear to be much lower than with LSG [10].

Primary Obesity Surgery Endoluminal (POSE) Procedure

Primary obesity surgery endoluminal (POSE) employs a similar concept as ESG, but instead of suturing, full-thickness plications are created by suture anchor pairs. POSE is performed using the Incisionless Operating Platform (IOP, USGI Medical, San Clemente, CA, USA) that was FDA approved for tissue apposition in 2006 but is not specifically approved for weight loss therapy. The original POSE procedure targeting the fundus and proximal stomach demonstrated limited efficacy and has since been refined to POSE-2 or the distal POSE which more closely mimics the ESG plication strategy targeting the gastric body.

Technical Aspects and Procedural Considerations

The IOP is comprised of four major components: (1) the Transport Multi-lumen Access Platform, (2) the g-Lix Helical Endoscopic Tissue Grasper, (3) the g-Prox Grasper/Tissue Approximation Device, and (4) the g-Cath tissue anchor delivery catheter with expandable tissue anchors. The transport is a multi-lumen, flexible device with two steering wheels that allow for deflection of the tip in all four directions. It has four large working channels for insertion of various instruments with a designated side port for an ultra-thin gastroscope. Each plication is made by anchoring and grasping the target tissue with the g-Lix and retracting it into the teeth of the g-Prox device. The g-Prox has wide jaws that can close around a large amount of tissue to approximate full-thickness folds. Once the target tissue is captured in the g-Prox, the needle on the g-Cath delivers the pair of snowshoe anchors to create a plication. Suture anchors are cinched to bring the approximated tissue to an appropriate tension. The proximal end of the suture is then cut with the g-Prox. Throughout the procedure we use a laparoscopic CO_2 insufflator set at 8–10 mmHg to maintain gastric distension.

The goal of the original POSE procedure was to place three to four suture anchors in the distal gastric body/antrum and seven to nine in the fundus. In the modified POSE-2, plications are limited to the gastric body like ESG. We begin in the distal gastric body with a horizontal plication to create the "neo-pylorus" as the boundary of a smaller gastric reservoir that will trigger satiety (Fig. 55.2). We then proceed with a combination of horizontal and vertical plications, a pattern which has been described as "belt and suspenders" that effectively reduces both the width and the length of the stomach, respectively [11]. The distal POSE is more similar to ESG with a greater effect on motility through changing the shape and function of the stomach.

Outcomes

The original POSE procedure targeted the fundus and proximal stomach and was designed to affect gastric accommodation. Randomized studies showed mixed results with good outcomes from Europe [12], but suboptimal findings in the sham-controlled ESSENTIAL trial in the United States demonstrated <5% TBWL at 1 year [13]. Taken together, it is possible that these results reflect confounding from other factors such as lifestyle intervention, post-procedure care, and study design. Nevertheless, these findings along with the success of ESG using a different suturing pattern influenced modifications to the technique and development of POSE-2. Lopez-Nava et al. from Spain reported their experience in 75 patients who underwent POSE-2 with high rates of technical success (98.7%) and low rates of adverse events (5.3%) [14]. Of the 46 patients who reached 1-year follow-up, mean TBWL was 17.8%, and BMI decline was 7 kg/m^2.

In a large meta-analysis of RCTs and observational studies evaluating POSE (7 studies, 613 patients), TBWL was 13.45% at 3–6 months and 12.68% at 12–15 months [15].

The impact of POSE on comorbid conditions was examined in the ESSENTIAL trial [13], where more than half of patients were able to reduce their diabetes medication and achieved a significant decrease of 2.1 mg/dL in fasting blood sugar. These patients also demonstrated a numerical but not

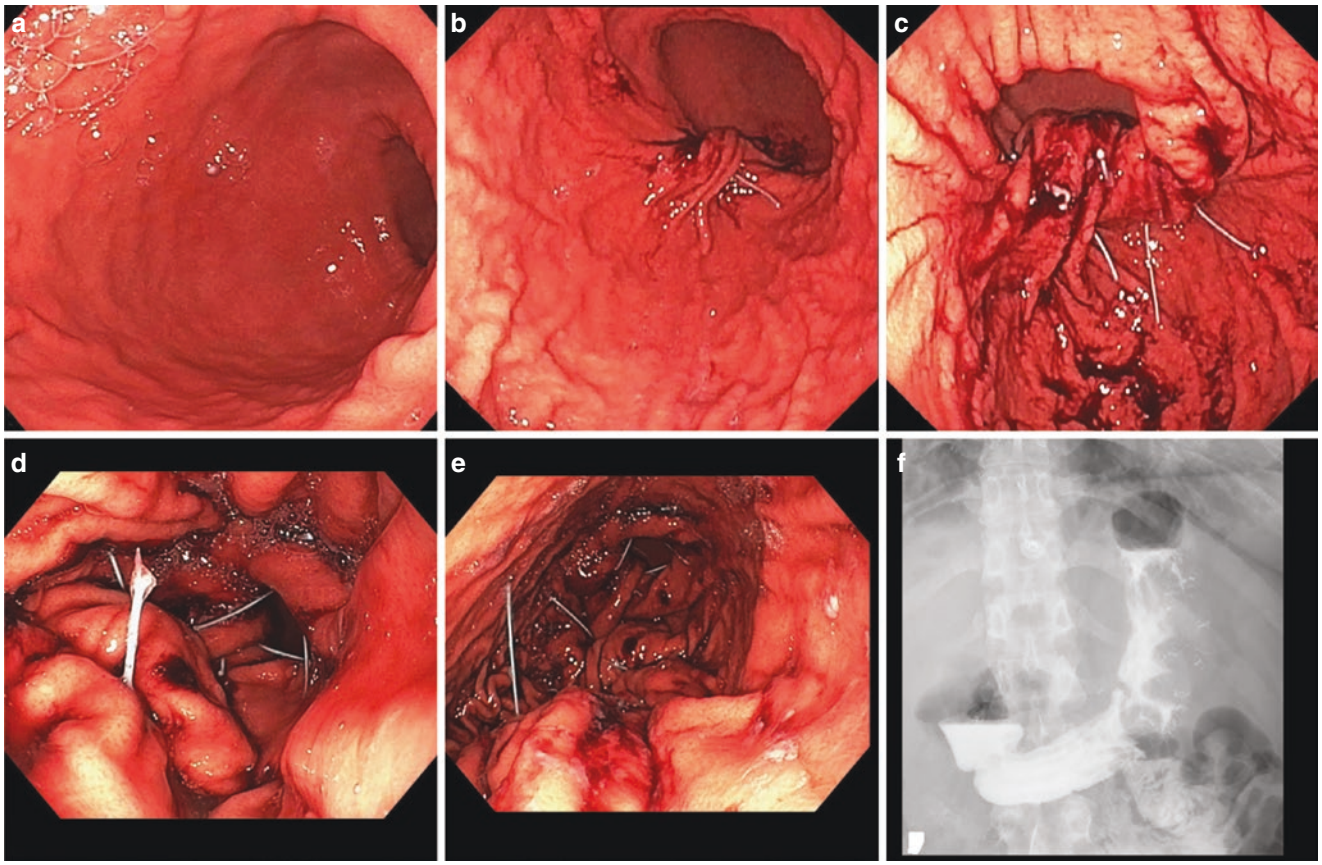

Fig. 55.2 POSE. (**a**) Stomach, long view, at baseline. (**b**, **c**) Initial plication at the distal gastric body to create a neo-pylorus. (**d**) Additional plications in the gastric body. (**e**) Stomach, long view, after POSE. (**f**) Post-procedure upper GI series

statistically significant decrease in systolic blood pressure, triglycerides, and LDL compared with the lifestyle modification cohort.

Safety

AEs with POSE are minimal. The pooled incidence of serious AEs from a meta-analysis of all the major trials was 2.84% and included GI bleeding, intraabdominal bleeding, hepatic abscess, and severe pain, nausea, and vomiting [15]. Minor adverse events included post-procedure abdominal pain (43.75%), sore throat (26.5%), nausea (20.2%), and vomiting (17.3%) that resolved with supportive care [12, 16].

ESG Versus POSE

While there are no comparative studies between ESG and POSE, two meta-analyses suggest that ESG may result in greater weight loss [17, 18], though these included studies of the original proximal POSE which may have inferior outcomes to POSE-2. There are a few key differences in the approach and technique that may also impact choice of procedure and results. ESG relies on full-thickness mucosal-based suturing with apposition of mucosa to mucosa with the goal to pull in the greater curvature and create a tight sleeve. Endoscopic suturing is relatively reversible and can also loosen over time. On the contrary, POSE captures large plications to facilitate serosa to serosa apposition and scarring, which is more permanent and can't be easily or readily removed. Therefore, plications are thought to offer improved physical durability, though longer-term studies are needed to determine if sustained weight loss is achieved with POSE over ESG. Also, it is important to keep in mind that the final appearance of the stomach will be very different in POSE, as the goal is simply to shorten and narrow the stomach, and not necessarily tighten it. Given the technical variation between the two procedures, there are unique considerations for the patient possibly considering surgery in the future. For example, it would be difficult to do a sleeve gastrectomy after POSE if there are a lot of plications in the gastric body, but since the cardia and fundus are relatively spared, a gastric bypass could be performed. Future comparative studies of ESG and POSE and surgery will be useful to provide data to patients who are deciding on which weight loss options are best suited for them.

Endoscopic Revision After Bariatric Surgery

Weight gain after bariatric surgery occurs in approximately 20–30% of patients, and the mechanisms are typically maladaptive eating behaviors and sedentary lifestyle [19]. Therefore, the first step is to emphasize nutrition and lifestyle modifications. There are also several reversible structural issues including a gastro-gastric fistula, gradual enlargement of the gastric pouch, or dilatation of the gastrojejunal anastomosis (GJA) that may require revisional therapy (Fig. 55.3). Although surgical revision is an effective option, it is often avoided given high rates of complications and surgical mortality. This has led to the development of alternative endoscopic techniques aimed mainly at reduction of the gastric pouch and GJA post RYGB. The size of the GJA appears to be strongly correlated with weight regain after RYGB, with data showing an 8% increase in the percentage of maximal weight loss after RYGB that was regained for every 10 mm increase in the GJA [20]. Therefore outlet reduction has been a primary target for both surgical and endoscopic revisional procedures. Preliminary data suggest possible utility of endoluminal functional impedance planimetry (EndoFLIP) to measure the distensibility of the GJA as an additional metric for symptom evaluation and procedural planning given variation and lack of gold standard in endoscopic visual estimation of GJA size [21].

Argon Plasma Coagulation

The simplest approach to outlet reduction uses argon plasma coagulation (APC) alone to resurface the tissue at the GJA. Application of this focal coagulation injury in a circumferential manner causes edema, ulceration, and fibrosis, thereby reducing the aperture of the GJA. This results in a physical reduction in the size of the outlet as well as a delay in gastric emptying. A report from Brazil in 2015 using a total of three APC treatment sessions over 8 weeks resulted in reduction of the GJA of 17 mm (67%) and 15.5 kg weight loss, with a 6.7% rate of GJA stenosis [22]. A larger multicenter observational study from Brazil and the United States including 558 patients demonstrated 6–10% TBWL at 12 months and average weight loss of 7.7 kg [23].

High-dose APC (70–80 W) is recommended as it leads to greater weight loss compared to low-dose APC (45–55 W) through deeper tissue injury leading to more effective scarring at the anastomosis [24]. Numerically higher rates of GJA stenosis seen with high-dose APC may signal caution (7.6% versus 3%, $p = 0.06$), but fortunately all stenoses in this cohort could be treated endoscopically.

Transoral Outlet Reduction Endoscopy (TORe)

The transoral outlet reduction endoscopy (TORe) procedure should be considered for a very large and dilated GJA. TORe

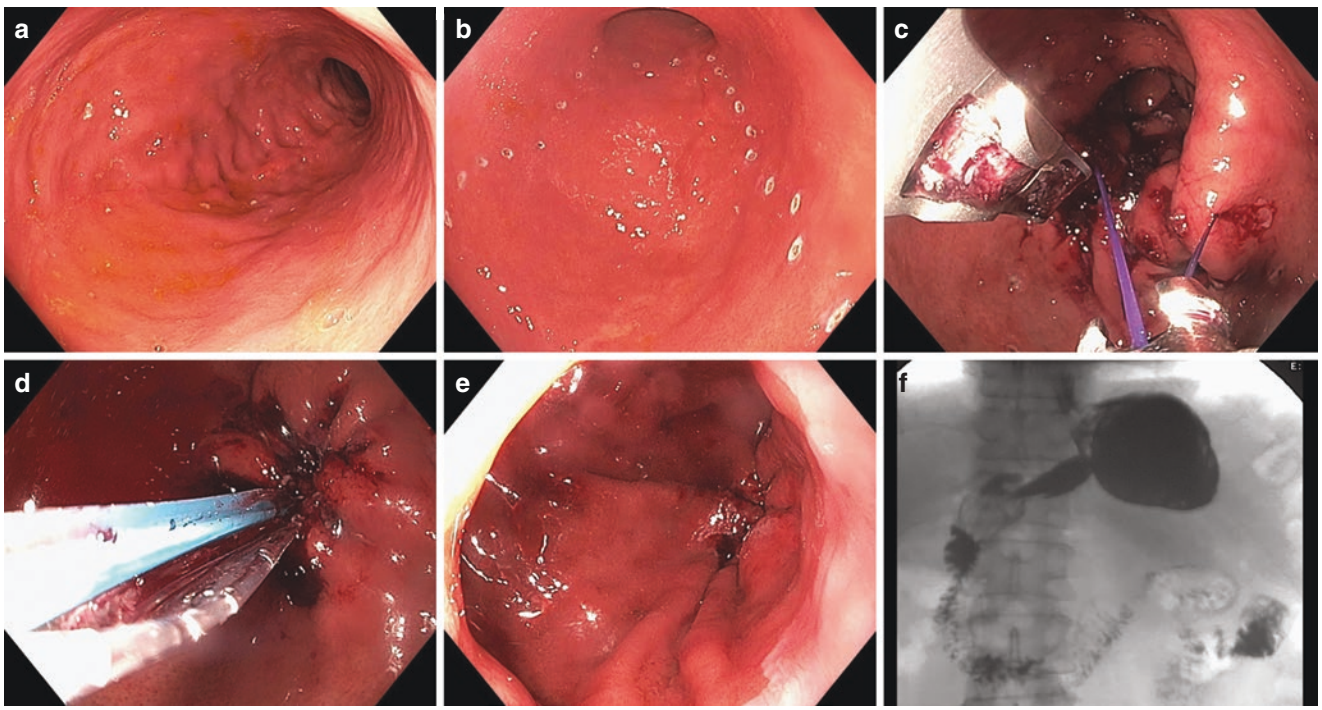

Fig. 55.3 Endoscopic revision with pouch and outlet reduction. (**a**) Stomach, long view, at baseline. (**b**) Marking with APC. (**c**) Endoscopic suturing for pouch reduction. (**d**, **e**) Outlet reduction with purse-string suture tightened over dilating balloon. (**f**) Upper GI series demonstrates small pouch with narrow outlet similar to gastric bypass

utilizes APC or endoscopic submucosal dissection (ESD) followed by full-thickness endoscopic suturing to reduce the outlet. APC prior to suturing is most ideal for a GJA 15 mm or smaller or a compliant opening and can be applied to approximately 1 cm of tissue on the gastric side to create scarring and denude the mucosa to facilitate better tissue capture during suturing. An alternative option is to perform ESD of this circumferential area to expose the muscle for greater tissue penetration and full-thickness suturing. Any additional visible mucosa can be treated with APC until it is completely removed. ESD seems to provide more durable weight loss, though may be more technically demanding than APC. A small, matched case series of patients undergoing TORe demonstrated greater weight loss at 12 months with ESD compared to APC (12.1% TBWL vs. 7.5%, $p = 0.036$) [25]. After APC/ESD, a single running suture is placed in a purse-string fashion starting at the 5 o'clock position and rotating counterclockwise, typically taking at least 14 bites. It can be helpful to place an external loop in the scope to pre-rotate (clockwise) and shorten the scope. The suture is then tightened over a 6 mm balloon, and as the outlet closes around the balloon, the cinch is deployed. For the outlet, the purse-string technique provides greater durability and subsequent weight loss compared to the interrupted stitch [26]. In addition, we typically provide two reinforcements with an interrupted stitch on the right and the left (3 and 9 o'clock) that can be done prior to or after the purse-string.

TORe is an effective and potentially repeatable procedure that can achieve 5–10% TBWL with a favorable risk profile. In a series of 130 patients with 25% weight regain post RYGB who subsequently underwent TORe, weight loss at 6, 12, and 18 months was 9.31, 7.75, and 8 kg. These results were consistent with pooled data showing 8.5 kg weight loss at 12 months [27]. Long-term data demonstrating durability comes from a retrospective cohort of patients who underwent TORe at different time points with varying suturing techniques and achieved 8.5%, 6.9%, and 8.8% TBWL at 1-, 3-, and 5-year follow-up, respectively [28]. Recent data demonstrating lower rates of AEs and serious AEs with an endoscopic versus surgical approach (6.5% vs. 29%, $p = 0.043$ and 0% vs. 19.5%, $p = 0.02$) with similar weight loss outcomes make endoscopy a desirable option for revision after RYGB [29].

Restorative Obesity Surgery Endoluminal (ROSE)

The ROSE procedure is an alternative approach for weight regain after bariatric surgery that uses the same IOP as POSE to create full-thickness plications to reduce the size of the gastric pouch and the diameter of the GJA. In a series of patients with weight regain after RYGB undergoing ROSE, patients lost 32% of this additional weight at 6 months with no documented AEs [30]. While there is no data comparing TORe to ROSE, the choice of procedure can be tailored to the clinical scenario. For example, if the pouch is large and the outlet is not that big, a ROSE focusing mostly on the pouch with simple APC of the outlet would be appropriate. If the outlet is very large, TORe with purse-string suturing may be better.

Revisional Endoscopic Sleeve Gastroplasty of Laparoscopic Sleeve Gastrectomy

ESG can be used as salvage therapy in patients who have weight regain from a dilated pouch after LSG. Like a primary ESG, revisional ESG utilizes the OverStitch device to place sutures for gastric volume reduction. In a multicenter prospective study of 82 patients with weight regain after LSG followed by revision ESG, TBWL exceeded 10% in 72% of patients at 6 months [31]. No serious AEs occurred. The revisional ESG has many advantages including ease of procedure and safety, and since it is organ sparing, further revisions can be done if needed. If the ESG loosens over time, additional tightening up or touching up can be performed. It should be mentioned that some patients may fail ESG and need to proceed with a reoperative surgery, which is technically feasible.

Training and Program Development

Significant efforts have been made to establish endoscopic bariatric professional societies with opportunities for specialized training as well as implementation of bariatric endoscopy programs across US institutions. The ASGE Training Committee and Association for Bariatric Endoscopy have established an obesity core curriculum which provides a framework for teaching the technical and cognitive aspects of bariatric endoscopy to gastroenterology fellows [32]. They also offer guidance on training and privileges for endoscopic bariatric therapies for individuals and institutions [33]. Additionally, there are pathways in place for interested gastroenterologists and bariatric endoscopists to obtain board certification in obesity medicine.

Cost of Endobariatric Therapies

Despite considerable growth and success developing in the field of endobariatrics, one of the biggest challenges remains lack of insurance coverage. There are currently no specific CPT codes for ESG or POSE. Most endoscopists use 43499

(unlisted procedure, stomach) along with supporting documentation such as clinical diagnosis, procedure indication, and the time, effort, and equipment required to complete the procedure. Reimbursement is variable and depends on the payor, but in general is inadequate. Therefore, these procedures are typically cash pay with the amount determined by the hospital to cover global costs of the procedure.

There are several examples of pathways for reimbursement that seem to work best within a larger healthcare system and may be institution, state, or insurance company specific. Ongoing efforts by GI and bariatric endoscopy professional societies through policy change and advocacy, in conjunction with continued research efforts demonstrating impactful outcomes, will hopefully lead to meaningful changes in reimbursement and allow for more widespread implementation of endobariatric programs nationwide.

Conclusion and Future Directions

This is an exciting time for the field of endobariatrics with remarkable improvements in technology and incredible innovation in the management of patients with obesity. New techniques with different mechanisms of action will be important as we continue to learn more about the pathophysiology of obesity and concomitant metabolic disorders. Although many questions remain unanswered, such as who should be doing these procedures (bariatric surgeons, interventional GI, or both), what are the ideal interventions (gastric remodeling, balloons, duodenal resurfacing, surgical or endoscopic anastomoses), which patients are appropriate candidates, and who should be paying for these procedures, the obesity epidemic is quickly growing and needs to be met head on. This will require collaboration from all members of the healthcare team, the institution and payors, industry partners, and clinical researchers. As new data becomes available, procedures should continue to meet or exceed the PIVI threshold of 25% EWL at 12 months and ≥5% TBWL with a serious AE rate of <5% as put forth by the ASGE and American Society for Metabolic and Bariatric Surgery [34]. More research is needed to understand how endoscopic bariatric procedures can go beyond just reducing gastric volume and achieve the metabolic changes seen in bariatric surgery, with long-term durability. Results from studies comparing endoscopic and surgical approaches will be useful to help patients make informed decisions based on effectiveness and safety profile. In this new era of personalized medicine, we must strive to develop an individualized approach to obesity management and tailor our therapies and interventions to each unique patient to optimize outcomes.

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Strategies in Management of GERD in the Severely Obese Undergoing Bariatric Surgery

56

Ninh T. Nguyen, Ava Runge, and Kenneth J. Chang

Objectives

1. Understand the relationship between GERD and obesity.
2. Understand the current surgical options for the management of patients with GERD and severe obesity.
3. Understand the potential mechanisms of antireflux surgery.
4. Discuss the potential pathophysiology of GERD associated with bariatric surgery.
5. Discuss innovative strategies for the surgical management of patients presenting with GERD and severe obesity.

Gastroesophageal reflux disease (GERD) and obesity are two of the most common digestive conditions, and the prevalence of GERD is high in those undergoing bariatric surgery [1]. Because of the high association between obesity and GERD, it is critically important to evaluate patients undergoing bariatric surgery for the presence of GERD in addition to the appropriate pre-operative work-up for bariatric surgery. The conventional diagnostic evaluation for GERD should involve objective testing, including esophageal manometry, upper gastrointestinal contrast study, upper endoscopy with pH testing, and, when clinically indicated, testing for other causes of GERD such as delayed gastric emptying. For patients presenting with severe obesity and GERD, it is important to provide counseling on the efficacy of bariatric surgery in potentially improving many obesity-related comorbidities, including type II diabetes, hypertension, hyperlipidemia, cardiovascular disease, and obstructive sleep apnea. However, outcomes for reflux disease following bariatric surgery are variable. Gastroesophageal reflux is one condition in which weight loss associated with bariatric surgery does not consistently improve outcomes [2–4]. This chapter aims to outline current surgical options in the management of patients with GERD undergoing bariatric surgery, discuss the potential pathophysiology of GERD associated with bariatric surgery, and highlight innovative strategies in the surgical management of patients presenting with GERD and severe obesity.

Current Surgical Options in the Management GERD and Severe Obesity

For patients with both severe obesity and GERD/hiatal hernia, surgical options have always revolved around the performance of a bariatric operation such as sleeve gastrectomy or Roux-en-Y gastric bypass in combination with a hiatal hernia repair. Studies have shown that GERD symptom control is superior after Roux-en-Y gastric bypass than it is after sleeve gastrectomy [2–4]. However, a recent randomized trial comparing sleeve gastrectomy versus Roux-en-Y gastric bypass found that among patients who received Roux-en-Y gastric bypass, 27.1% had no change in GERD symptoms, and 10.7% actually developed new-onset GERD following surgery [3]. The Roux-en-Y gastric bypass procedure is able to indirectly reduce reflux volume through the construction of a small pouch, which diverts the majority of the parietal cell mass and gastric acid away from the gastroesophageal junction. However, the Roux-en-Y gastric bypass operation itself is not a true antireflux surgery as it does not affect the antireflux barrier. Therefore, while Roux-en-Y gastric bypass may be a better operation than sleeve gastrectomy for patients with GERD and obesity, it can still be associated with persistent GERD. Additionally, many patients do not want to pursue a gastric bypass as their primary weight loss operation given issues inherent to the procedure such as late chronic marginal ulceration and an increased life-long risk of internal herniation with the potential for associated bowel ischemia [3].

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Despite Roux-en-Y gastric bypass being the preferred operation for the management of patients presenting with GERD, sleeve gastrectomy continues to be the most commonly performed bariatric operation both for patients with and without preexisting GERD. While weight loss associated with sleeve gastrectomy can lead to GERD symptom improvement, the operation has also been reported to worsen GERD, and a proportion of patients develop new onset GERD postoperatively [3]. Following early experiences with the sleeve gastrectomy procedure, postoperative GERD was thought to be primarily related to the construction of a high-pressure, non-compliant system and technical issues associated with narrowing of the gastric incisura leading to a partial distal obstruction [5]. However, despite technical improvements over the years that have limited the incidence of distal gastric narrowing, GERD continues to be an issue after sleeve gastrectomy. Considering our knowledge of antireflux surgery and the antireflux barrier, we surmised that GERD after sleeve gastrectomy or even after Roux-en-Y gastric bypass is not related to individual skill level in performing these procedures but rather is due to these operations inherently disrupting the anatomy of the antireflux barrier. Some investigators have advocated for the performance of a true antireflux operation (hiatal hernia repair and Nissen) in combination with the sleeve gastrectomy to improve postoperative GERD outcomes [6, 7]. However, the proposed Nissen fundoplication combined with sleeve gastrectomy is an operation that requires the use of a large portion of the gastric fundus and hence has the potential for a negative impact on weight loss.

Pathophysiology of GERD Associated with Bariatric Surgery

Why does GERD continue after bariatric surgery despite significant weight loss, even when the majority of other obesity-related comorbidities improve or resolve as weight loss progresses? The answer may lie in our understanding of the antireflux barrier and the body's inherent antireflux mechanisms [8]. The components of the antireflux barrier are noted in Fig. 56.1 and include (1) the crura of the diaphragm, (2) the lower esophageal sphincter (LES), and (3) the gastroesophageal flap valve (GEFV) [8–11]. The pathophysiology of GERD includes the development of a hiatal hernia and loss of the intraabdominal esophageal segment, resulting in loss of the GEFV and subsequent impaired LES function. Conventional antireflux surgery (hiatal hernia and fundoplication) is effective and has proven the test of time in the management of GERD [11]. The time-tested surgical principles of antireflux surgery reverse the above processes by reducing the hiatal hernia, repairing the crura, reestablishing the intraabdominal esophageal segment, and recreating and accentuating the GEFV and the LES through some form of fundoplication [12]. These principles should be adhered to in the management of patients with GERD and obesity [12, 13].

For patients with severe obesity and GERD, the main surgical option is either a hiatal hernia repair with Roux-en-Y gastric bypass or sleeve gastrectomy, with the majority of surgeons leaning toward the Roux-en-Y gastric bypass. In terms of antireflux barrier correction, the hiatal hernia repair corrects one of the three defective antireflux barriers, while

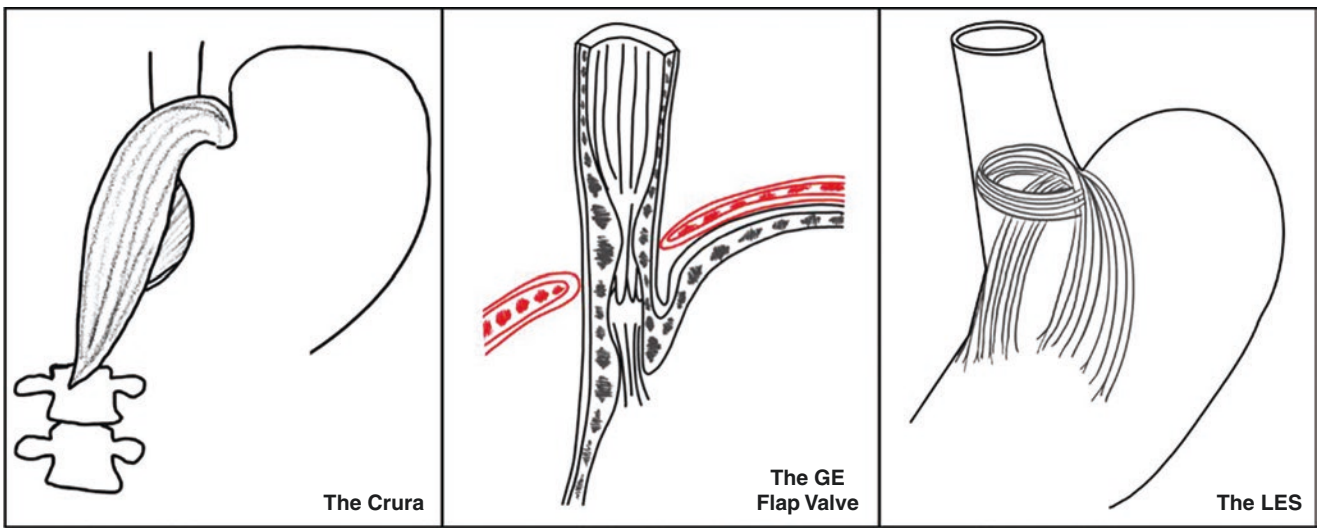

Fig. 56.1 Components of the antireflux barrier

the Roux-en-Y gastric bypass and sleeve gastrectomy surgically disrupt the other two antireflux barriers (the LES and GEFV). The LES encircles the lower esophagus and extends to the gastric cardia along the lesser curvature in the form of the sling fibers [14]. The GEFV is formed by 1–2 cm of the intraabdominal esophagus with the distal esophagus entering the stomach at an oblique angle, leading to apposition of the distal esophagus and the gastric cardia/fundus at the level of the angle of His [11]. The oblique entry between the intraabdominal esophagus and the gastric cardia/fundus creates a natural 120°–180° musculomucosal flap valve otherwise known as the GEFV [11]. Both the sleeve gastrectomy and gastric bypass operations essentially eliminate the naturally occurring GEFV and LES as they surgically divide the LES gastric sling fibers and the gastric fundus at the level of the angle of His (Fig. 56.2). Anatomically, the sleeve gastrectomy and the construction of a small pouch during the Roux-en-Y gastric bypass convert an oblique entry to a direct entry from the esophagus to the stomach that is a prone to reflux [14]. Therefore, development of GERD after sleeve gastrectomy or Roux-en-Y gastric bypass operations is likely related to the inherent anatomic disruption of the LES and GEFV antireflux barriers during surgery.

In summary, although the sleeve gastrectomy and Roux-en-Y gastric bypass are excellent bariatric operations, they are not themselves antireflux operations and can actually induce reflux by disrupting the natural antireflux barriers. The Roux-en-Y gastric bypass is the preferred operation in the management of patients with GERD as the procedure diverts the majority of the parietal cell mass. However, Roux-en-Y gastric bypass is also not an antireflux operation, and the remaining gastric pouch can often produce enough acid to lead to ongoing troubling reflux symptoms. The conversion of an oblique to a direct entry also may explain the

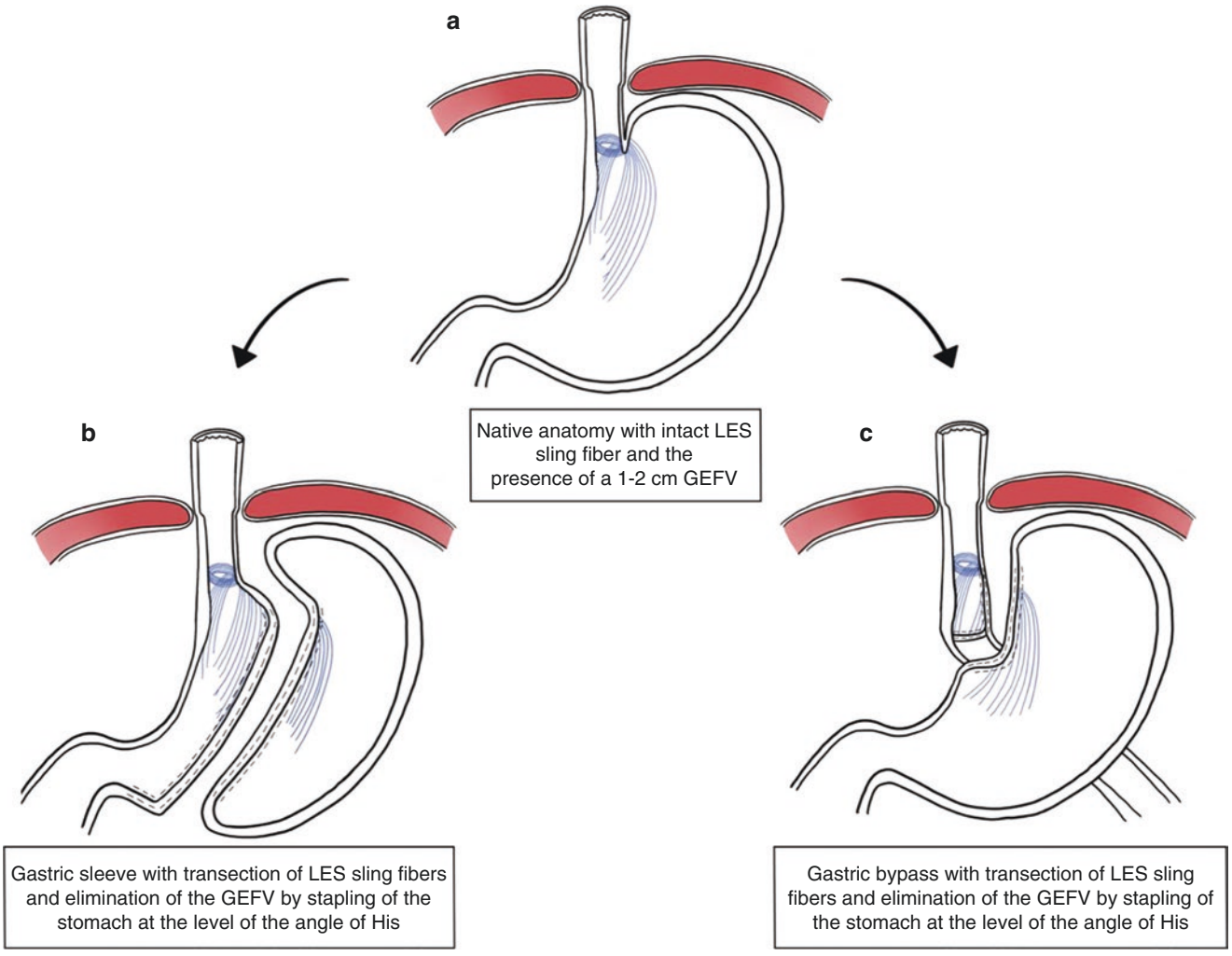

Fig. 56.2 Pathophysiology of GERD in bariatric surgery, which includes mechanical disruption of the LES and surgical transection at the level of the angle of His, essentially eliminating the gastroesophageal flap valve. (**a**) Native anatomy with intact lower esophageal sphincter and its sling fibers and the presence of a 1–2 cm flap valve. (**b**) Gastric sleeve with transection of the lower esophageal sphincter and its sling fibers leading to loss of the flap valve. (**c**) Gastric bypass with transection of the lower esophageal sphincter and its sling fibers leading to loss of the flap valve

development of de novo GERD following bariatric surgery despite the significant weight loss following the operation. By converting the natural oblique entry to direct entry of the esophagus into the stomach, such procedures lead to construction of a hollow tube that completely eliminates the naturally occurring flap valve [11]. Although hiatal hernia repair combined with sleeve gastrectomy or Roux-en-Y gastric bypass can support one of the antireflux barriers (the crura), studies have shown that de novo GERD can still develop after hiatal hernia repair with sleeve gastrectomy [15]. The GEFV is one of the most important mechanisms to prevent reflux [11]. We hypothesize that loss of the flap valve is likely one of the main contributors to the development of de novo GERD after bariatric surgery.

Innovative Strategies in the Management of Patients with GERD and Obesity

Staged Procedures: Antireflux Surgery Followed by Bariatric Surgery

Instead of offering the conventional hiatal hernia repair with Roux-en-Y gastric bypass or sleeve gastrectomy for patients with documented objective GERD and obesity, a strategy employed at the University of California, Irvine, is to manage GERD and obesity in staged procedures. The first stage addresses GERD through the performance of a concomitant laparoscopic hiatal hernia repair with transoral incisionless fundoplication (cTIF). This antireflux operation has been shown to be effective in the management of GERD [16]. The rationale for using this specific antireflux surgical technique is that it utilizes the gastric cardia for the fundoplication, while conventional laparoscopic fundoplication such as the Nissen, Dor, or Toupet utilizes a large portion of the gastric fundus. Therefore, in cTIF, the gastric fundus can still be removed or excluded as part of a bariatric operation at a later date. This bariatric procedure (sleeve gastrectomy or Roux-en-Y gastric bypass) is typically performed approximately 3–6 months after the cTIF. Since GERD is addressed prior to bariatric surgery in this case, it is not a requisite to perform a Roux-en-Y gastric bypass in these patients. There are some technical details that need to be considered when performing the bariatric operation after cTIF. It is critical to avoid mobilization of the angle of His and the gastric fundus complex and leave the newly formed GEFV intact. This is done by stapling the stomach lateral to the angle of His to avoid disrupting the angle of His/gastric cardia/distal esophageal complex. Maintaining this acute angle of His will in turn maintain the oblique entry of the esophagus and the GEFV. This staged approach sequentially addresses GERD first followed by managing obesity. Since GERD is managed separately by an antireflux operation, there is no need to continue to select the Roux-en-Y gastric bypass as the preferred operation in this patient population. The authors are currently conducting a prospective study of cTIF followed by sleeve gastrectomy in the management of patients with GERD and severe obesity.

Single Stage Procedure: Flap Valve Preserving Bariatric Surgery

Alternatively, we propose a technique in which the surgeon performing the sleeve gastrectomy or Roux-en-Y gastric bypass minimizes disruption of the antireflux barrier through following antireflux surgical principles, including (1) repairing the crura of the diaphragm, (2) obtaining an appropriate intraabdominal esophageal length, and (3) reestablishing the angle of His and maintaining the oblique entry of the esophagus in an effort to preserve the naturally occurring GEFV. Upon completion of the above steps, the sleeve gastrectomy or Roux-en-Y gastric bypass can be performed as usual, with extra attention paid to maintaining the approximated gastric fundus/distal esophagus complex at the level of the angle of His to preserve the newly constructed GEFV. This operation is termed a flap valve preserving bariatric operation.

The procedure begins with assessment of the hiatus, which often shows a diaphragmatic defect for patients presenting with GERD (Fig. 56.3). A hiatal dissection is then performed with division of the phrenoesophageal ligament and reduction of the hiatal hernia to achieve an appropriate intraabdominal esophageal length (Fig. 56.4). The hiatus is then repaired with interrupted sutures over a 40 F bougie (Fig. 56.5). At this point, the distal esophagus and the gastric cardia/fundus are approximated with multiple interrupted sutures to reestablish the angle of His in an approximate 120°–180° fashion (Fig. 56.6). Reestablishment of the angle of His between the distal esophagus and the gastric cardia/fundus maintains and accentuates the naturally occurring

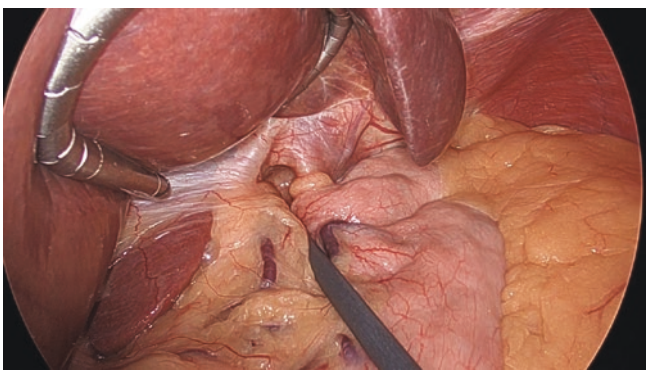

Fig. 56.3 Laparoscopic view of a hiatal defect at the time of planned hiatal hernia repair and sleeve gastrectomy

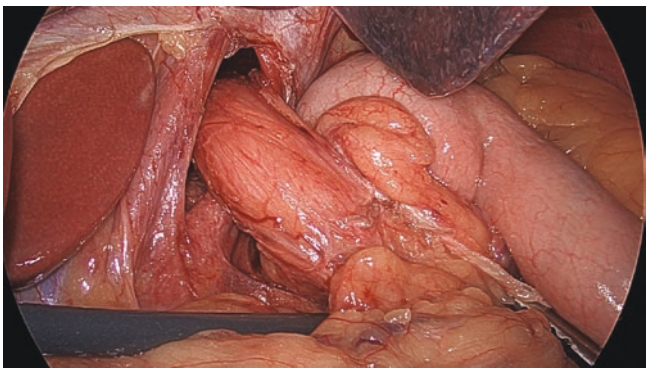

Fig. 56.4 Laparoscopic esophageal lengthening of the intraabdominal esophageal segment in preparation for hiatal hernia repair

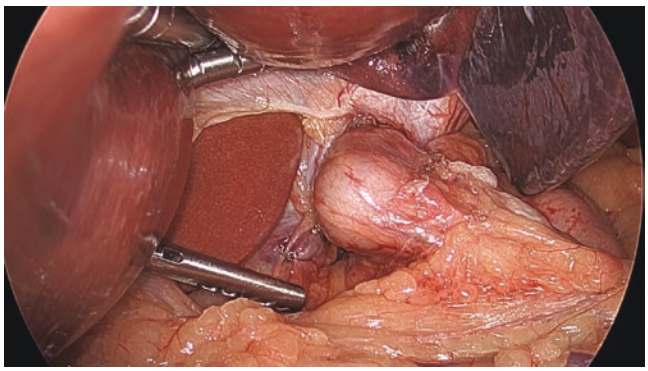

Fig. 56.5 Laparoscopic hiatal crural closure with a 40 F bougie positioned within the esophagus

GEFV. Upon completion, a 40 F bougie is positioned along the lesser curvature of the stomach, and performance of the sleeve is completed in the conventional fashion with care to avoid narrowing of the gastric incisura (Fig. 56.7). At the level of the gastric cardia, the stapler is placed approximately 2 cm lateral to the recently reestablished angle of His. This maneuver is critical to avoid compromising the recently constructed GEFV (Fig. 56.8). Endoscopy is then performed to ensure patency of the gastroesophageal junction and test for leaks.

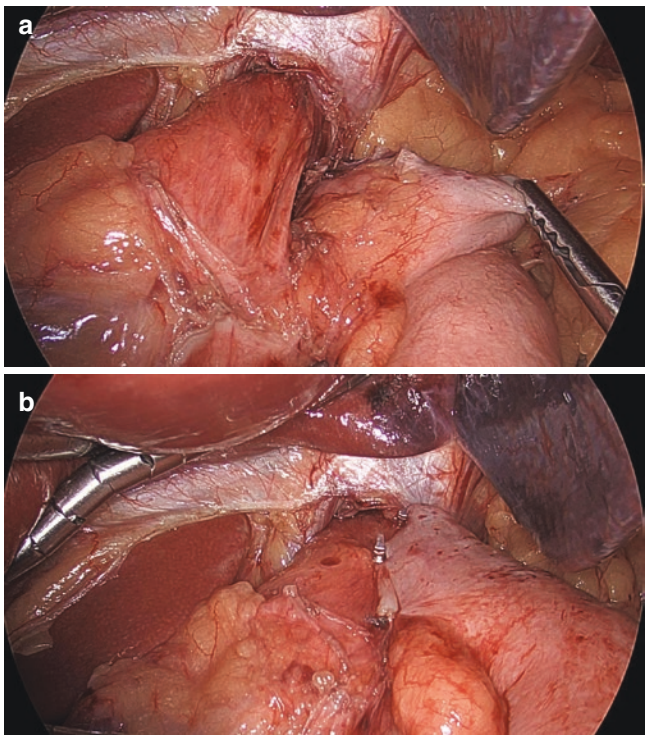

Fig. 56.6 (**a**) Laparoscopic initial reestablishment of the angle of His by approximating gastric cardia/fundus to the left crura and the esophagus and (**b**) completion of laparoscopic reestablishment of the angle of His complex to construct an approximately 180° gastroesophageal flap valve

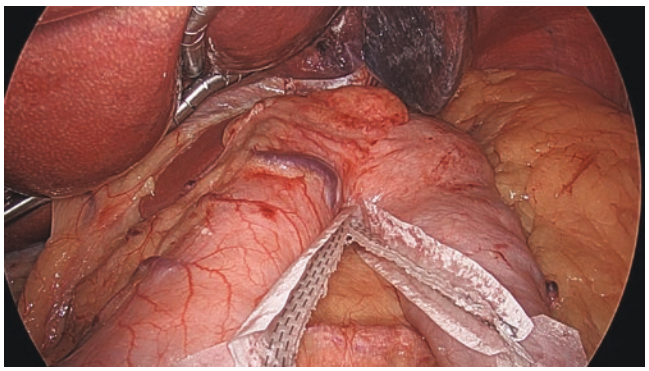

Fig. 56.7 Laparoscopic sleeve gastrectomy over a 40 F bougie after hiatal hernia repair and reestablishment of the angle of His

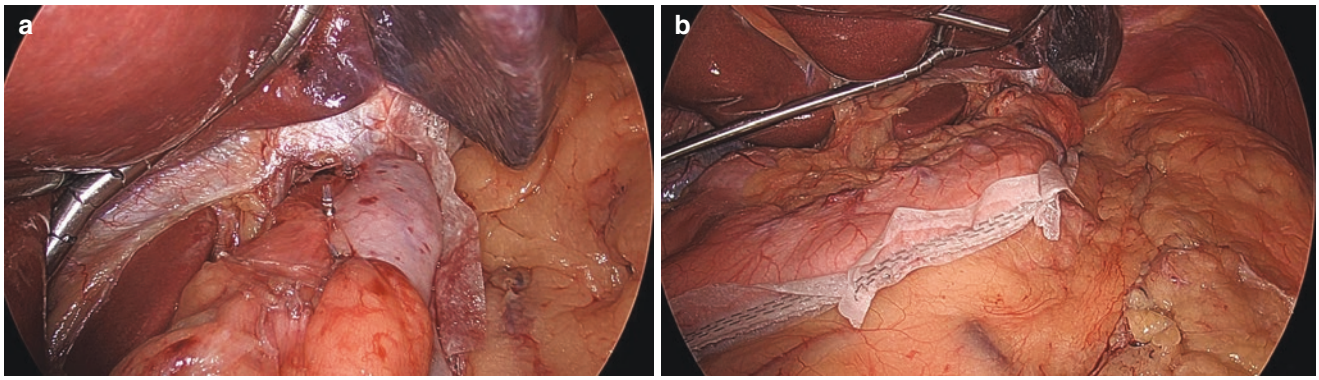

Fig. 56.8 (**a**) Laparoscopic view of sleeve gastrectomy with hiatal hernia repair and reestablishment of angle of His with preservation of the gastroesophageal flap valve and (**b**) close-up laparoscopic view of the gastroesophageal junction showing preservation of the gastric fundus, angle of His, and distal esophageal complex

Conclusions

Sleeve gastrectomy and Roux-en-Y gastric bypass are now the two most commonly performed bariatric operations in the world. These operations are associated with significant weight loss and improvement/resolution of comorbidities. However, there is one condition that continues to plague these operations—persistent or de novo GERD. GERD symptoms can worsen after sleeve gastrectomy and Roux-en-Y gastric bypass, and a proportion of patients develop new onset GERD symptoms after the surgery [3]. Considering our knowledge of antireflux surgery and the antireflux barrier, we surmised that GERD after sleeve gastrectomy and gastric bypass is due to these operations inherently disrupting the anatomy of the antireflux barrier. Specifically, the division of the LES and the transection of the gastric fundus at the level of the angle of His essentially eliminates the naturally occurring flap valve. Although hiatal hernia repair in addition to bariatric surgery provides support for one of the antireflux barriers (the crura), studies have shown that de no GERD can still develop after hiatal hernia repair with sleeve gastrectomy [15]. The anatomic disruption caused by both the sleeve gastrectomy and Roux-en-Y gastric bypass converts the natural oblique entry of the esophagus to a direct entry path into the stomach, creating a hollow tube that completely eliminates the naturally occurring flap valve. The proposed staged procedure or flap valve preserving bariatric operation is a technical variation of the conventional bariatric operation, which preserves the gastric cardia/angle of His complex and hence preserves the GEFV (Fig. 56.9) and its oblique entry.

In conclusion, sleeve gastrectomy and gastric bypass are excellent bariatric operations. However, they are not antireflux operations but rather reflux-inducing operations that disrupt the natural antireflux barrier. The Roux-en-Y gastric bypass is a good antireflux operation as it diverts the majority of the parietal cell mass. However, the remaining gastric pouch, no matter how small, can often produce enough acid to lead to continued reflux. The strategies presented in this chapter for the management of patients with GERD and severe obesity included (1) a staged procedure with performance of an antireflux operation (cTIF) followed by a bariatric operation or (2) a bariatric operation with a specific technique that preserves the antireflux barrier, specifically maintaining the gastroesophageal flap valve.

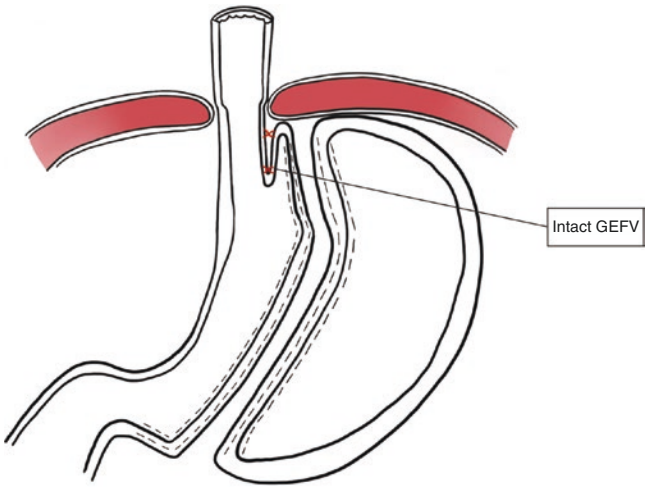

Fig. 56.9 Schematic drawing of the flap valve preserving sleeve gastrectomy

Question: Which of the below is a component of the antireflux barrier?

1. The crura of the diaphragm
2. The gastric fundus
3. The gastric incisura
4. Gastric emptying

Answer: 1, components of the antireflux barrier include the crura of the diaphragm, the lower esophageal sphincter and its sling fibers, and the gastroesophageal flap valve.

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Endoscopic Management of Bariatric Complications

57

Vitor Ottoboni Brunaldi, Christopher C. Thompson, and Manoel Galvao Neto

Objectives

1. To get familiar with the most common bariatric complications that can be addressed endoscopically.
2. To summarize the most updated evidence on the several modalities to help close bariatric leaks.
3. To understand the role and limitations of endoscopy in treating bariatric anastomotic complications such as strictures and marginal ulcers.
4. To differentiate isolated sleeve gastrectomy stricture from those associated with leak and to treat them accordingly.

Introduction

Bariatric surgery is the most effective therapy to address moderate to severe cases of obesity [1]. It leads to sustained long-term weight loss associated with a reduction in mortality rates, amelioration of co-morbid conditions, and improvement in quality of life [2, 3]. Unsurprisingly, there is an exponential growth in the number of bariatric procedures worldwide [4].

The laparoscopic approach is the current standard of care. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most common procedures and account for almost 80% of all bariatric operations [5]. Both techniques are highly standardized and safe and carry a 90-day mortality rate as low as 0.1% [6]. However, non-fatal complications are far more common [7, 8]. In that situation, prompt diagnosis and treatment are critical to restrain clinical deterioration and minimize further sequelae. Flexible endoscopy is pivotal in the diagnosis and management of bariatric complications. This chapter presents the most relevant adverse events arising from bariatric surgery and discusses the therapeutic role of endoscopy.

Leaks (RYGB and SG)

Overall Clinical Management

Leaks are significant adverse events associated with higher overall complication rates, higher mortality rates, and longer length of stay [9, 10]. The mainstays of treatment entail not only local but also systemic therapy. In this case, systemic therapy includes adequate drainage (either internal or external); infection control by broad-spectrum intravenous antibiotics; the establishment of a dietary route (enteral is preferred over total parenteral nutrition) [11]; and chemoprophylaxis for deep venous thrombosis [12].

Accordingly, treating leaks demand a well-coordinated multidisciplinary team and daily panel discussion on the patient's clinical status. As to the local treatment, the clinical stability at presentation is central for deciding between the operative and non-operative therapeutic modality. The doctor should refer patients with diffuse abdominal pain and peritonitis or those clinically unstable to emergency surgery. In the absence of those signs, non-operative treatment is recommended [12].

Endoscopic modalities are local therapies that should accompany the above-mentioned systemic treatment. There are three physiologically distinct groups of endoluminal techniques: internal drainage, closure, and diversion. They are not mutually exclusive; on the contrary, the endoscopist

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should combine them to achieve higher resolution rates while minimizing adverse events.

The first step of non-operative management is to confirm that the leak or adjacent collection has adequate drainage. That is key since the gastrointestinal fluid is permanently contaminated and may lead to peritonitis, sepsis, or abscess formation if not correctly addressed [13]. Surgical drains from the primary procedure are usually enough to guarantee fluid flow. In the absence of surgical drains, the patient should be referred to surgical, endoscopic, or interventional radiology drainage. The choice should be at the discretion of the multidisciplinary team. Determinant factors in deciding among those modalities include local expertise, availability, and the distance between the orifice and the collection [14].

The second step is to identify and treat factors that impair healing, such as a distal stricture or foreign bodies inside the leak orifice (drains or loose staples). If present, distal strictures should be dilated, and foreign bodies should be removed.

Finally, the endoscopist should employ local therapy to expedite the leak closure. Several procedures, techniques, and devices are currently available in this setting: self-expandable metallic stents (SEMS), double-pigtail stents (DPS), endoscopic-assisted vacuum therapy (EVT), septotomy, over-the-scope clips, sealants, biomaterial plugs, and endoscopic suturing. Table 57.1 details each endoscopic modality's positive and negative aspects, and Fig. 57.1 depicts a suggested algorithmic approach to treat bariatric leaks.

Diversion/Exclusion Technique

SEMS

Self-expandable metallic stent is a generic term that refers to several different types of devices. They vary in length, diameter, coverage (uncovered, partially, or fully covered), and presence of antireflux valves and may entail fixation (shim's technique). Currently, most experts employ fully covered esophageal stents. Some authors report fixation with endoscopic suturing or clipping to prevent migration, which may occur in up to 30% of cases [15].

A recent meta-analysis pooled evidence concerning the efficacy and safety of stents as a single therapy for bariatric leaks. One hundred and eight patients with leaks following RYGB were enrolled. The overall closure rate was 76%, with an average of 1.31 stents per patient and a mean indwelling time of 42 days. Concerning SG leaks, the authors pooled 187 cases, and the average closure rate of SEMS was 72%, with an overall 28% migration rate [15]. An earlier systematic review on post-RYGB leaks had reported even better outcomes: 87% and 16% of closure and migration rates, respectively. Of note, this last article included studies describing stenting as combined therapy, which might explain such better results. Nonetheless, there was a retrieval failure rate of 8%, and three patients (4.5%) required surgical removal of the stents [16].

Some other reports described the use of longer and larger stents to reduce the migration rate of esophageal stents in this context. However, the alleged "mega-stents" have been shown painful and overly ulcerogenic. Moreover, data suggest that augmenting the size and length of stent does not significantly impact migration rates [17–20]. Finally, a recent meta-analysis showed the conventional esophageal stent to be superior to the customized bariatric stent to manage SG leaks [21]. However, one should acknowledge that the quality of evidence is very low, which warrants further investigation. Therefore, conventional esophageal stents should be the device of choice in clinical practice, while refinements of modified stents should be stimulated under research protocols.

Internal Drainage Techniques

All internal drainage techniques have the interesting rationale of inverting the leak fluid flow. Instead of going from the lumen to the collection, it facilitates flow from the collection

Table 57.1 Subjective pros and cons of each endoscopic modality to address gastrointestinal leaks

	Exclusion	Internal drainage			Closure				
Approach	SEMS	DPS	EVT	Septomy	Clipping (OTSC)	Sealants	Biomaterial plug	Suturing	Septal occluder
Early/acute	++++	+	+++	–	+++	+++	+++	+++	+
Late/chronic	+	++++	++++	++++	+	+	+	+	+++
Healing time	+++	+	+	+	+++	+++	+++	+++	++++
Cost (devices)	Medium	Low	Low	Low	Medium	Medium	Medium	High	High
Need for admission	Usually (pain)	No	Yes	No	No	No	No	No	No
Sessions needed	~02	~02	Several	Several	1	1	1	1	1
Availability	Broadly	Broadly	Broadly	Broadly	Broadly	Restricted	Restricted	Broadly	Restricted
Expertise needed	Low	Low	Moderate	Moderate	Low	Low	Low	High	Moderate

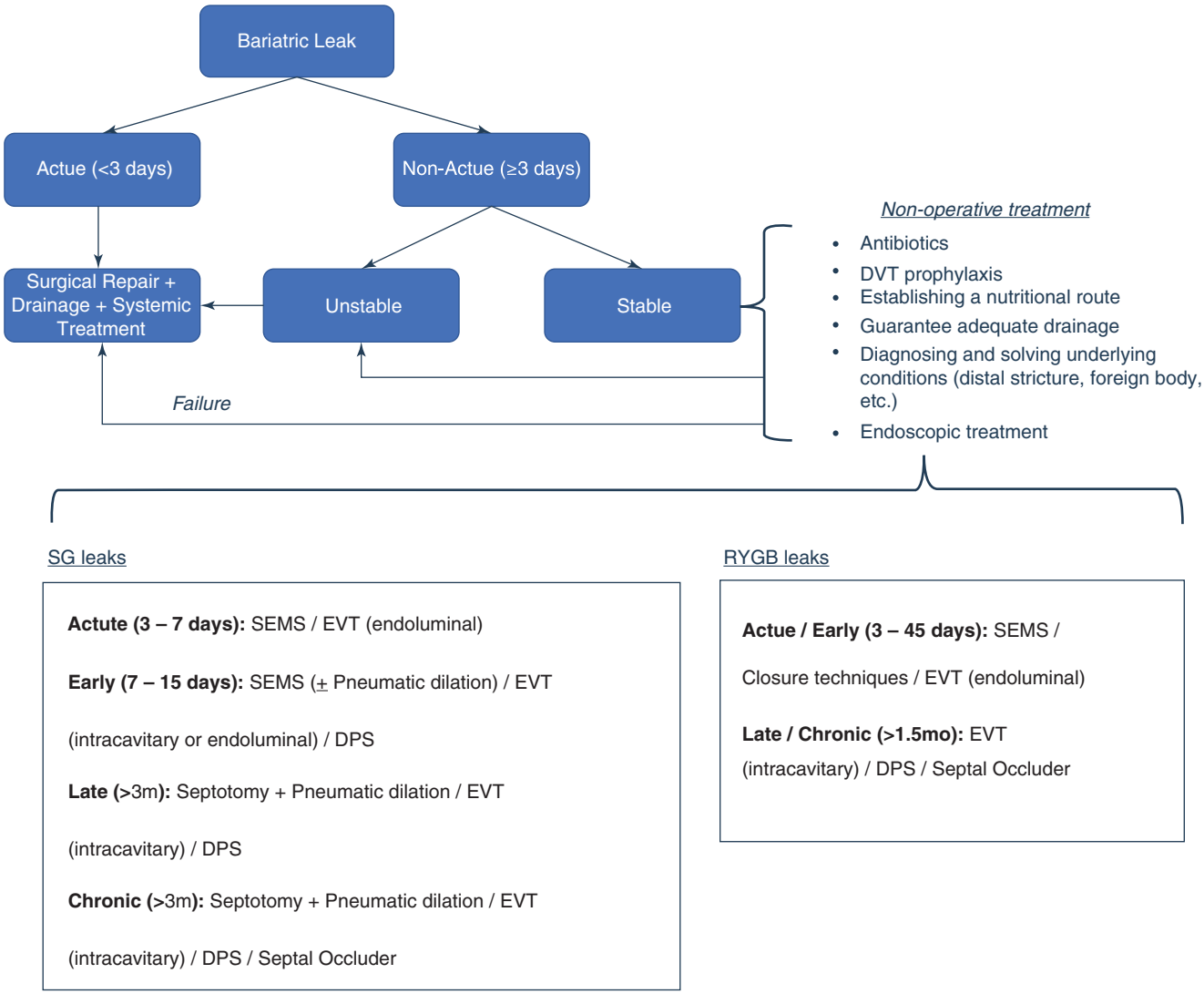

Fig. 57.1 Proposed algorithm for the primary approach of patients with bariatric leaks. *DVT* deep venous thrombosis, *SEMS* self-expandable metallic stent, *EVT* endoscopic vacuum therapy, *DPS* double pigtail stent

to the lumen. Therefore, the internal drainage diminishes the volume, helps control infection, and propitiates second intention healing.

Double Pigtail Stents (DPS)

This technique refers to the insertion of a DPS through the orifice of the leak under fluoroscopic guidance. The distal pigtail is deployed in the adjacent collection or fistulous tract, while the proximal pigtail stays in the lumen. If the size of the orifice and collection allows, two or more stents may be deployed. There is no specific need for post-procedural fasting, and this stent usually causes no symptoms. Consequently, the patient may be discharged on the same day if other clinical parameters allow [22].

Several studies have been published reporting the effectiveness and safety of DPS modality in the context of a post-bariatric leak. The closure rate in the literature ranges from 78% up to 97% [22–24]. Few adverse events have been described, but splenic hematoma is the most serious one [22]. In post-SG leaks associated with stricture or twist of the sleeve, Rebibo et al. demonstrated that the combination of stents and DPS provides substantially better outcomes than DPS alone [25]. In the absence of stents in this situation, dilation of the sleeve with a 30 mm pneumatic balloon might address the concomitant stricture, thus alleviating luminal pressure to facilitate leak healing [26]. In a comparative cohort with 100 SG leak patients, Lorenzo et al. demonstrated that internal drainage with DPS is superior to closure (clipping) and exclusion (stenting) techniques. In collections >5 cm, the DPS is even more efficient as the primary approach [23].

Finally, Donatelli et al. recently reported the outcomes of 617 consecutive patients with leaks, fistulas, or collections fol-

lowing SG treated in a French referral center. The overall clinical success of DPS was 84.7%. According to the type of presentation, the authors reported 89.5%, 78.5%, and 90% closure rates for leaks, fistulas, and collections, respectively [27].

Endoscopic Vacuum Therapy (EVT)

The negative pressure has been used in surgery for decades. Four main mechanisms of action explain the effectiveness of vacuum at treating infected sites: clearance of exudate leading to bacterial control; an increase of local concentration of vascular endothelial growth factor (VEGF) leading to enhanced angiogenesis; macrodeformation of the cavity; and microdeformation of the cavity (shrinking at a cellular level) [28].

The EVT delivers negative pressure at the leakage or fistula site through a nasogastric tube. The classic technique employs an open-pore polyurethane sponge that is cut according to the size of the abscess cavity and fixed at the tip of the tube [29]. More recently, a group from Brazil described a low-cost technique that employs gauze and surgical drapes instead of the sponge [30]. The endoscopist places the tube inside the cavity using a foreign body forceps and connects its proximal end to a continuous negative pressure source. It must be replaced periodically to avoid adherences and to allow shrinking until complete closure [31].

A recent meta-analysis comparing EVT to stents at treating upper GI tract transmural defects reported that EVT significantly increases closure rates and reduces mortality, duration of treatment, and overall adverse event rates [32]. Another recent non-comparative meta-analysis assessing the effectiveness of EVT to manage post-esophagectomy leaks reported an overall 81.6% closure rate [33]. In 2013, Seyfried et al. firstly proposed the EVT to treat a case of post-bariatric leak after stenting had failed to achieve healing [34].

EVT is an interesting option for late and chronic cases, especially when the cavity seems infected. Despite highly effective, it has some major drawbacks: it requires multiple sessions; it is an in-hospital modality; the tube usually causes moderate to severe throat pain; it requires oral fasting; and it demands the insertion of a second tube (nasoenteral) placed distally to the defect so that one can guarantee enteral feeding. Therefore, cases amenable to EVT should be carefully selected since patient compliance is central to achieve success.

Septotomy

A septum is how the boundary between the fistulous and the luminous tract appears endoscopically. Usually, it arises from leaks at the His angle, which are more common in SG patients [35]. Similar to Zenker's diverticulum, the septum drives food bolus to the fistulous tract, perpetuating the leak and collection.

The rationale of the septotomy is to take down the septum so that the lumen becomes the preferred pathway for food and saliva. The endoscopist may employ either a needle knife or APC to perform the procedure, and more than one session may be necessary. In 2007, Campos et al. firstly described the septotomy for a SG patient with a chronic gastrobronchial fistula [36]. Combined with other endoscopic techniques (mainly distal pneumatic dilation), the septotomy may reach up to 100% leak closure even for chronic cases [37, 38]. It is a cost-effective and straightforward modality that should always be considered in the presence of a marked septum.

Closure Techniques

Clipping

Through-the-scope (TTS) clips are helpful to address acute perforations and promote hemostasis in cases of upper GI bleeding. However, TTS clips are limited by their small opening and low closure force [39]. In chronic, late, and even early leaks, the tissue around the orifice is thickened, which impairs adequate tissue apposition with TTS clips. Consequently, recent articles have described the use of over-the-scope clips (OTSC) in this setting.

The over-the-scope clip (OTSC) is a sizeable bear-claw clip deployed similarly to a band ligation [40]. Hypothetically, prior mucosal ablation with a thermal method (APC) increases the chance of healing [41].

Most studies report OTSC combined with other endoscopic modalities to address post-bariatric leaks as sole OTSC carries poor outcomes [42]. The most common association is with SEMS [18, 43]. Shehab et al. proposed a therapeutic algorithm combining stents and OTSC with an overall closure rate of 82% [18]. In a retrospective comparative study, Schiesser et al. reported a similar success rate and safety of OTSC plus SEMS compared to surgical treatment [43]. Of note, if a local infection is suspected, one should avoid closure techniques.

Sealants

Both fibrin glue and cyanoacrylate have been described as adjunct endoscopic modalities to address leaks. The first has been more extensively reported in the literature. However, the success rate ranges widely from 36% [44] to 86% [45], deeming the results unreliable. Still, considering the low rates of related adverse events, the use of sealants is a possible option but only as a combined modality.

Biomaterial Plug

Maluf-Filho et al. reported a case series enrolling 25 patients with bariatric leaks treated with the Biomaterial plug (SurgiSIS®). This plug is an acellular matrix cone-shaped device that works as a scaffold to fibroblasts, ultimately promoting healing. The authors reported an 80% closure rate of post-RYGB leaks as single endoscopic therapy [46]. However, the majority of patients required at least two sessions to achieve complete closure. On the other hand, Toussaint et al. reported five cases treated with SurgiSIS® as

adjunct therapy with a 100% closure rate [47]. As the fibrin glue, the cone-shaped plug has few related adverse events and thus may be employed as a combined approach if available.

Endoscopic Suturing

Endoscopic suturing, mainly with the Apollo Overstitch device (Apollo Endosurgery, Austin, Texas, USA), has already been proposed to address bariatric leaks and fistulas. Similar to other closure techniques, suturing provides greater success chances in acute and early presentation cases. Granata et al. reported 20 patients treated with suturing alone (9/20), in combination with SEMS (7/20), or anchoring the SEMS (4/20). Fourteen out of the 20 cases presented within the 30th postoperative day, and the overall closure rate was 80%. Considering the 17 cases of GI tract surgery or bariatric procedures, the closure rate was 94% [48]. Lamb et al. treated five patients with suturing, but four received a stent at some point during their treatment. The closure rate was 80%. These articles suggest that endoscopic suturing has a role in managing leaks, especially in association with SEMS. Nevertheless, costs and availability must be taken into consideration when indicating such a modality [49].

Finally, considering gastro-gastric fistulas, the current evidence reveals elevated immediate closure rates but exceedingly high long-term recurrence rates [50, 51].

Septal Occluder

The septal defect occluder is a cardiac device developed to treat atrial septal defects. It is a lumen-apposing metal stent-like device that is deployed through the fistulous tract. Its large occluded flanges anchor at both communicating sides to avoid migration. More recently, some experts have proposed using SO to address chronic epithelized fistulas in the GI tract. In an international multicenter series, Baptista et al. reported 43 cases of post-bariatric leaks (35 late or chronic) with clinical success in 39 patients (90.7%). Regression analysis showed that chronicity correlated with higher closure rates: in late/chronic cases, the success rate was 97.1% versus 62.5% in early/acute ones [52].

If available, the septal occluder seems an interesting option for chronic and recurrent leaks/fistulas. However, one must consider that no study to date described the long-term management of this therapy as the device must be permanently left in place. Therefore, further studies are needed to elucidate the safety of the septal occluder in the long term.

Gastrojejunal Anastomosis (GJA) Stricture

GJA strictures are uncommon complications that affect 1 among 1000 patients undergoing RYGB. Interestingly, it seems more frequent after open than laparoscopic surgery [53]. The patient usually presents severe vomiting within 3 months postoperatively. Either a contrast study or an upper endoscopy may confirm the diagnosis. Through-the-scope balloon dilation is the recommended initial approach. Diameters from 12 to 15 mm safely address most cases [54]. Usually, one or two sessions are enough to treat the anastomotic stricture so that the patient remains permanently asymptomatic [53, 55]. Adverse events are rare, but perforation and bleeding have already been described [56]. For refractory cases, incisional therapy with corticoid injection should be employed to avoid a revisional surgery [57].

Marginal Ulcers (RYGB)

Marginal ulcers (MUs) are chronic ulcers arising at the jejunal side of the GJA, typically between the first and the sixth postoperative month. The incidence ranges from 0.6% to 16% in the literature. Epigastric pain, nausea, vomiting, and bleeding are the main symptoms. Non-steroid anti-inflammatory drug use, augmented gastric acid secretion, local ischemia, alcoholism, smoking, and foreign body reaction to sutures or staples in the GJA are possible underlying conditions [58, 59]. The upper endoscopy is the gold-standard diagnostic method [60].

Concerning treatment, pharmacological therapy is the initial approach, and it carries high healing rates if associated with lifestyle interventions (mainly cessation of alcohol and tobacco consumption). Proton pump inhibitors (PPIs) and sucralfate are the most commonly employed drugs in this context. Following complete healing, the recurrence rate is extremely low [60]. Of note, a retrospective cohort study showed recently that open PPI capsules led to shorter ulcer healing time, less need for endoscopic intervention, and lower overall treatment cost compared to intact capsules [61].

As to the therapeutic role of endoscopy, it should be restricted to refractory cases. Initially, removal of loose staples or embedded sutures is recommended [62, 63]. Ryou et al. reported that more than 70% of symptomatic patients experienced pain relief after endoscopic foreign body removal [63].

More recently, some studies have reported covering the ulcer bed with suturing or stenting in recalcitrant cases. Barola et al. enrolled 11 patients with refractory marginal ulcers to undergo endoscopic suturing or fully covered SEMS placement depending on the GJA diameter. Ulcers with small anastomoses (<12 mm) received SEMS, while those with large stomas were sutured. At 8 weeks, surveillance endoscopy revealed complete ulcer healing in 10/11 patients (90.9% clinical success rate) [64]. This a promising procedure, but the number of cases

in the literature is yet small. Long-term follow-up and larger studies are needed to confirm the efficacy and safety of such an approach.

Isolated Sleeve Gastrectomy Stricture

Isolated sleeve gastrectomy strictures (SGS) refer to cases with stenotic segments or twist of the sleeve with no associated leaks. If present, treatment should be tailored by the leak and not by the stricture since that is a more urgent condition [65].

Isolated strictures may be present in up to 3.9% of cases [66], and the patient typically presents with mild-to-moderate nausea and vomiting. Nonetheless, severe cases complicated with malnutrition have also been described [67]. Brunaldi et al. recently published a meta-analysis comprising 419 SGS patients. This article analyzed and compared outcomes of conservative, endoscopic, and surgical approaches. As primary treatment, clinical resolution rates were 68% (11/16), 82% (296/361), and 75% (34/45), respectively. There was no statistical difference in terms of success, but the endoscopy had significantly fewer complications than surgery. The pneumatic dilation had the highest success rate (80.3%) among the endoscopic modalities [26]. Further data demonstrated that the resolution of symptoms is perennial [68].

Therefore, the therapeutic algorithm for SGS includes an initial attempt of medical treatment during the first 3 weeks postoperatively. Then, endoscopic pneumatic dilation should be the next step, followed by SEMS placement, if necessary. Surgical conversion to RYGB should be reserved for refractory and non-responsive cases.

Silastic Ring and Band-Related Complications (Fobi-Capella Procedure)

Silastic ring slippages are late adverse events following Fobi-Capella procedures. Slippage refers to the distal migration, while erosion refers to the endoluminal migration of a band or a ring. The first usually presents with obstructive symptoms, but weight regain may also arise [69]. On the other hand, patients with band or ring erosion may present with abdominal pain, food intolerance, bleeding, and even fever due to the formation of a localized abscess [70–72].

Even though erosion and migration are similar complications, the treatment differs considerably. Campos et al. reported a series of 35 patients with ring slippage successfully treated with 30 mm pneumatic balloon dilation. Fluoroscopy allowed the operator to assess for rupture of the thread. The balloon was kept inflated for 30 min if it remained intact, which usually caused the ring to stretch, relieving obstructive symptoms. Patients with persistent symptoms underwent further sessions until complete resolution. The authors reported 100% clinical success with an AE rate of 14.3%. There were no SAEs, but most patients experienced weight regain [73].

As to band or ring erosion, the treatment necessarily entails removing the device to avoid further complications. Since surgery is challenging due to postoperative peritoneal adhesions, endoscopic removal may be attempted [74]. In cases of significant erosion (>50% of circumference), single-session retrieval is usually successful. Endoscopic scissors, APC, or a looped guidewire connected to a mechanical lithotriptor may be employed to transect the ring or the band (Fig. 57.2). Then, the endoscopist employs a foreign body forceps or a polypectomy snare to grasp the device and retrieve it transorally [75].

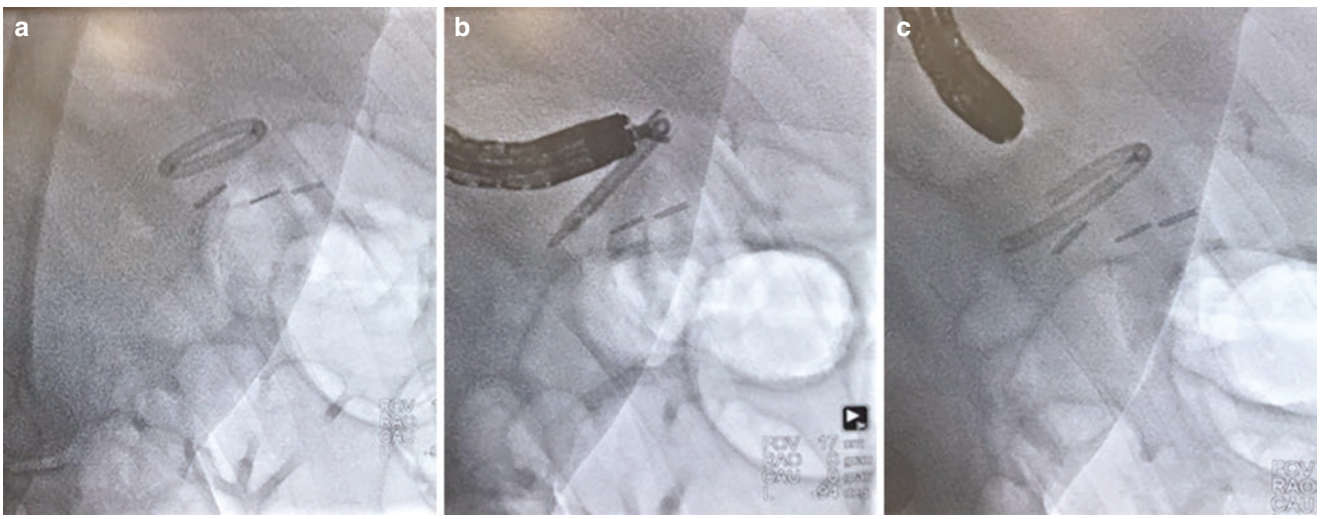

Fig. 57.2 Fluoroscopic view of the transection of an eroded migrated silastic ring using endoscopic scissors. (**a**) Intact sylastic ring; (**b**) Endoscopic transection; (**c**) Open ring

In cases of partial erosion (<50% of circumference), adjunct modalities are usually necessary. Stenting has been reported in this context, although GJA strictures are common afterward [70, 76]. The expansion force of the stent promotes overpressure of the wall against the ring or the band, leading to ischemia and expediting the erosion process. After removing the stent, cutting and retrieval of the band/ring follow the technique described earlier.

Campos et al. published the largest series describing outcomes of the endoscopic removal of sylastic rings. Forty-one patients underwent removal of partially eroded rings with self-expandable plastic stent placement [70]. As to band erosion, Galvao Neto et al. reported a series of 82 patients treated with endoscopic removal. The success rate was 95% (78/82), being 85% in a single session. Five patients presented post-procedural pneumoperitoneum, but only two required further intervention [75].

Questions

1. Which of those is the best situation for self-expandable metallic stents?
   A. Sleeve gastrectomy leak diagnosed at POD 2 with diffuse abdominal tenderness
   B. Sleeve gastrectomy leak diagnosed at POD 5 during methylene blue ingestion test, without abdominal pain
   C. RYGB leak presenting 6 months after surgery with chronic cough and a contrast study showing gastrobronchial fistula
   D. Sleeve gastrectomy presenting at 2 months after surgery with recurrent intermittent output of gastric content through the orifice of the surgical drain

Answer: B: Early and acute leaks are the most responsive to exclusion techniques such as SEMS; however, diffuse peritonitis demands surgical cleansing and drainage.

2. Which of those endoscopic modalities could be adequately employed in a patient with chronic enterocutaneous fistula after SG?
   A. Septotomy plus pneumatic dilation
   B. Double pigtail stent
   C. Endoscopic vacuum therapy
   D. All of the above

Answer: D: All internal drainage modalities adequately address chronic leaks.

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Bariatric Surgery Complications and Management

58

Christopher Pearcy, Andre Teixeira, Muhammad Ghanem, and Natan Zundel

Introduction

The World Health Organization estimates that around 650 million people worldwide are considered obese. This number is expected to rise significantly over the coming decades due to a sharp rise in childhood obesity from 4% in 1975 to 18% in 2016 [1]. With the increasing prevalence of obesity, bariatric operations are becoming common. The ASMBS estimates that 256,000 bariatric operations were performed in 2019. The breakdown of these bariatric procedures can be seen in Fig. 58.1 [2].

In general, bariatric surgery has been shown to be a safe and effective option for weight loss. Additionally, research has shown that the all-cause mortality reduction in patients undergoing bariatric surgery outweighs the risk of associated complications. With the increasing incidence of bariatric operations, complications are being seen more frequently albeit at a lower rate than in previous decades. The rate of complications associated with bariatric surgery has declined sharply from 11.7% in 1998 to 1.4% in 2016. Over that same time, mortality related to bariatric surgery has decreased from 1% to 0.04% [3]. Nonetheless, complications will continue to occur, and it is important for the bariatric surgeon, as well as the general and acute care surgeon, to understand management of these complications.

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Estimate of Bariatric Surgery Numbers, 2011-2.19

Published March 2021

	2011	2012	2013	2014	2015	2016	2017	2018	2019*
Total	**158,000**	**173,000**	**179,000**	**193,000**	**196,000**	**216,000**	**228,000**	**252,000**	**256,000**
Sleeve	17.8%	33.0%	42.1%	51.7%	53.6%	58.1%	59.4%	61.4%	59.4
RYGB	36.7%	37.5%	34.2%	26.8%	23.0%	18.7%	17.8%	17.0%	17.8%
Band	35.4%	20.2%	14.0%	9.5%	5.7%	3.4%	2.7%	1.1%	0.9%
BPD-DS	0.9%	1.0%	1.0%	0.4%	0.6%	0.6%	0.7%	0.8%	0.9%
Revision	6.0%	6.0%	6.0%	11.5%	13.6%	14.0%	14.1%	15.4%	16.7%
Other	3.2%	2.3%	2.7%	0.1%	3.2%	2.6%	2.5%	2.3%	2.4%
Balloons	–	–	–	–	0.3%	2.6%	2.8%	2.0%	1.8%

The ASMBS total bariatric procedure number are based on the best estimation from available data (BOLD,ACS/MBSAQIP, National Inpatient Sample Data and outpatient estimations).

**New methodology for estimating outpatient procedures done at non-accredited centers.*

Fig. 58.1 Estimate of bariatric surgery numbers, 2011–2019

Complications of Sleeve Gastrectomy

Laparoscopic sleeve gastrectomy (LSG) is currently the most performed bariatric operation. LSG is generally safe and due to the lack of a minimally invasive anastomosis is considered less difficult to perform. LSG is associated with comparable weight loss to Roux-en-Y gastric bypass (RYGB), and it is associated with an overall low incidence of complications [4–6] (Fig. 58.2).

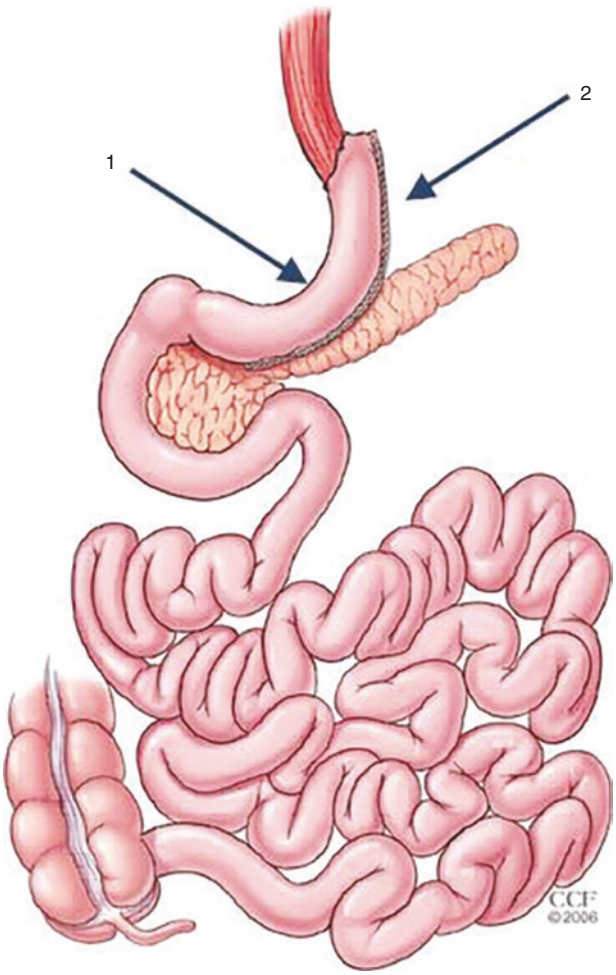

Fig. 58.2 Normal anatomy after sleeve gastrectomy [7]

Staple Line Leaks

Staple line leak following laparoscopic sleeve gastrectomy is an infrequent but potentially devastating complication. The incidence of staple line leaks is reported to be 0.8–2.7% according to MBSAQIP database [4, 8]. Leaks have been reported in as high as 7% of cases. Incidence does seem to increase with increasing BMI [9]. The most frequent site of leaks is along the proximal staple line near the esophagogastric junction at the angle of His. The cause is multifactorial and may be related to improper staple height choice, increased intraluminal pressure from a concomitant stenosis, ischemia related to thermal injury, or over-dissection of the posterior wall of the stomach [10]. Of note, the use of staple line reinforcement has not been shown to reduce the risk of leak following LSG [11–13]. Symptoms of leak include tachycardia, pain, fever, nausea, emesis, peritonitis, and sepsis. Abdominal exams are known to be less reliable in the morbidly obese patient, and leaks may present with unexplained tachycardia alone. Index of suspicion for leak should be high in any patient with persistent tachycardia after laparoscopic sleeve gastrectomy. Diagnosis of leak can be made with computed tomography (CT) scan which demonstrates evidence of free intraperitoneal air, fluid collection, and often location of the leak. Upper gastrointestinal series is another useful option but is considered less sensitive. Upper endoscopy is also a useful option and may provide diagnostic and therapeutic benefit. Finally, if index of suspicion for leak is high, negative imaging studies should not preclude re-operation to rule out staple line leak.

Management of these leaks depends on the size of the leak, associated signs of sepsis, and the chronicity of the leak itself. Small, contained leaks can be managed conservatively with percutaneous drainage, antibiotics, and nutritional support via enteral or parenteral routes. Endoscopic options are available with variable results. Studies have shown endoscopic stenting to be effective in up to 66.7% of cases. Success rates are higher in early leaks, while chronic leaks/fistulas are less likely to close with stenting alone. Endoscopic stenting is associated with stent migration in up to 22% of patients. Tolerance of stents is variable but can cause pain and worsening reflux as these stents often span the EGJ through the incisura angularis [14]. A 2017 systematic review of endoscopic clip placement for management of LSG leak showed an 86.3% success rate for closure of small leak with overall low complication rate [15]. An alternative option is endoscopic internal drainage via placement of a double pigtail catheter between leak and lumen. Again, systematic review of several small series has shown a success rate around 83% for fistula closure [16]. Fibrin glue deposition is also an option but has variable results (Fig. 58.3).

Patients presenting with larger leaks or signs of intraabdominal sepsis require more aggressive management. Patients who are unstable or with signs of peritonitis require urgent surgical exploration. This often can be done through laparoscopic or robotic-assisted laparoscopic approaches. Operative management in the acute setting includes irrigation and wide drainage with or without oversewing of the leak. Placement of feeding jejunostomy tube for enteral feeds should also be considered. Around 82% of these leaks will heal with expectant management alone. Some of these will progress to chronic fistula. In the case of a chronic leak, it is important to rule out distal obstruction at the incisura

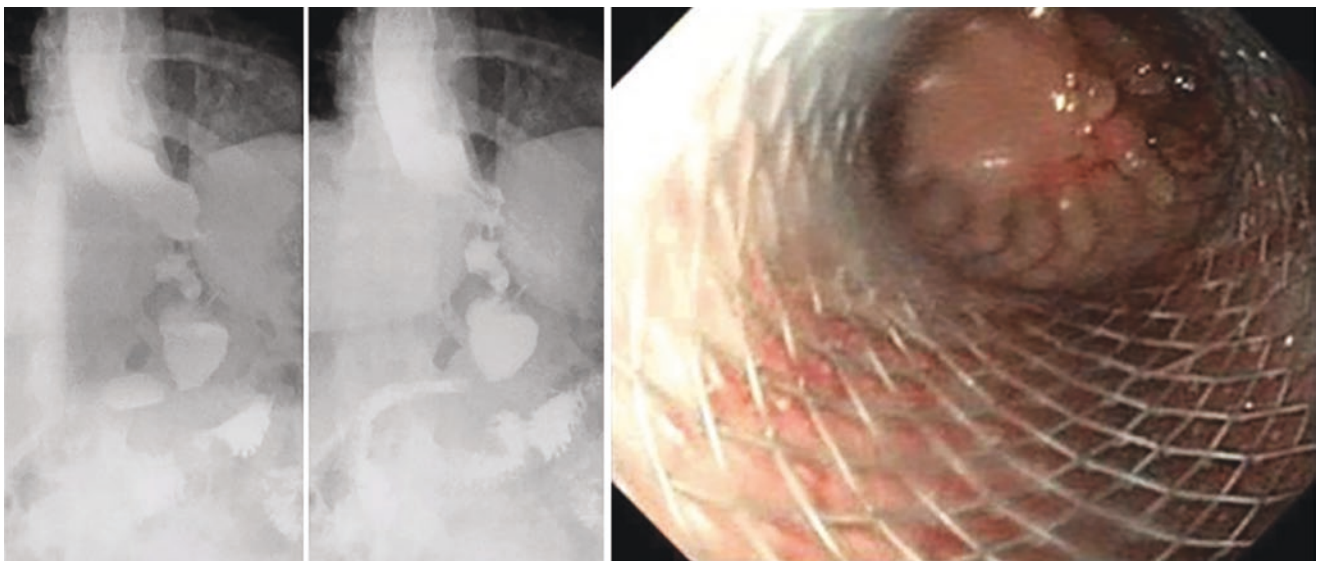

Fig. 58.3 Postoperative upper GI study demonstration leak from the proximal gastric pouch. Leak went on to be fixed endoscopically with stent from EGJ extending well beyond leak to pylorus. Follow-up imaging revealed resolution of the leak [17]

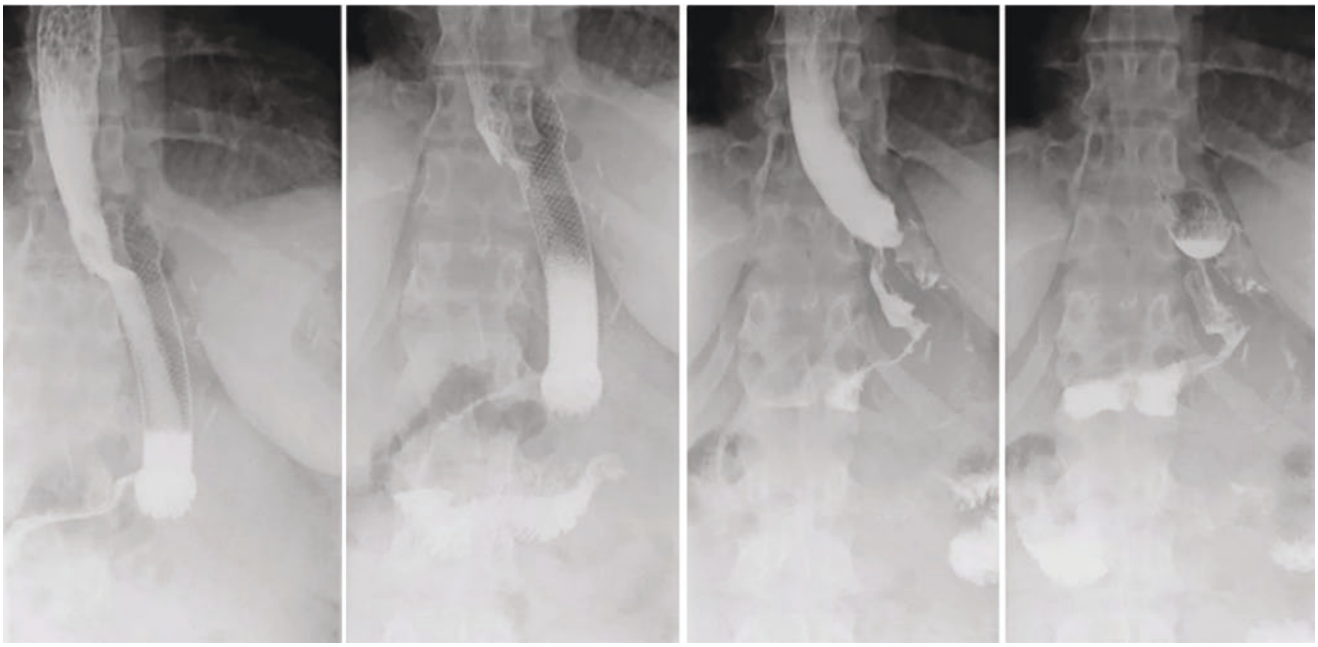

Fig. 58.3 (continued)

angularis, and if stenosis exists, it should be treated. Treatment of the stenosis alone with controlled radial expansion or stent placement may heal a proximal leak, but often more definitive operative management is required. One option for chronic leak is conversion of the sleeve to RYGB. This is technically difficult because exclusion of the fistulous segment can be difficult in the already narrowed stomach. There is emerging data on this technique, but it is not yet recommended by this group of authors. Another option is completion gastrectomy with Roux-en-Y esophagojejunostomy (RYEJ) [18]. Newer data show some success with Roux-en-Y fistulojejunostomy (RYFJ) for the treatment of chronic leaks. Identification of the fistulous tract can be difficult in the setting of chronic inflammation and may be aided by preoperative placement of double pigtail stent through the tract. Multiple studies have been performed on this technique demonstrating eventual closure rate of 100%, but RYFJ has not been investigated on a large scale [19, 20] (Fig. 58.4).

Among these options for reoperation, at least one systematic review has been performed. Most of the patients included underwent total gastrectomy with Roux-en-Y esophagojejunostomy (RYEJ) for definitive management. Overall, the rate of leaks is significantly higher in revisional operations with 38% of revision to RYGB, 22% of revision with fistulojeju-

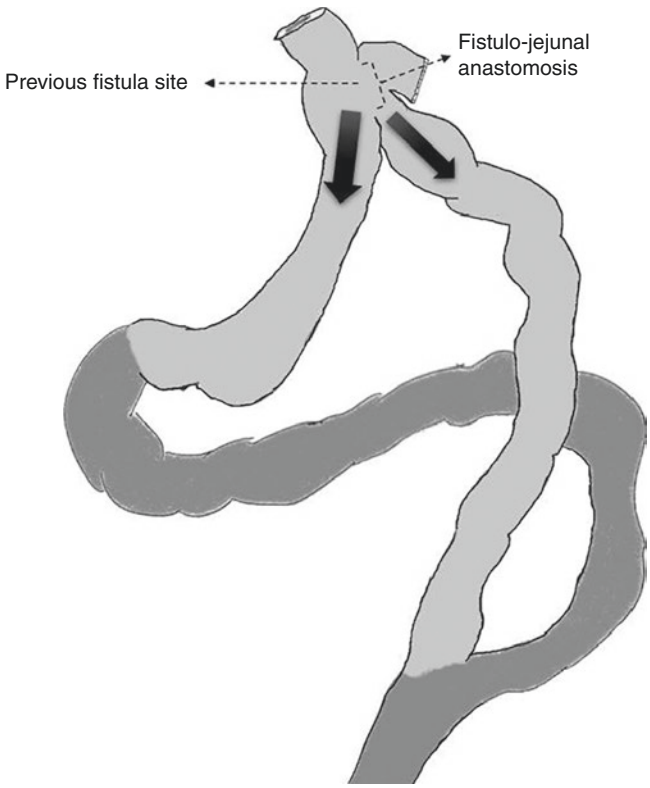

Fig. 58.4 Orientation of Roux-en-Y fistulojejunostomy [20]

nostomy, and 8% of revision to RYEJ ultimately developing a secondary leak [21, 22]. Additional described operations include segmental resection of the sleeve with esophago- or gastro-gastrostomy. Finally, serosal patch closure has been described by buttressing the leak with a loop of small bowel to close the gastric defect. There is insufficient evidence to recommend these operations currently.

Stenosis/Stricture

Sleeve gastrectomy stenosis occurs with an incidence of about 0.1–3.9% [23]. The most common site of stricture is at the incisura angularis. Symptoms of stricture include obstructive symptoms of nausea, vomiting, inability to tolerate PO intake, pain, and worsening reflux. These symptoms can progress to severe dehydration and malnutrition. Diagnosis is made typically with upper gastrointestinal series under fluoroscopy or upper endoscopy. Upper GI will show narrowing of the sleeve typically at the incisura, possibly with proximal dilation and pooling of contrast. On upper endoscopy, proximal dilation may be seen, and there may be difficulty in passing the endoscope beyond the narrowed area. CT is also an option although this is considered less specific. Stenosis can occur during both the early (<6 weeks) and late (>6 weeks) postoperative period. Stenoses can be seen for a variety of reasons. Twisted sleeve gastrectomy can occur. A twisted sleeve can be difficult to diagnose because upper GI imaging or endoscopy may reduce the twist making the sleeve appear normal. Twisting is avoided by ensuring equal tension across the stomach to flatten the stomach for staple firing. Mechanical obstructions occur at the incisura angularis and are most often due to using inadequate bougie size. We recommend using at least a 40 Fr bougie to ensure a patent sleeve. Meticulous surgical technique can help prevent these issues. Additionally, strictures raise the risk of postoperative leak due to proximal gastric distention and increased tension on the staple line (Fig. 58.5).

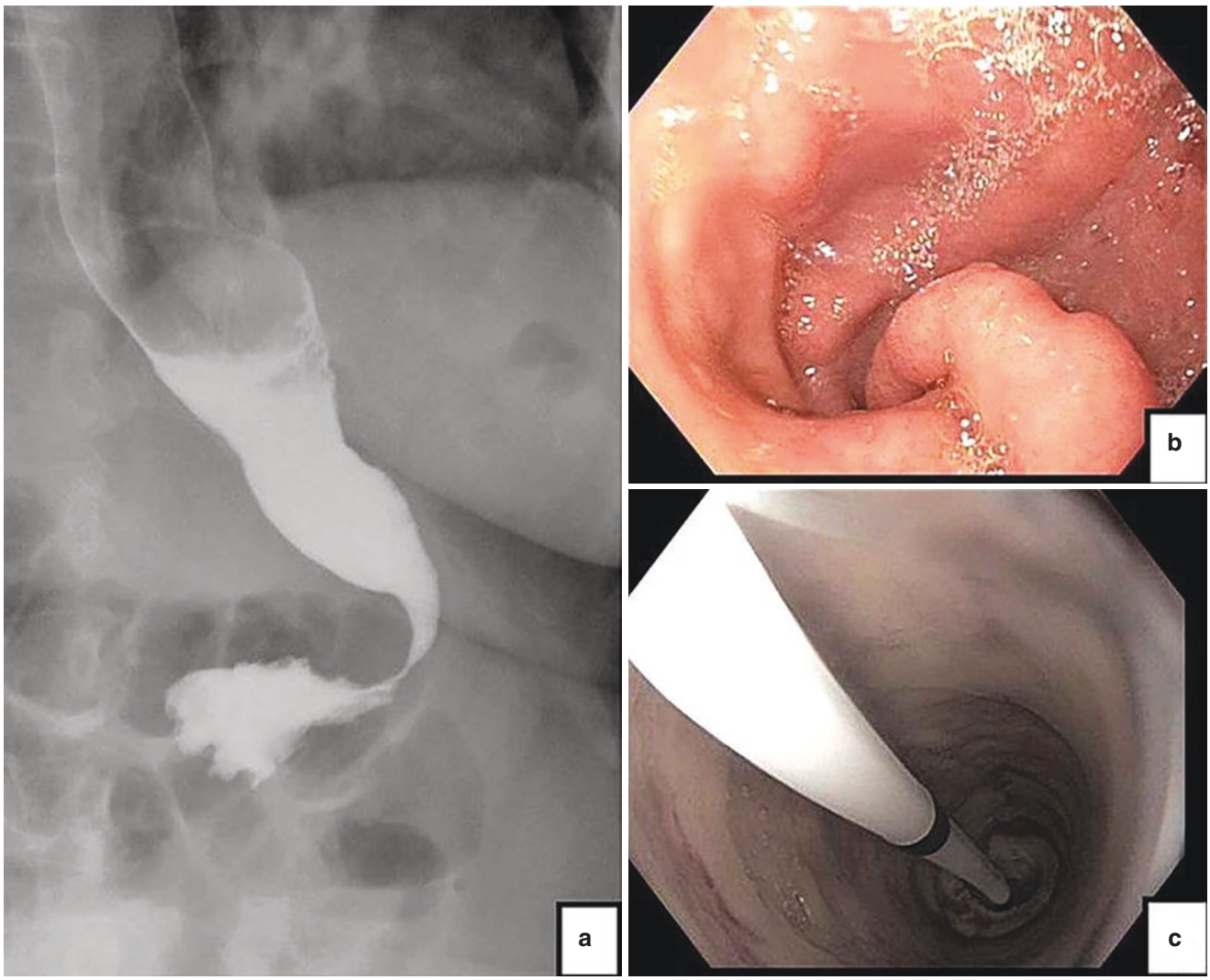

Fig. 58.5 Stricture of sleeve gastrectomy with hiatal hernia. The stricture was diagnosed and treated using endoscopic balloon dilation [4, 24]. (**a**) Radiological image of a LSG Stricture. (**b**) Endoscopic view of LSG Stricture. (**c**) Endoscopic Baloon Dilation of LSG Stricture

There are both endoscopic and surgical options for management. The mainstay of endoscopic therapy is balloon dilation. These are usually achalasia balloons and can dilate up to a diameter of 20–35 mm. Serial dilations are occasionally required [25]. Another option is placement of self-expanding stent. These stents usually extend from the esophagus to the duodenum to achieve good apposition to surrounding tissue. Patients may experience significant worsening of reflux symptoms, inability to tolerate PO, and pain from stent migration. Studies have shown success on the efficacy of balloon dilation and self-expanding stent placement. Balloon expansion alone appears to have a successful stenosis resolution rate close to 50%. Patients often require multiple interventions to durably treat a stenosis. Additional studies have shown >80% success with endoscopic therapy through subsequent larger caliber dilation or combination use with self-expanding stent [14, 23, 24, 26, 27].

When endoscopic management fails, surgery is indicated. Options for sleeve revision include a Heineke-Mikulicz-type stricturoplasty with longitudinal gastrotomy at the incisura and transverse closure. Gastric seromyotomy may also be performed to relax the stomach at the level of the incisura angularis. There is new data suggesting a gastric per oral endoscopic myotomy (G-POEM) approach is technically feasible and provides similar results to surgical seromyotomy, but data is limited. Finally, resection of the stenotic area with reanastomosis by gastro-gastrostomy may be performed but has also not been well studied. Conversion to RNYGB is the recommended revisional surgery after laparoscopic sleeve gastrectomy. This is performed by a minimally invasive approach successfully in 89.9% of cases. Conversion is performed by division of the stomach above the level of stenosis for creation of the gastric pouch. This approach can ameliorate symptoms of reflux as well as provide durable weight loss [28].

Bleeding After Laparoscopic Sleeve Gastrectomy

Clinically significant bleeding can occur following laparoscopic sleeve gastrectomy (LSG). This bleeding can occur intraabdominal, intraluminal, or from a trocar site. Intraabdominal bleeding typically arises along the greater curvature of the stomach from the short gastric vessels, splenic vessels, or the spleen itself. Reoperation is sometimes required, and the use of suture, clips, and topical hemostatic agents is typically sufficient to control bleeding. In the case of small capsular tears of the spleen, direct pressure and hemostatic agents can control hemorrhage. In the unstable patient with ongoing hemorrhage from the spleen, splenectomy may be required. The long staple line of a gastric sleeve is at risk for both intraabdominal and intraluminal bleeding. Intraabdominal hemorrhage from a staple line with hemodynamic instability will require reoperation including abdominal washout and control of hemorrhage. The bleeding has frequently self-limited at the time of surgical exploration although occasionally oversewing or clip placement on the staple line is necessary. Intraluminal bleeding can present with hematemesis or melena. Most of the intraluminal bleeds are self-limited with a small number requiring traditional endoscopic methods to control hemorrhage. On rare occasion reoperation is required.

Complications of Gastric Bypass

Gastric bypass has been around since 1967 as a weight loss surgery. This is perhaps the most "tried and true" weight loss surgery performed. It is associated with reproducible weight loss and an overall low complication rate. The mortality of laparoscopic RYGB has decreased from 2.6% in the early 2000s to 0.09–0.12% by 2010, and this number continues to decline [6, 29]. Like laparoscopic sleeve gastrectomy, gastric bypass risks include leaks and stricture which are managed similarly. The rerouted anatomy associated with gastric bypass, however, has its own set of risks which includes marginal ulceration, gastro-gastric fistula, and obstruction from internal hernia (Fig. 58.6).

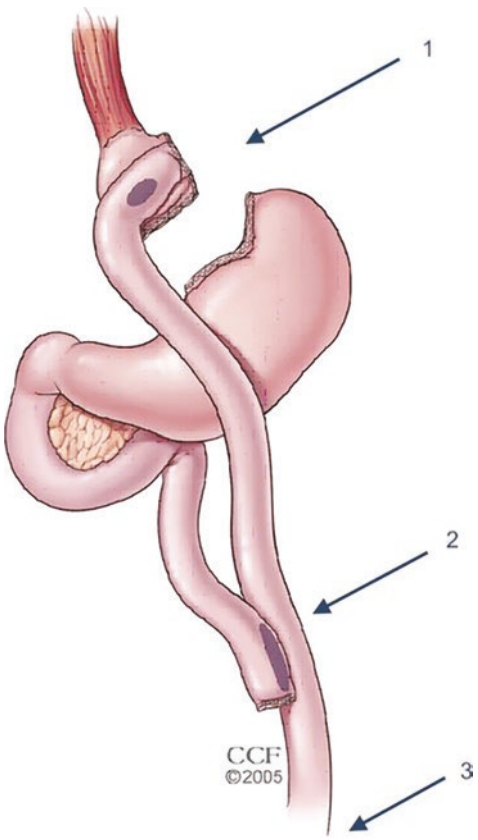

Fig. 58.6 Orientation of RYGB. Note the potential locations for leak including the pouch staple line, the gastrojejunostomy, the gastric remnant staple line, jejunal stump (not shown in this image), or the jejuno-jejunostomy [7]

Leaks After Gastric Bypass

Extraluminal leak is a serious complication following gastric bypass occurring in up to 6% of cases. Leaks are associated with high morbidity and mortality and often require reoperation [30, 31]. Good surgical technique with tension-free, well-vascularized anastomosis is the best way to prevent morbidity and mortality associated with leak. Most leaks present within 10 days of operation. Signs and symptoms include tachycardia, fever, abdominal pain, respiratory decompensation, and nausea. Any unexplained tachycardia should raise suspicion for ongoing leak. Leaks may be diagnosed on upper gastrointestinal series under fluoroscopy or on CT scan. Management of these leaks must occur in a timely manner as a delay in diagnosis is associated with a significant increase in morbidity and mortality. General principles of leak management are similar in LSG and RYGB leaks. Contrary to leaks after LSG which occur almost exclusively at the proximal staple line, leak after RYGB may occur at the gastrojejunal anastomosis, the gastric pouch near the EGJ, the gastric remnant, the jejunal stump near the GJA, and rarely the jejunojejunal anastomosis. Leaks at the jejunojejunal anastomosis have been shown to have the highest mortality but are uncommon and usually due to technical error. In a hemodynamically stable patient, percutaneous drainage of intraabdominal collections can be attempted for source control. In any unstable patient, urgent exploration is required. Abdominal washout, wide drainage, with or without attempted repair of the leak, and feeding access are the mainstays of surgical treatment. Feeding access post gastric bypass may be accomplished by placing a feeding tube into the gastric remnant rather than feeding jejunostomy placement. Special considerations should be made based on the location of the leak [32, 33].

Gastrojejunostomy leaks are the most common leak post gastric bypass. With operative drainage, antibiotics, NPO, and nutritional support around 65–67% of these leaks will heal without revisional surgery [34]. Some studies recommend oversewing of any visible defect if found early (<5 days). These leaks have a higher rate of closure, and the surgeon may be able to forego feeding tube placement with prompt identification and intervention. Leaks found late (>10 days) demonstrate a lower closure rate, more often require feeding tube placement, and show no benefit in oversewing defects at the time of initial surgery. Endoscopic stent placement has also shown successful treatment in up to 1/3 of these patients. Pouch staple line leaks are often due to stapler misfires and are relatively uncommon. These should be widely drained and oversewn if identified early. Jejunal stump blowouts are often from distal obstruction and can occur if too long of a stump is left. These typically require drainage and revision of the GJ anastomosis if the leak fails to heal with conservative management. In an unstable patient, a jejunal stump leak can be controlled by placing a drain into the leak. The drain is then externalized into a controlled fistula which can be taken down around 12 weeks later when the patient has recovered from the initial operation. Gastric remnant leaks are also rare but should raise concern again for distal obstruction. When presenting early, the JJ anastomosis should be inspected to ensure patency. Resection of the remnant staple line can be performed if identified early. Late presentations can be from a variety of downstream obstructions which still include JJ stricture but also adhesive disease or internal hernia. Around 65% of these leaks will respond to conservative management. The median time to closure is around 34 days which highlights the need for good feeding access in any patient with a leak. Although many will close spontaneously with adequate drainage and nutritional support, operative intervention remains our best therapy for leak. Leaks which fail to close spontaneously become chronic and can be very difficult to manage. Endoscopic therapies are providing some benefit in the closure of chronic leaks and again include endoscopic stenting across a leak, placement of clips, double pigtail drainage, and fibrin glue injection. Ultimately, surgical conversion by total gastrectomy with RYEJ may be required to remove diseased tissue and allow the leak to heal [21, 32, 33, 35, 36].

Strictures After Gastric Bypass

Strictures following gastric bypass are common occurring in as high as 10% of patients [37]. It was originally thought that circular stapled anastomoses were more likely to stenose; however, the data is mixed. There now seems to be no difference in stenosis rates with variable techniques (i.e., hand sewn, circular stapled, or linear stapled). Stenosis can occur at any point after surgery, early or late. Signs and symptoms include intolerance to oral intake, nausea and vomiting, dehydration, and malnutrition. Stenosis of the gastrojejunal anastomosis is often due to marginal ulceration although technical errors also occur. Technical causes are more likely to present early, whereas ulceration causing stenosis presents later [38–40]. The mainstay of intervention for GJ stricture is endoscopy. Balloon dilation with or without stent placement is highly successful in treating a stricture. Dilations are performed with max dilation by 3–4 mm at a time to a max of 15 mm dilation. Stenosis of the distal jejunojejunal anastomosis is very rare and is due primarily to technical error. The symptoms of JJ anastomotic stricture include bloating and fatigue, abdominal pain, early satiety, and unexpected weight regain. Diagnosis can be made with upper GI series or oral contrasted CT scan. Any evidence of dilation of the gastric remnant, biliopancreatic limb, or Roux limb are highly sug-

gestive of downstream obstruction. When operation for stricture is required, it involves complete revision of the GJ or JJ anastomosis depending on the location of stricture. Revision of the JJ involves creation of a second anastomosis in addition to the new JJ, and consequently the risk of complications increases. These revisional surgeries have higher major complication rates and are typically reserved for when endoscopic therapy has failed [37, 41].

Marginal Ulceration and Gastrogastric Fistula After Gastric Bypass

The incidence of marginal ulceration after Roux-en-Y gastric bypass ranges in the literature from 0.6% to 16% [38–40, 42, 43]. Marginal ulceration has variable presentation including signs of bleeding, perforation, or obstruction. The symptoms depend on the presentation but typically involve mid-epigastric abdominal pain. Obstructed patients will present with nausea, vomiting, and dehydration. Bleeding patients can present with hypotension, tachycardia, dizziness, altered mental status, and shortness of breath. Perforated patients often present with peritoneal signs. An abdominal radiograph is an acceptable first step when perforation is suspected. Diagnosis is made with endoscopy in patients without evidence of frank perforation. CT scan with oral contrast can be ordered to assess for related gastrogastric fistula. Symptoms of GGF include pain as well as weight regain. Risk factors for marginal ulceration include smoking, alcohol use, high-dose NSAID and aspirin use, long gastric pouch, rapid weight loss, white race, older age, increased BMI, and *H. pylori* [44]. Medical management of non-perforated, non-obstructing marginal ulceration is highly successful. Several studies have reported successful healing of 85–95% of ulcerations at 8 weeks, with a few studies reporting 100% success [37, 38, 41, 42]. Medical therapy consists primarily of proton pump inhibitor (PPI) or H2 blocker and sucralfate. Eradication of *H. pylori* with appropriate antibiotic therapy is essential in affected patients. There is some data suggesting obstructed patients may be treated with combination medical therapy followed by endoscopic dilation once the ulceration has healed if stenosis persists. Marginal ulceration perforation presents with signs of peritonitis which should prompt emergent surgical intervention. These patients should be resuscitated and taken to the OR for either minimally invasive or open exploration. Small perforations can be managed successfully with minimally invasive Graham patch repair and abdominal washout [45]. Larger perforations often require resection and revision of the gastrojejunal anastomosis. In any case, thorough washout and wide drainage are essential, and consideration should be made to place enteral feeding access. Furthermore, patients with refractory marginal ulceration and those with gastrogastric fistulas are more likely to require operative revision [38, 46]. There is emerging technology for endoscopic closure of GGF. Operative options classically involve resection of the ulcerated tissue and revision of the gastrojejunostomy, with or without truncal vagotomy. Ensuring reduction in pouch size to around 50 mL or less has been shown to reduce marginal ulceration from 3.8% to 0.98% and should be considered during revisional surgery [42].

Obstruction

Post-RYGB bowel obstructions occur with an incidence of around 3–5% [47]. Symptoms include nausea, vomiting, abdominal distention, constipation, or obstipation. Bowel function can still occur in the presence of proximal obstruction and does not preclude diagnosis of SBO. Adhesive disease (47.6%) is likely the leading cause of post-RYGB obstruction; however, a high index of suspicion is required for internal hernia (27.6%) [47, 48]. This typically occurs late around the 2–3-year mark after weight loss has occurred due to loss of visceral fat. This can result in an internal hernia defect even at a previously closed space. Internal hernias are more common with the increased use of minimally invasive techniques due to less postoperative adhesive disease. Previous research has shown a higher association with post RYGB bowel obstruction in patients undergoing retrocolic vs. antecolic bypass [48, 49]. There are three potential spaces specific to RYGB through which internal hernias and associated closed loop bowel obstructions can occur. Internal hernias occur between the mesentery of the Roux limb and the transverse mesocolon in a space known as Petersen's defect. In retrocolic RYGB, bowel can herniate through the defect created in the transverse mesocolon. Finally, herniation can occur between the mesenteries of the two jejunal limbs at the JJ anastomosis (Fig. 58.7).

Because these create closed loop obstructions, they must always be considered in a post bariatric surgery patient. Normal laboratory values should not preclude exploration in any patient with an obstruction post gastric bypass. Diagnosis can be made with CT scan which may show mesenteric swirling, edematous mesentery, engorgement or absence of contrast of the mesenteric vessels, or small bowel sequestration; however, diagnostic laparoscopy or laparotomy is indicated in any patient with high index of suspicion. Negative laparoscopy or exploration demonstrates good clinical judgment in the post bariatric patient rather than treatment failure. Diagnostic laparoscopy should consist of running all three limbs (Roux, BP, and common channel) to assess for hernia. When an internal hernia is identified during exploration, treatment involves reduction of the herniated bowel and assessment of viability. Any frankly necrotic or ischemic bowel should be resected. Second look operations are some-

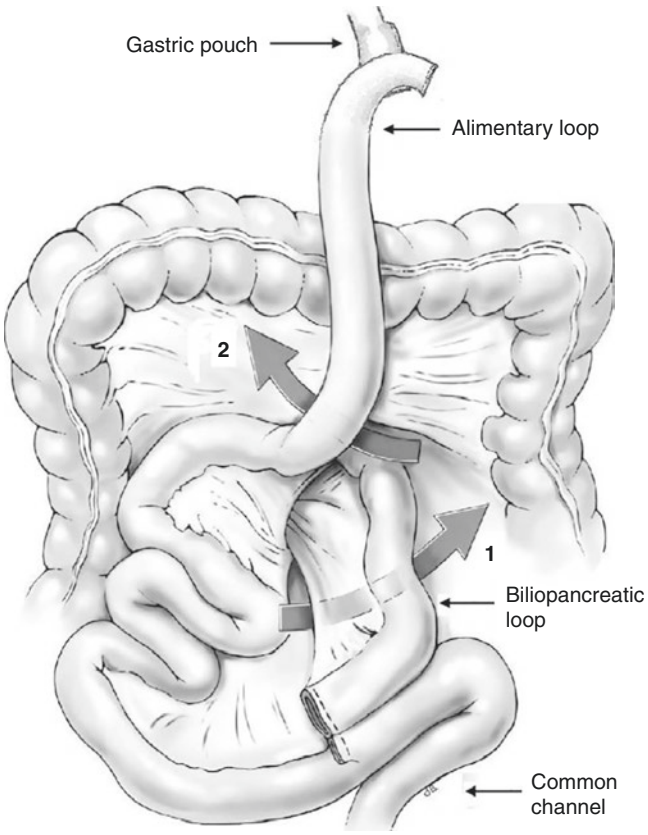

Fig. 58.7 The potential hernia spaces associated with a retrocolic reconstruction RYGB [50]

times necessary to avoid resection of viable bowel and future short gut syndrome. Any remaining mesenteric defects should be closed to decrease risk of recurrence. In the case of patients left with short gut, reversal of the gastric bypass anatomy for lengthening of the remaining small bowel is one option. Finally, obstruction can occur due to ventral incisional hernia, and management is the same as in the non-bariatric patient.

Roux-en-O Bypass

Roux-en-O gastric bypass configuration occurs with the BP limb is connected inadvertently to the gastric pouch. The JJ is then created to the mid BP limb and the distal jejunum. Patients present with bilious emesis and occasionally a clinical picture of bowel obstruction. CT scan may be used to aid in diagnosis, but surgical exploration is the gold standard. Surgical revision involves takedown of the Roux-en-O configuration and transition to a Roux-en-Y configuration. Steps that may be taken to avoid this include maintaining a short BP limb, clear identification of the ligament of Treitz, and marking of the Roux limb shortly after division of the bowel [51] (Fig. 58.8).

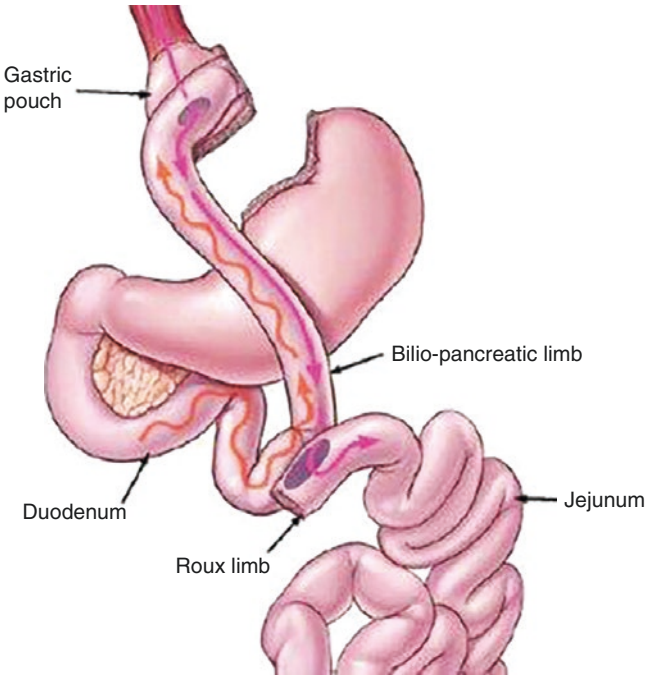

Fig. 58.8 Roux-en-O configuration of gastric bypass [51]

Complications After Biliopancreatic Diversion with Duodenal Switch

Biliopancreatic diversion with duodenal switch is another weight loss option often reserved for the super morbidly obese population. The associated mortality of the operation is quoted between 0.5% and 1.4% and is recognized to be slightly higher than other bariatric operations [52, 53]. This is partially because the patients have higher overall BMI and higher number of comorbid conditions. The procedure combines the restrictive and malabsorptive approach. It is technically more difficult than gastric sleeve and RYGB contributing to a slightly higher complication rate [54]. The major complications associated with duodenal switch are like those for gastric sleeve and gastric bypass. Leaks are estimated to occur in <2% of cases [53]. Leaks can occur from the gastric sleeve staple line, the duodenoileostomy, or the ileoileostomy. These are managed in principle like leaks associated with sleeve gastrectomy and gastric bypass. All hemodynamically unstable patients should return to the operating room for control of intraabdominal sepsis, wide drainage, attempted repair when indicated, and feeding access. Hemodynamically stable patients have more treatment options including surgical or percutaneous drainage. Gastric sleeve leaks following BPD-DS are managed the same as LSG staple line leaks. These have been discussed in previous sections. Duodenoileostomy leaks are uncommon but should be managed with source control,

antibiotics, and distal feeding access. Most of these leaks should resolve without operation. A small percentage will continue to chronic fistula [55, 56]. Endoscopic options have been tried including self-expanding metal stent placement, but these have shown low rates (19%) of successful fistula closure [24]. Revisional surgery is occasionally needed which involves conversion to RYGB. Ileoileostomy leaks are also quite rare [52, 53, 56–58]. One variation of the BPD-DS is the single-anastomosis duodenoileal bypass (SADI). This differs from traditional BPD-DS in its loop, rather than Roux-en-Y configuration. Duodenoileostomy leaks in the setting of the loop construction again are managed with source control and nutritional support; however, those which progress to chronic leaks will require revision of the duodenoileostomy and necessary conversion to BPD-DS (Figs. 58.9 and 58.10).

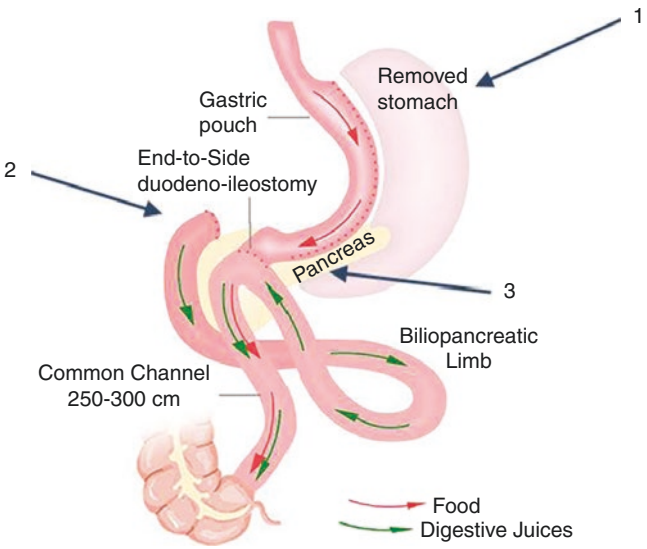

Fig. 58.9 Normal anatomy of the SADI (single anastomosis duodenoileal bypass) procedure [7]. Leaks from the duodenoileostomy can be taken down and converted to traditional BPD-DS seen below

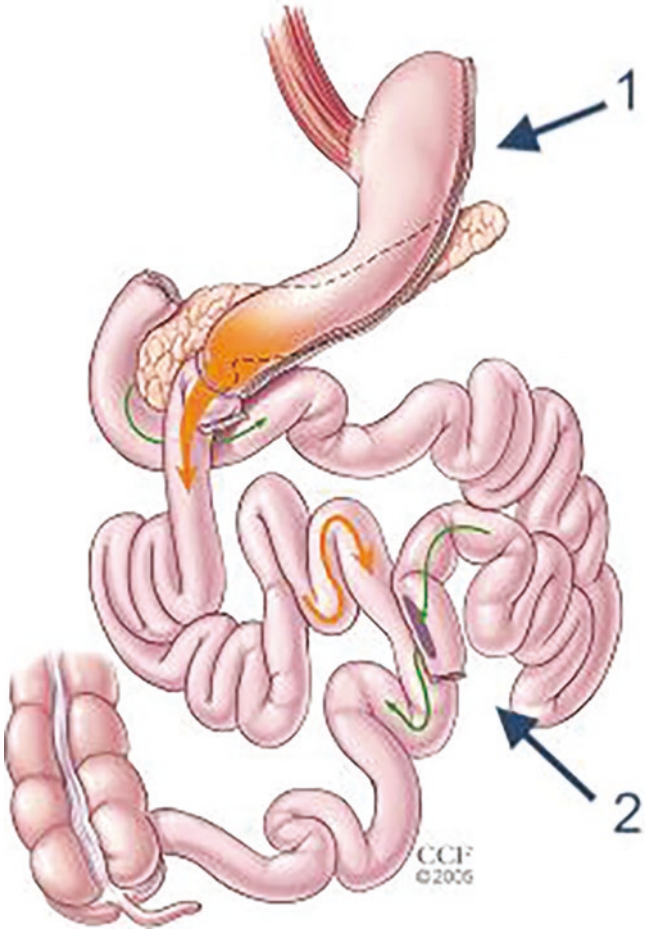

Fig. 58.10 The normal anatomy after biliopancreatic diversion with duodenal switch [7]

Complications of Laparoscopic Adjustable Gastric Band

Laparoscopic adjustable gastric band (LAGB) was formerly one of the most common weight loss operations. The procedure involves placement of a silicon ring around the proximal stomach to create a restrictive pouch to limit oral intake. In the early 2000s, this operation comprised about 24% of all operations. This had decreased to 9.5% by 2014 and continues to decline [59]. The band has fallen out of favor likely due to its lower degree of weight loss, higher rate of complications requiring revision, and weight re-gain [60, 61]. Two of the most significant complications of LAGB include band erosion and band slippage. Band erosion is often evidenced first by port infection. Erosion occurs in around 7% of all operations and is seen between the first- and second-year post-placement [62]. Band erosion occurs slowly over time and for this reason rarely causes free perforation [63]. Rather the band slowly migrates through the stomach wall until it can be visualized intraluminal. Band erosion is best diagnosed with endoscopy which may also be therapeutic. Previous studies have shown a very high success rate up to 95% for endoscopic removal when the buckle of the band is visible internally [63, 64]. Another technique involves placement of a self-expanding stent across the band to promote tissue ischemia and more expedient migration of the band. The second stage of this procedure involves return at 6–8 weeks for repeat EGD and removal of the band [64]. If revisional bariatric surgery is planned following band erosion and removal, it should be delayed 8–12 weeks before reoperation is attempted [60].

Band slippage is another complication in which a portion of the stomach herniates through the band which leads to obstruction. Early on this was very common due to use of the perigastric dissection technique. Pars flaccida technique has replaced this, and the rate of band slippage has decreased tremendously from 24% to <12% [60, 61]. Patients present with abdominal pain, nausea, vomiting, or worsening reflux. Diagnosis can be made on plain film occasionally, but upper gastrointestinal series is considered gold standard. Surgery is required in these patients urgently and involves deflation and removal of the band (Fig. 58.11).

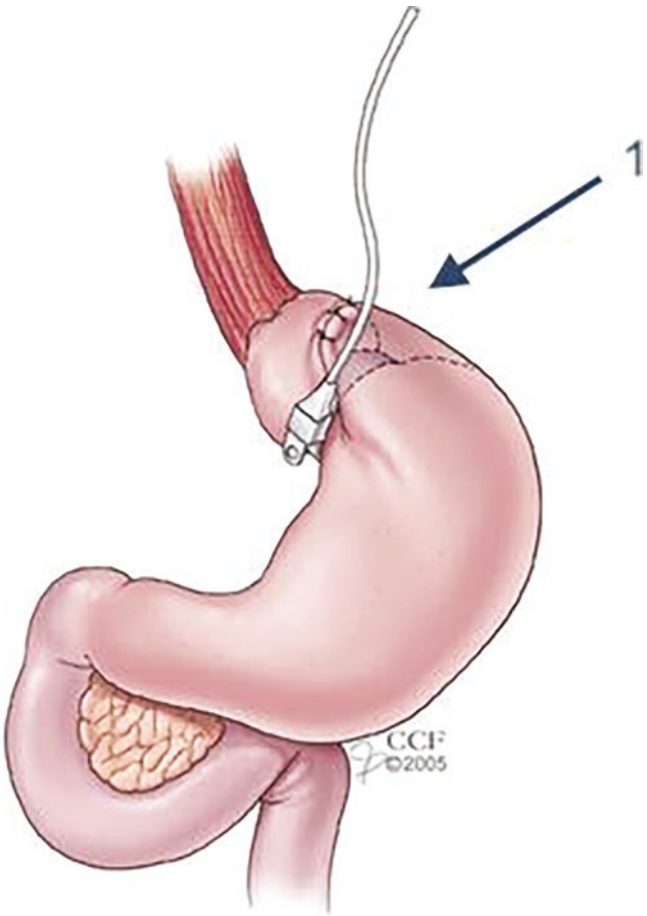

Fig. 58.11 Normal positioning of laparoscopic adjustable gastric band placement [7]

Conclusions

Complication rates of bariatric surgery are decreasing; however, with the vast increase in number of total cases performed, the overall number of complications continues to increase. It should be noted that thromboembolic events and micronutrient deficiencies are among the most common bariatric surgery complications. Complications specific to prior surgery pose management challenges for even basic general

surgical problems like gallbladder disease. Familiarity with the anatomical variations commonly performed by bariatric surgeons and knowledge of basic management principles are essential when managing these patients. Bariatric surgery patients will be encountered by both general and acute care surgeons, in addition to the bariatric surgeon. Recognition of major complications and timely intervention is directly linked to lower mortality.

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Post-bariatric Surgery GERD

59

Babusai Rapaka, Kevin D. Platt, Allison R. Schulman, and Barham K. Abu Dayyeh

Normal Anti-reflux Mechanism

Gastroesophageal reflux disease (GERD) is the result of gastric acid as well as other irritants refluxing above the lower esophageal sphincter (LES). There are two main mechanisms that comprise the normal anti-reflux barrier, the LES and crural portion of the diaphragm that functions as an external sphincter [1]. Under normal conditions, there is a positive pressure gradient across the gastroesophageal junction. The intra-abdominal pressure is approximately 5 mmHg greater than intrathoracic pressure. GERD is the result of increases in intra-abdominal pressure by various mechanisms great enough to overcome the pressure barrier formed by the LES and diaphragm. There are multiple mechanisms by which GERD occurs including impaired LES sphincter tone, increased frequency of transient lower esophageal sphincter relaxations (TLESRs), and anatomic disruptions such as the presence of a hiatal hernia. Hiatal hernias contribute to the development of acid reflux by hindering the integrity of the LES and serving as a reservoir for gastric acid that refluxes during LES relaxation during swallowing [2].

Lower Esophageal Sphincter

The LES and the crural diaphragm are the main components of the anti-reflux mechanism. The LES is a 3–4 cm segment of the distal esophagus comprised of smooth muscle that remains tonically closed at baseline to maintain gastroesophageal competence.

Crural Diaphragm

The diaphragm can be divided into two portions, the costal diaphragm and crural diaphragm. The costal diaphragm is primarily involved in ventilation. The crural diaphragm is involved in ventilation; however it is also involved in the prevention of reflux. The crural diaphragm provides a sphincter-like action on the LES. It not only prevents reflux by providing extrinsic squeeze to the intrinsic LES increasing resting tone but also prevents reflux during straining. This is because the LES is located within the hiatus of the right crus of the diaphragm and is anchored to the diaphragm via the phrenoesophageal ligament. Furthermore, the crural diaphragm receives part of its innervation from the vagus nerve. During periods of esophageal distension, vomiting, or TLESRs, the crural diaphragm is inhibited by the vagus nerve allowing retrograde flow of contents [2].

Lastly the esophagus enters the stomach at an oblique angle forming the angle of His or the esophagogastric angle. This acute angle marked by the junction of the cardia and the esophagus acts as an anatomical barrier that prevents reflux.

Mechanisms of Reflux

The main mechanisms of GERD include decreased or impaired LES tone, TLESRs, and the presence of hiatal hernia.

Decreased tone of the LES (defined as less than 10 mmHg during fasting) is only present in a minority of individuals and leads to reflux by strain-induced reflux or free reflux. Strain-induced reflux occurs when the LES is forced open by a sudden increase intra-abdominal pressure. Previous studies have demonstrated that strain-induced reflux rarely occurs when

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the LES pressure is greater than 6 mmHg [3, 4]. Decreased tone of the LES also allows for free reflux which is when there is decreased intraesophageal pH without a change in intra-abdominal pressure [5]. This mechanism of reflux is only responsible for a small portion of all acid reflux cases.

Most individuals with GERD have normal LES tone, suggesting an alternative mechanism for the development of GERD. TLESRs are the most common reason for GERD comprising up to 70% of all acid reflux episodes [6]. TLESRs are LES relaxations that are not induced by swallowing. It is a vagally mediated reflex in response to gastric distension that allows for belching [6]. TLESRs differ from swallow-induced relaxations of the LES as they are longer in duration, are not associated with pharyngeal contraction, and are not in conjunction with esophageal peristalsis. The frequency with which TLESRs are associated with acid reflux than just gas venting from eructation is a primary determinant of symptomatic GERD. In normal patients, 40–60% of TLESRs are accompanied by reflux, whereas in those with GERD, it is up to 70% of the time [2]. Gastric distension increases the frequency of TLESRs which is why acid reflux occurs most frequently postprandially. Many studies have demonstrated that individuals with GERD do not have more frequent TLESRs than those without GERD; however the proportion of TLESRs associated with acid reflux is higher in those with GERD. The cumulative acid load and time of exposure to the lower esophagus are greater in patients with GERD because a higher proportion of TLESRs is associated with reflux [7]. Furthermore, if there is an anatomic disruption such as a hiatal hernia or another process increasing compliance of the LES, this can lead to an increased cross-sectional area for refluxate to pass through during TLESRs exacerbating reflux symptoms [8].

Hiatal hernias occur when the proximal stomach is pushed through the diaphragmatic hiatus into the chest. This process displaces the crural diaphragm from the LES, and the hernia sac serves as a reservoir for gastric refluxate. Furthermore, the presence of a hiatal hernia leads to a decrease in the LES pressure, increasing frequency of TLESRs, and impairs esophageal clearance [9, 10].

Obesity and GERD

The pathophysiology of GERD in obesity is incompletely understood; it is thought to be multifactorial in nature. Multiple studies have shown an association between obesity and increased frequency and severity of GERD symptoms. One study showed that BMI was independently associated with the severity of GERD. For each five-point increase in body mass index (BMI), the DeMeester score increased by 3 units [11]. Furthermore, multiple studies have demonstrated that obese patients had increased esophageal acid exposure compared to nonobese patients.

There are multiple mechanisms theorized in obese patients that increase GERD. TLESRs have been observed to be more common in obese patients. One study comparing normal, overweight, and obese patients with comparable LES pressures, LES lengths, and peristaltic functions demonstrated a 2.5 times increase in 2-h rate of TLESRs in obese patients as well as a higher proportion of TLESRs with associated acid reflux (normal weight 17.6% vs. obese 63.5%) [12].

Multiple studies have aimed to elucidate a relationship between BMI and LES tone, as lower tone predisposes to GERD. However, these studies have been inconsistent with studies demonstrating an inverse relationship between BMI and LES as well as other studies showing LES pressure was higher in obese patients, with a hypertensive LES presented by a significant portion of patients [11, 13].

Hiatal hernias are more common in obese patients. Studies have shown the prevalence as high as 50% in all obese patients, and these patients were also more likely to have esophagitis compared to those patients without a hiatal hernia. Furthermore, obese patients have higher intra-abdominal pressures than their nonobese counterparts due to the gravitational force of adipose tissue into the abdominal cavity. This increased intra-abdominal pressure increases reflux of gastric contents [13, 14]. All of these mechanisms in conjunction contribute to the development of GERD in the obese patient (Fig. 59.1).

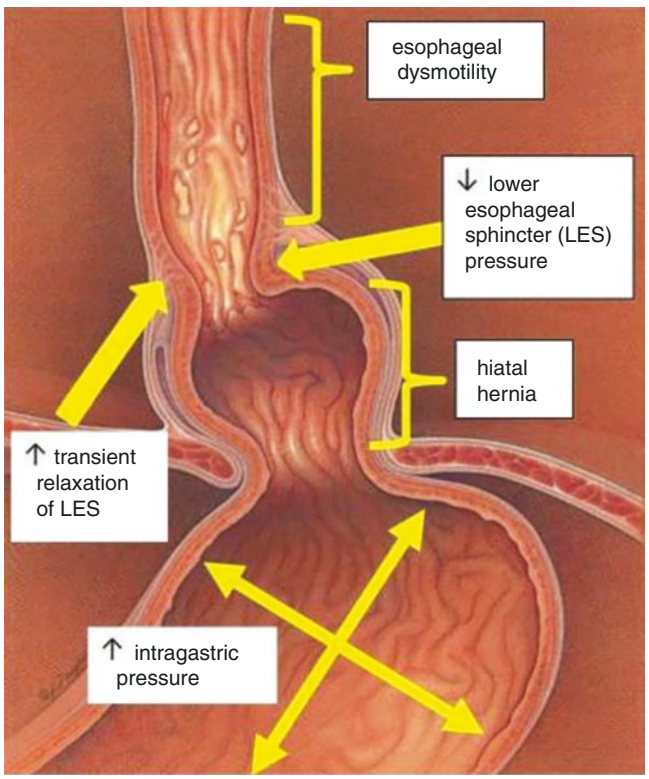

Fig. 59.1 Pathophysiologic mechanisms of GERD in obesity. (Adapted from Chang and Friedenberg [13], pending permission)

Bariatric Surgical Interventions

Bariatric surgical procedures induce weight loss by one of two primary mechanisms, either through restriction or malabsorption. Restrictive procedures limit caloric intake by reducing the volume of the gastric reservoir. These procedures include the laparoscopic adjustable gastric band and laparoscopic sleeve gastrectomy (LSG). Malabsorptive procedures induce weight loss by decreasing nutrient absorption via reduction of the small bowel absorptive length via bypass of the functional small intestine or through diversion of the biliopancreatic secretions. Malabsorptive procedures include duodenal switch procedure, jejunoileal bypass, and Roux-en-Y gastric bypass. This chapter will focus on the most commonly performed bariatric procedures, laparoscopic sleeve gastrectomy, and Roux-en-Y gastric bypass.

Laparoscopic Sleeve Gastrectomy (LSG)

Laparoscopic sleeve gastrectomy (LSG) is a bariatric procedure in which the stomach is reduced to about 15% of its original size. The stomach is resected along the greater curvature and fundus of the stomach. The result is a tubular stomach with a diminished capacity that is also resistant to stretching due to lack of a fundus preventing gastric accommodation (Fig. 59.2). Furthermore, LSG also induces weight loss via anorexia through removal of the ghrelin-producing cells of the fundus [15]. Sleeve gastrectomy has been shown to be very effective in producing durable weight loss. Studies have shown the average patient loses about 60% of excess body weight at 5 years after LSG.

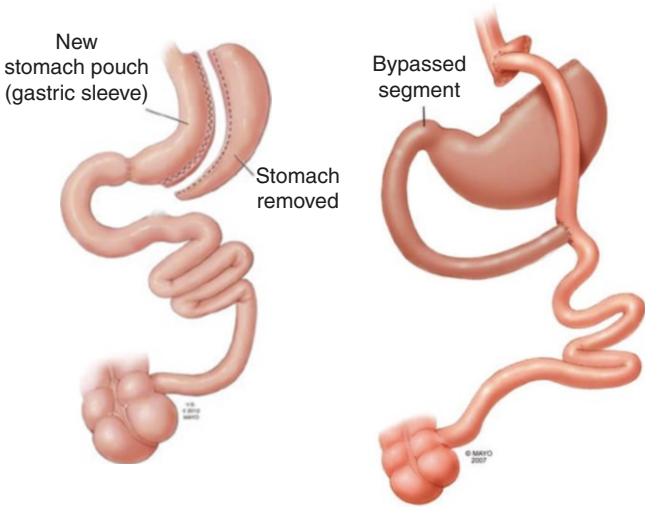

Fig. 59.2 Anatomical changes seen with laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. (With permission from the Mayo Clinic Division of Gastroenterology and Hepatology)

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) is a laparoscopic procedure which induces weight loss via restriction as well as malabsorption. It produces the most durable weight loss as compared to sleeve gastrectomy and has a lower rate of complication than other malabsorptive procedures such as biliopancreatic diversion/duodenal switch. This procedure involves the creation of a small gastric pouch that restricts caloric intake. This gastric pouch is then connected to the jejunum known as the Roux limb, bypassing the stomach, duodenum, and proximal portion of the jejunum which comprise the biliopancreatic limb. The length of the Roux limb determines the degree of malabsorption as the longer the Roux limb, the longer the physical distance between digested contents mixing with biliopancreatic secretions. The length of this limb can vary between patients (Fig. 59.2).

The expected weight loss with RYGB is approximately 70–75% of excess body weight at 2 years. At 5 years after RYGB, the sustained weight loss is approximately 60–70% of the excess weight. RYGB has also been shown to have statistically significant improvements in glycemic control, hyperlipidemia, OSA, blood pressure, and NAFLD. In one large retrospective study, RYGB was shown to improve GERD symptoms in 50% of all patients, and the incidence of GERD decreased 41% in this cohort which was seen for a minimum of 3 years after RYGB [16].

Both of these procedures induce multiple manometric and pH changes which are illustrated in Table 59.1.

Table 59.1 Summary of manometric and pH changes seen with LSG and RYGB

	LSG	RYGB
Manometric findings		
LES resting pressure	↓	↑
LES length	↔	↔
Esophageal body amplitude	↓	↔
Intragastric pressure	↔	↓
Ineffective peristalsis	↑	↑
pH monitoring		
DeMeester score	↔	↓
Acid exposure time	↑	↓
Recumbent acid exposure time	↑	↓
Upright acid exposure time	↔	↓
Total number of reflux episodes	↑	↔
Non-acid reflux episodes	↑	↑
Acid reflux episodes	↔	↓

GERD After Sleeve

As previously discussed, obesity causes GERD via different mechanisms such as increased intragastric pressure, increased gastroesophageal pressure gradient, and increased incidence of hiatal hernias, while RYGB has been shown to improve GERD. The effect of LSG on GERD has been mixed. Some studies have shown improvement in GERD with a decrease in prevalence of GERD as high as 20%. However, these studies were plagued by significant heterogeneity of the patients and study design. Mechanisms proposed for the improvement in GERD after LSG include accelerated gastric emptying and decreased abdominal obesity resulting in less intra-abdominal pressure, reduced acid production, and a reduced gastric volume [17, 18].

While some patients do have improvement in their GERD symptoms, de novo development of GERD or pre-existing worsening of GERD symptoms is a complication of LSG. GERD after LSG presents with burning epigastric pain, regurgitation of food and acid, and heartburn. One meta-analysis demonstrated an increase of postoperative GERD after LSG of 19% and development of de novo reflux was 23% [19].

There are multiple mechanisms by which GERD worsens or develops after LSG. From an anatomical perspective, the angle of His (also known as the esophagogastric angle) is disrupted. Normally, the angle of His is an acute angle created by the junction of the cardia at the entrance to the stomach as well as the esophagus which prevents reflux of acid into the esophagus. However, in patients who undergo LSG, this angle is blunted creating more of a funnel shape favoring regurgitation and GERD. Also, the sling fibers of the distal LES are often transected in LSG leading to decreased tone of the LES. Furthermore, initially after the LSG, the gastric sleeve has decreased compliance due to the lack of a fundus. The volume restriction leads to increased intragastric pressures as well. The lack of gastric compliance, increased intragastric pressures, blunted angle of His, and a lower LES sphincter pressure lead to development or exacerbation of GERD in patients after LSG [17, 18, 20].

Delayed gastric emptying due to a lack of ghrelin-producing cells may also play a role in the development of GERD. LSG leads to the removal of a large portion of all ghrelin cells of the stomach leading to delayed gastric emptying. This delayed emptying in conjunction with the multiple anatomic mechanisms can predispose patients to GERD. However, the changes in gastric motility have not been completely elucidated as some studies have demonstrated delayed gastric empty, while others demonstrate accelerated gastric emptying [17, 18, 21].

Table 59.2 Adapted from Laffin, Chau [17], with permission with Dr. Richdeep Gill, MD

Mechanisms for de novo GERD after sleeve gastrectomy
Hypotensive LES
Blunting of angle of His
Decreased gastric compliance and volume (leading to increased gastric pressure)
Delayed gastric emptying
Dysmotility from decreased plasma ghrelin
Increase in hiatal hernias
Funnel shape of sleeve

Lastly, hiatal hernias are also responsible for development or exacerbation of GERD in patients after LSG. Studies have shown that they are underdiagnosed on routine endoscopy alone and may persist after an LSG. Endoscopic studies done on post-LSG patients who have developed GERD demonstrate the incidence of de novo hiatal hernia ranging between 5% and as high as 45% [22, 23]. One study using laparoscopic visualization demonstrated new hiatal hernias postoperatively in up to 73% of post-LSG patients [24]. While the primary mechanism for the development of hiatal hernias after LSG is unclear, it is an important contributory factor for worsening of and de novo GERD (Table 59.2).

Clinical Presentation of GERD After RYGB

RYGB has long been considered the reflux-protective bariatric surgery. Moreover, it is felt to be the most effective and advantageous treatment option for GERD in patients with morbid obesity [25]. According to the American College of Surgeons Bariatric Surgery Center Network (ACS-BSCN), 70% of patients achieve reflux symptom improvement or remission at 1 year following RYGB. Furthermore, conversion to RYGB is considered in patients following sleeve gastrectomy who develop significant GERD. However, despite considerable evidence that RYGB leads to improvement in GERD symptoms, there are still some reports of GERD following RYGB, as well as the development of BE and esophageal adenocarcinoma (EAC).

Compared to LSG, there are several anatomic changes which should *decrease* the risk of GERD following RYGB. Through the creation of a small gastric pouch, the majority of the stomach where the parietal cells reside is bypassed, resulting in significantly less acid exposure in the esophagus. Similarly, the duodenum is bypassed, thereby minimizing bile acid exposure. Given its effects on weight loss, there should also be reduced intra-abdominal pressure. However, there are patients that report reflux following

RYGB which has been attributed to either excessive retained gastric pouch permitting continued acid production by parietal cells or a short Roux limb resulting in bile acid reflux. Furthermore, overfilling and/or food stasis in the small gastric pouch may alter the dynamic function of the gastroesophageal junction or impact symptoms.

Recent studies have sought to better understand the physiologic changes created by RYGB in the form of esophageal manometry and pH impedance. One recent systematic review and meta-analysis of these studies and a decrease in the DeMeester score and in acid exposure time were found. While manometry studies found an increased rate of ineffective motility, it seemed to have minimal impact on esophageal motor function, with no postoperative changes in LES pressure, LES length, or esophageal body amplitude.

Interestingly, there were no changes in the total number of reflux episodes, with acid reflux episodes decreasing and non-acid reflux episodes increasing. However, these non-acid reflux events might still contribute to GERD in a subset of patients.

As RYGB appears to decrease acid reflux, the effect on the development of Barrett's esophagus or EAC remains unclear. While there are multiple cases of EAC reported after RYGB, there is no data to suggest an increased incidence of EAC after RYGB compared to controls.

Progression of GERD to Barrett's Esophagus After Bariatric Surgery

While development of GERD following bariatric surgery can negatively impact quality of life, more concerning is the potential for Barrett's esophagus (BE) and esophageal adenocarcinoma.

As detailed above, of the commonly performed bariatric surgeries, sleeve gastrectomy appears to pose the greatest risk of increased reflux. In long-term clinical trials comparing RYGB with sleeve gastrectomy, severe reflux resistant to medical treatment has been the leading cause for reoperations. The question regarding the risk of BE following SG has become ever more prudent as it is the most commonly performed bariatric surgery in the United States.

While results of initial studies were mixed regarding an increase in GERD and BE, more recent studies, which have allowed for longer follow-up, have demonstrated a more consistent link with GERD symptoms, esophagitis, and BE. Initial prospective studies showed rates of 10–15% of BE in patients following SG. More recently, two meta-analyses have also substantiated an increased risk of BE in this patient population. In a meta-analysis involving 680 patients, the pooled prevalence of BE was 11.4%, of which all cases were de novo and nondysplastic. Interestingly, there was no correlation with the development of BE and GERD symptoms [26]. Also, there was a linear relationship between time after SG and rate of esophagitis, with an increase of 13% each year. Another meta-analysis involving 10,718 patients found a long-term prevalence of esophagitis of 28% and BE 8%. This study also highlights that there does not seem to be a correlation of symptoms with the prevalence of esophagitis and BE [19].

Although these studies show a risk of de novo BE, the risk of progression in patients with BE *before* SG remains unknown. In a survey involving bariatric surgeons, the majority reported they would *not* perform SG on patients with known pre-operative BE. What should be taken into account, however, is that obesity is itself a risk factor for both BE and progression to EAC, and treatment with SG could provide these patients with protection against the metabolic and cardiovascular diseases associated with obesity, which are far more prevalent than dysplastic BE and EAC. Endoscopic findings of BE and EAC are demonstrated in Fig. 59.3.

Data on Barrett's progression after RYGB is scarce. However, consistent with the pathophysiologic anti-reflux nature of RYGB discussed above, there is data suggesting that RYGB is an effective therapy for patients with BE and reflux after SG, associated with BE regression and remission [27, 28].

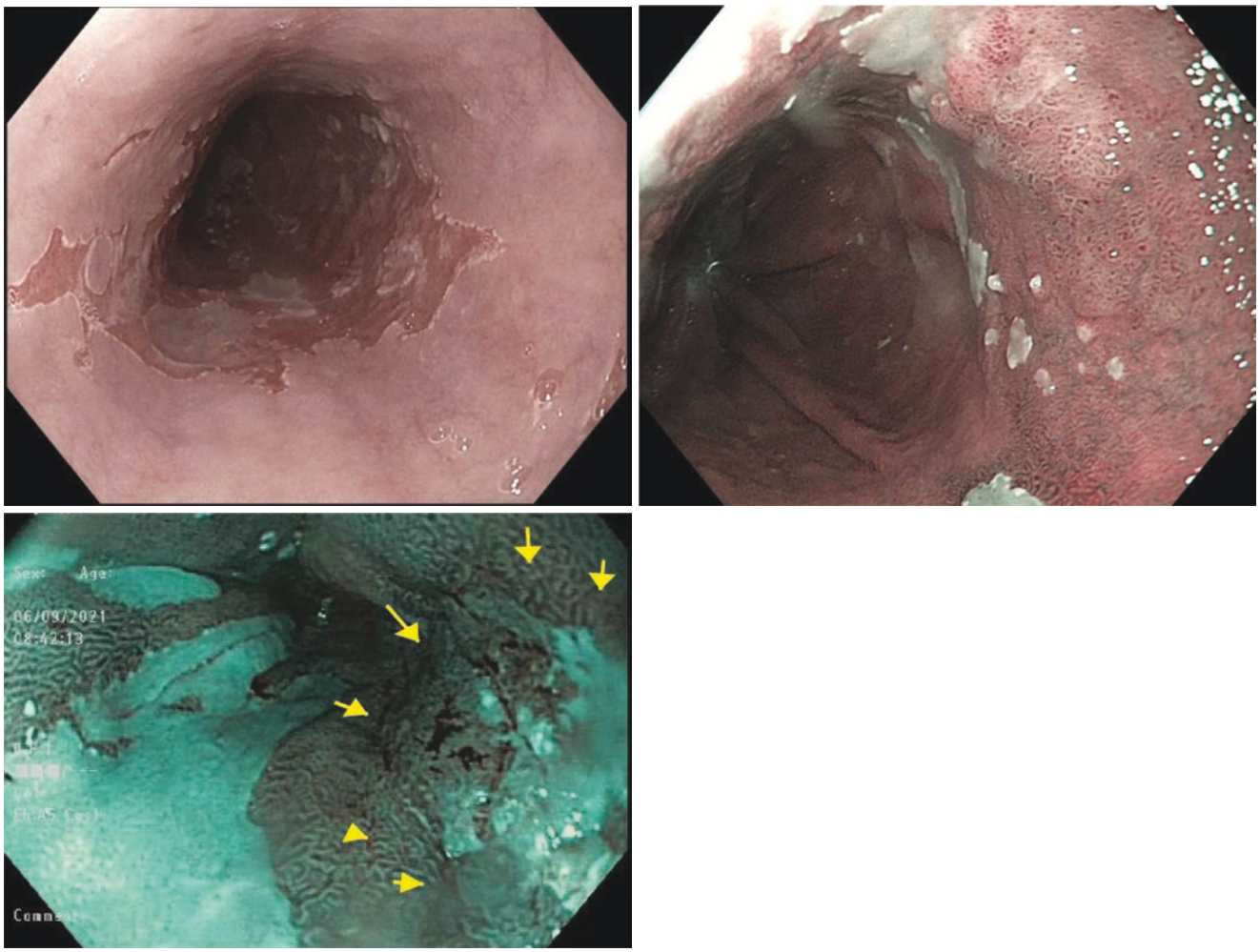

Fig. 59.3 Barrett's esophagus (top two images), esophageal adenocarcinoma arising from Barrett's (third image). (With permission from Dr. Allison Schulman)

Approach to Management of Post-bariatric Surgery GERD

The initial approach to management of GERD after bariatric surgical procedures typically involves lifestyle modifications and pharmacologic treatment with proton pump inhibitors (PPI) and/or H2 receptor antagonists. If symptoms persist or progress despite medical management, further evaluation and characterization may be pursued with various studies including upper endoscopy, barium esophagogram, pH impedance, manometry, and endoluminal functional impedance planimetry (EndoFLIP). Upper endoscopy may reveal complications of reflux such as esophagitis, Barrett's esophagus, or neoplasia. Impedance studies may help differentiate acid from non-acid reflux. Barium esophagogram may further elucidate anatomic issues that may be contributing such as a hiatal hernia or dysmotility. More recently, EndoFLIP is being used to identify patients with post obesity surgery esophageal dysfunction (POSED).

For patients without prior foregut surgery, there are a growing number of surgical and endoscopic interventions, such as Nissen fundoplication and transoral incisionless fundoplication (TIF). However, in patients who have undergone bariatric surgery, the altered foregut anatomy precludes fundoplication, thereby limiting the options, in addition to the technical challenge and risk of revisional surgery. In patients with GERD following SG, conversion to RYGB has been shown to be safe and successful, with >90% reduction in GERD, and is typically the preferred approach. In patients with GERD following RYGB, revision of the bypass to lengthen the Roux limb and/or downsize the gastric pouch or fundoplication using the bypassed stomach may be considered. However, there are also alternative endoscopic and surgical approaches, further described below.

Endoscopic Approaches

Radiofrequency Ablation

One currently available endoscopic option in post-bariatric surgery patients with medically refractory GERD involves delivery of radiofrequency ablation to the gastroesophageal (GE) junction. The radiofrequency energy controls transient relaxations of the LES and reduces the compliance of tissue at the GE junction, in turn helping to prevent GERD. The Stretta procedure (Curon Medical, Sunnyvale, CA) involves a balloon assembly with needle electrodes that are positioned 1 cm above the GE junction and deliver radiofrequency energy to the submucosa to achieve target temperature of 85 °C. The procedure has been shown to be safe and effective for treating GERD, with a morbidity rate less than 0.6%. There is now 10-year follow-up data in non-bariatric patients with significant improvement in quality of life and decreased use of PPI therapy [29].

There is limited data on Stretta in patients following bariatric surgery. In a small study involving 15 patients, Stretta did *not* improve GERD symptoms in patients following LSG at short-term follow-up, and one case was complicated by hematemesis. Two-thirds of patients were not satisfied, and two patients underwent RYGB [30].

Anti-reflux Mucosectomy (ARMS)

The ARMS procedure is another recently developed endoscopic therapy for GERD, which may have a role in post-bariatric patients with medically refractory GERD who are not candidates for surgical revision or conversion to RYGB. The procedure involves endoscopic mucosal resection (EMR) of the GE junction at the cardia from a retroflexed view. To perform ARMS, argon plasma coagulation is used to mark 85% of the circumference of the gastric cardia to be treated (leaving 15% untreated to preserve a mucosal valve). The area is then injected to provide submucosal lift, followed by EMR using a band or cap EMR kit.

In a recent case report of ARMS in a patient with GERD post-sleeve gastrectomy, the patient noted improvements in sensation of heartburn, regurgitation, and need for over-the-counter medications, without significant adverse events [31].

Surgical Approaches

Magnetic Sphincter Augmentation (MSA): LINX

Another option in patients with reflux following bariatric surgery is MSA, whereby a ring of titanium beads with a magnetic core is laparoscopically placed around the esophagus at the GE junction, thereby recreating a physiologic LES by resisting abnormal opening and relation of the sphincter due to transient relaxation or hypotensive sphincter. Peristaltic pressure is large enough to disrupt the magnetic force between the beads and allow the sphincter to relax during swallowing. However, as the esophageal pressure drops, the magnetic attraction of the beads draws the device back in to maintain LES tone. The LINX Reflux Management system (Torax Medical, St Paul MN) has been shown to reduce esophageal exposure to acid, improve symptoms of GERD, decrease the need for anti-reflux medications, and improve quality of life. While there are overall low risks of complications, there is a risk of dysphagia that can appear later and may require endoscopic dilation.

In non-bariatric patients, a study showed that 90% of patients were off their anti-reflux medication at the end of 1 year, with 90% normalization of esophageal acid exposure after 2 years and 86% patient satisfaction [32].

While there is similarly limited data on LINX in patients following bariatric surgery, the preliminary data is more promising than Stretta. In one study involving 13 patients with previous bariatric surgery, all patients reported improved GERD, with 70% discontinuing their medications and 100% reporting overall satisfaction post-procedure. 2 patients did experience dysphagia requiring endoscopic dilation after LINX placement [33].

Conversion to RYGB

Following sleeve gastrectomy, refractory GERD has traditionally been treated with conversion to RYGB. This has been shown to be safe and successful with rates of symptom resolution exceeding 90% [34, 35].

Concurrent or Subsequent Treatments of GERD in the Setting of Bariatric Surgery Currently Available

While the previously described procedures are for postoperative control of GERD following bariatric surgery, particularly following sleeve gastrectomy, there are a variety of procedures that can be performed during the initial surgical intervention to mitigate the incidence of postoperative GERD.

Hiatal Hernia Repair

Concurrent repair of existing hiatal hernia at the time of SG has been shown to be effective in decreasing incidence of GERD. A systematic review showed favorable results in 16 of 17 studies comparing effects of concurrent hiatal hernia repair during SG [36]. However, there remain some concerns

regarding the safety of concurrent repair. Recent data using the Metabolic and Bariatric Accreditation and Quality Improvement Program (MBSAQIP) data showed significantly increased rate with 30-day adverse events including readmission, reoperation, and re-admission.

Concurrent Fundoplication

Concurrent fundoplication at the time of sleeve gastrectomy has been proposed to decrease the risk of GERD by shaping an anti-reflux valve to cover the angle of His and moving the staple line to a better vascularized area. Remission of GERD ranged 88–95%. However, more than 50% required revision to address weight gain.

These concurrent procedures can also be done endoscopically, with same-session endoscopic sleeve gastroplasty and transoral incisionless fundoplication [37].

Concurrent Magnetic Sphincter Augmentation (MSA)

While some have proposed using MSA at the time of primary bariatric surgery, the American Foregut Society believes this violates basic surgical principles and should be considered a contraindication [38, 39].

Questions

1. Which of the following interventions has the most available data for treating GERD that develops after Laparoscopic Sleeve Gastroplasty?
   A. Radiofrequency ablation
   B. Revision to Roux en Y gastric bypass
   C. Magnetic sphincter augmentation
   D. Transoral incisionless fundoplication

Answer: B. Following sleeve gastrectomy, refractory GERD has traditionally been treated with conversion to RYGB. This has been shown to be safe and successful with rates of symptom resolution exceeding 90%

2. Which of the following is NOT a proposed mechanism by with RYGB decreases GERD?
   A. Increase in hiatal hernias
   B. Bypassing parietal cells decreased acid exposure
   C. Bypassing duodenum minimizing bile reflux
   D. Reduced intra-abdominal pressure by inducing weight loss

Answer: A. Creation of a small gastric pouch, the majority of the stomach where the parietal cells reside is bypassed, resulting in significantly less acid exposure in the esophagus. Similarly, the duodenum is bypassed, thereby minimizing bile acid exposure. Given its effects on weight loss, there should also be reduced intra-abdominal pressure. Increase in hiatal hernias is more commonly seen with laparoscopic sleeve gastroplasty leading to de novo reflux in these patients.

Author Disclosure

BKA reports consultant roles with Endogenex, Endo-TAGSS, Metamodix, and BFKW; consultant and grant/research support from USGI, Cairn Diagnostics, Aspire Bariatrics, and Boston Scientific; speaker roles with Olympus and Johnson and Johnson; speaker and grant/research support from Medtronic and Endogastric solutions; and research support from Apollo Endosurgery and Spatz Medical.

ARS reports consultant roles with Apollo Endosurgery, Boston Scientific, MicroTech, and Olympus and is a recipient of research/grant support from Fractyl. (In addition to GI dynamics).

All other authors have no conflicts of interest to disclose.

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Gastroesophageal Reflux Disease and Metabolic Surgery

60

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Introduction

The obesity pandemic, accompanied by a long list of obesity-related comorbid conditions and their profound impact on longevity and quality of life (QoL), continues to rise affecting 42.4% of adults in the United States (US) and over 650 million worldwide [1, 2]. Gastroesophageal reflux disease (GERD) is estimated to coexist in patients with obesity at rates ranging from 31.4% to 50.0% with its prevalence shown to increase with rising body mass index (BMI) [3, 4]. The prevalence of GERD in patients pursuing metabolic surgery may be even higher, affecting up to 62.4% [5]. As part of an interdisciplinary program, metabolic surgery is safe and the most effective treatment for obesity resulting in notable weight loss and comorbidity resolution [6]. The number of metabolic procedures performed in the US has steadily risen each year reaching 256,000 in 2019. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are most commonly employed accounting for 59.4% and 17.8% of metabolic operations [7]. Though many questions remain, it appears the effects of these procedures on GERD differ by operation type. Moreover, removal or exclusion of the fundus in SG and RYGB limits the options for addressing medically refractory GERD following metabolic surgery. This chapter provides an overview of the complex and incompletely understood relationship between metabolic surgery and GERD including its epidemiology, pathophysiology, presentation, and workup. The available evidence on procedures technically feasible in patients with refractory GERD after metabolic surgery is reviewed, and guiding principles for the management of this challenging and growing problem are offered.

Epidemiology

Incidence and prevalence of GERD after metabolic surgery are influenced by the specific operation performed. Definitions of contemporary terminology used to describe the relationship of GERD and metabolic surgery vary. Notwithstanding this limitation, GERD is qualified as *persistent* if diagnostic criteria including symptoms and/or objective criteria (i.e., esophagitis on endoscopy, pH study data) are present pre- and postoperatively, *de novo* if diagnostic criteria were met following surgery but not pre-operatively, *improved* if relief was documented by subjective and/or objective criteria and/or reduction of medication, and *resolved* if cessation of symptoms and/or normalization of objective criteria and discontinuation of medication occurred. Several studies have explored the impact of SG and RYGB on GERD including a meta-analysis of 23 studies (6 randomized controlled trials, 6 prospective, and 11 retrospective observational studies) totaling 5000 patients [8–11]. From these data, we have learned that GERD may persist in as many as 84.1% of patients after SG and 37.2% following RYGB [9]. De novo GERD after SG can occur in as many as 34.9% of patients in some series with pooled rates reported between 10% and 20%. Following RYGB, de novo GERD tends to occur at much lower frequencies with pooled rates quoted at 2.3% [8–11]. Improvement or resolution of GERD has been reported at 40.4% after SG and 74.2% following RYGB [8]. When considering just GERD resolution, its occurrence has been described at 15.9% after SG and 62.8% following RYGB [9]. Overall, SG has been associated with over five times higher risk of GERD than RYGB [8]. Thus, enough evidence points to a differential impact on GERD following SG or RYGB with the latter operation resulting in comparatively better outcomes. The sur-

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geon must take these differences into account, in the context of shared decision-making, when choosing from the metabolic surgery toolbox.

Pathophysiology

Though not completely delineated, the association between GERD, obesity, and metabolic surgery is marked by several pathophysiologic mechanisms. Normal anatomy and physiology maintain esophagogastric hemostasis, thus preventing GERD, through a balance between defense mechanisms (i.e., gastroesophageal junction—GEJ—competence, esophageal acid clearance, mucosal integrity) and harmful stimuli (i.e., number of reflux events, acidity, esophageal hypersensitivity) [12]. Though a complete review of the pathophysiology of GERD is beyond the scope of this chapter, key derangements relevant to the procedural management of GERD in the metabolic surgery patient population follow. Obesity is associated with higher transdiaphragmatic pressure gradient favoring reflux, higher incidence of hiatal hernia (HH) with disruption of the angle of His and lower esophageal sphincter (LES) dysfunction, increased frequency of transient LES relaxations (TLESR), and reduced esophageal clearance with altered motility and hyposalivation [13–18].

The GEJ is at the center of GERD pathophysiology, and an understanding of the factors which may influence GEJ incompetence is thus instrumental. Physiologically, TLESR facilitate gas venting in response to gastric distention. TLESR occur more frequently in the setting of GERD, feature that predominates in mild disease. LES hypotension defined as a pressure <10 mmHg is another important component of GEJ incompetence appreciated in more severe disease. Likewise, disruption or laxity of the fibrous attachment between the LES and crura, often associated with a HH, is associated with more severe GERD. Moreover, the size of HH has been correlated to the severity of GERD. Impaired crura, low LES pressure, and reduced threshold for TLESR have been implicated as GEJ derangements associated with HH [19].

Esophageal acid clearance is greatly influenced by esophageal emptying [20]. The vigor of distal esophageal contraction is defined by the distal contractile integral (DCI). Impaired esophageal emptying may manifest as failed or hypotensive peristaltic contractions [21]. Interestingly, re-reflux or retrograde flow associated with HH is also seen with impaired esophageal emptying [22].

Factors which may promote GERD after SG include a reduction in LES pressure possibly due to resection of sling fibers; disruption and widening of the angle of His; decreased gastric compliance resulting in increased intragastric pressure; narrowing at the incisura, failure to detect and correct a HH or the appearance of one postoperatively inadequate fundal resection or the development of neofundus; reduced lower esophageal body amplitude with increased risk for ineffective esophageal motility; and increased total and recumbent acid exposure times [13, 14, 23–29]. Alternatively, reduced population of parietal cells resulting in lower acid production, weight loss, and lower intraabdominal pressure and enhanced gastric emptying are some of the mechanisms theorized to account for some of the GERD improvement reported in some patients undergoing SG [23, 30].

Diversion of biliary secretions from the pouch, reduction of parietal cell population and acid production in the pouch, accelerated pouch emptying, weight loss, and lower intraabdominal pressure have been proposed as mechanisms whereby RYGB improves GERD [13, 14]. Pathophysiologic changes appreciated after RYGB include an increased risk of ineffective esophageal motility, a reduction in the total and recumbent acid exposure times, and a reduction in acid reflux but unchanged total reflux episodes secondary to a proportional increase in non-acid reflux [29]. The effect of either procedure on LES function is mixed.

Presentation

The constellation of symptoms and signs attributable to GERD in the setting of metabolic surgery are comparable to those exhibited by patients with GERD without such surgical history. The hallmark of GERD is that of reflux which causes bothersome symptoms and/or complications. Classic or typical symptoms include heartburn and regurgitation, whereas chest pain, dysphagia, globus sensation, water brash or hypersalivation, odynophagia, nausea, and extraesophageal symptoms (e.g., chronic cough, hoarseness, wheezing) are considered non-classic or atypical symptoms. GERD can be further classified based on the endoscopic appearance of the esophageal mucosa as erosive, if esophagitis with mucosal breaks is present with or without symptoms, or nonerosive, if symptomatic patients show no evidence of esophagitis on endoscopy. Lastly, it is important to note that GERD complications, subdivided as esophageal (i.e., Barrett's, stricture, adenocarcinoma) or extraesophageal (i.e., chronic laryngitis, asthma exacerbation), may occur in the absence of classic symptoms.

Workup/Diagnosis

The diagnosis of GERD can be made clinically in patients with classic symptoms, while in others presenting with non-classic symptomatology, exclusion of alternative etiologies should be pursued before considering GERD as the causal pathology. Just as in patients without a history of metabolic

surgery, a wide differential should be considered in patients with a history of SG and RYGB, particularly in individuals presenting with non-classic GERD symptoms. In such cases, esophageal (e.g., achalasia, malignancy, motility disorders, esophagitis not related to GERD), gastric (e.g., gastritis, peptic ulcer disease, gastroparesis, *Helicobacter pylori* infection), complicated and uncomplicated gallstone diseases, intestinal (e.g., motility and functional disorders), and even cardiovascular (e.g., coronary syndromes) pathology are just some of the alternative diagnoses to consider. Additionally, in patients with a history of metabolic surgery, particularly if presenting with non-classic symptoms of new onset, worsening of their presurgical GERD symptoms or a change in symptomatology, complications of these procedures such as marginal ulcer, stenosis, small bowel obstruction including that resulting from internal herniation, gastric remnant distention, gastro-gastric fistula, candy cane Roux syndrome, and small intestinal bacterial overgrowth must be considered.

Coupled with a thorough history and physical examination, additional studies can help confirm the diagnosis, exclude alternative causes, and assess for complications. Esophageal pH testing is the gold standard for the diagnosis of GERD. Several modalities are available, and choosing one over the others mostly depends on the presence of classic vs. atypical symptoms. Standard ambulatory pH testing is used for patients with classic GERD symptoms to document abnormal distal esophageal acid exposure. The test can be done via a 24-h trans-nasal catheter or 48-h wireless probe following discontinuation of proton pump inhibitors (PPI) therapy for 7 days. While the test is ongoing, patients are asked to consume an unrestricted diet. A DeMeester score >14.7 or esophageal acid exposure time (AET) >6% is considered pathologic [31, 32]. There has been debate about whether this benchmark is applicable in RYGB patients who have an altered parietal cell burden. Multichannel intraluminal impedance (MII) detects esophageal bolus movement and, when combined with pH testing, can detect acid and non-acid gastroesophageal reflux. This modality can be considered in patients with symptoms refractory to PPI, high-volume regurgitation, or atypical symptoms to document weekly acidic or non-acidic reflux. Dual pH probe can be useful to document proximal (laryngeal) reflux events in patients with suspected laryngopharyngeal reflux (LPR). Usually during pH testing, patients are asked to record symptoms which are correlated with reflux events. Symptom association is automatically calculated by software and presented as the symptom index (SI) or symptomatic association probability (SAP) with values of >50% and >95%, respectively, considered positive. This is most useful to detect association of atypical symptoms with acid reflux. The association of symptoms with the incidence of reflux episodes also helps set expectations and outcomes following interventions for reflux.

Esophageal manometry, commonly in the form of high-resolution manometry (HRM), is a complex diagnostic tool that can reliably assess GEJ competence, exclude esophageal motility disorders, evaluate esophageal peristalsis, and accurately map the GEJ for pH probe placement. While a detailed review of HRM is outside the scope of this section, it is important to understand the significance of a few key metrics on esophageal and GEJ function. Physiologic LES pressures range from 10 to 45 mmHg, and its relaxation should be coordinated with more than 90% of wet swallows during which equilibration with intragastric pressure should be appreciated. The competence of GEJ relaxation with swallowing is assessed by the integrated relaxation pressure (IRP) defined as the lowest mean GEJ pressure for 4 s within 10 s of swallowing. Fifteen mmHg defines the upper normal limit. Distal esophageal contraction vigor is presented as the DCI expressed as the product of the amplitude over 20 mmHg, duration, and length of the contraction between the proximal and distal trough. Normal range for DCI is from 450 to 8000 mmHg s cm.

Upper endoscopy, upper gastrointestinal (UGI) series, and occasionally gastric emptying study round up the diagnostic workup of GERD. Upper endoscopy can detect Barrett's and esophagitis and exclude malignancy. It should be used in the presence of alarm features (i.e., dysphagia, odynophagia, age ≥60 years, etc.), risk factors for Barrett's (i.e., obesity, smoking, 5 years of symptoms, age ≥50 years, male, White race, etc.), or abnormal upper gastrointestinal tract imaging. In patients with a history of metabolic surgery, it is also helpful in excluding other pathology such as marginal ulcer, stenosis, HH, large gastric pouch or sleeve, or candy cane Roux syndrome. Reflux on UGI series is of limited diagnostic utility in GERD as this can be elicited in 20% of normal controls [33]. However, UGI series may detect esophagitis, ulceration, stenosis, HH, diverticulum, or neoplasm. UGI also helps assess function of the proximal GI tract. Lastly, a gastric emptying study may be of utility in patients with GERD if there are symptoms suggestive of gastric outlet obstruction or gastroparesis such as nausea, vomiting, bloating, postprandial fullness, or retained food after overnight fast.

GERD Around Metabolic Surgery

Patients undergoing metabolic surgery experience a wide variety of GERD symptoms pre-operatively, immediately postoperatively, and long-term. Depending on patient baseline pathophysiology, procedure type, and weight loss extent, GERD can go from debilitating to absent, or vice versa, or anywhere in between. Initial improvement in GERD after most metabolic procedures is commonly reported. In a review of the Bariatric Outcomes Longitudinal Database,

Pallati et al. described symptom improvement in over 22,000 bariatric patients with pre-operative GERD. All patients had either adjustable gastric banding (AGB), RYGB, or SG without concomitant HH repair or fundoplication. Patients with RYGB had a pre-operative GERD score of 2.80 ± 0.56, and mean postoperative score at 6 months was 1.33 ± 1.41 ($P < 0.0001$). AGB (2.77 ± 0.57 to 1.63 ± 1.37, $P < 0.0001$) and SG (2.82 ± 0.57 to 1.85 ± 1.40, $P < 0.0001$) patients also had significant improvement in GERD score [34]. Although early symptom improvement is common, it is not universal nor is it durable. A meta-analysis of 46 studies with 10,718 patients undergoing SG showed a 19% increase in postoperative GERD and 23% de novo reflux. The analysis also revealed a 28% prevalence of esophagitis and 8% Barrett's esophagus, leading to a 4% conversion rate to RYGB [35]. Another study by Silveira et al. showed no significant change in GERD symptoms or GERD medication use before and after SG for 191 patients at a mean follow-up time of 20.4 ± 2.7 months; however sub-group analysis of patients without pre-operative GERD symptoms showed worse GERD-HRQL scores postoperatively (2.4–4.5, $P = 0.233$) [36]. A randomized controlled trial by Peterli et al. explored the often-opposing trends of GERD development after surgery. In their trial of 101 SG patients and 104 RYGB patients with 5-year follow-up, 60.4% of RYGB patients had remission of gastric reflux compared to 25% in SG patients ($P = 0.002$). Gastric reflux worsened in only 6.3% of RYGB patients compared to 31.8% of SG patients ($P = 0.006$). Nine out of the 101 LSG patients underwent conversion to RYGB within 5 years for severe GERD [37]. Similar findings were seen in a retrospective review by Balla et al. Out of 100 patients undergoing SG, 55 patients had improved GERD-HRQL scores, 14 had no change, and 31 had worse scores including 10 who developed de novo GERD. A higher pre-op GERD-HRQL score was associated with an improved post-op score, and as expected, a higher post-op BMI was associated with a worse post-op score [38].

When the pathophysiology is considered, this apparent duality or conflict in postoperative gastric reflux symptoms is not surprising. After SG, weight loss decreases intra-abdominal pressure, and the nature of the gastrectomy reduces gastric volume and gastric acid production from parietal cells in the cardia—all mechanisms which may improve GERD. Conversely, SG causes a change in LES pressure gradient due to the altered angle of His and ligamentous dissection. Furthermore, a diminished gastric pouch with poor compliance increases intraluminal pressure, leading to worse GERD [39]. Other studies have also described worsening GERD symptoms after SG caused by a decrease in gastric ghrelin and gastric emptying with associated dysmotility [28]. After AGB, patients likely experience an early improvement in GERD symptoms related to their weight loss and the augmentation of the LES by the band, but over time, the band can slip, and the pouch can dilate and lead to esophageal stasis with GERD and/or regurgitation [40]. RYGB patients enjoy robust weight loss as well as diminished acid-producing cells in the small gastric pouch with improved gastric emptying, all of which support an improvement in GERD symptoms. Although worsening GERD is typically associated with SG or AGB, complications following RYGB can lead to GERD-like symptoms. Gastro-gastric fistula may allow persistent gastric acid reflux as well as diminished weight loss, while marginal ulcers or bile acid reflux may cause pain similar to GERD. In addition, the morphology of the sleeve cannot be ignored as a contributor of reflux following sleeve gastrectomy. Multiple causes of reflux after the sleeve were outlined earlier in the chapter.

Management

Non-procedural Management

The initial management of GERD following metabolic surgery is the same as that of patients without a history of metabolic operations. Though a detailed review of the non-procedural management of GERD is beyond the objective of this chapter, a few guiding principles are presented next. Initial management is dictated by clinical severity graded as mild or moderate/severe based on QoL impairment. Symptoms may be classified as intermittent if <2 episodes/week or frequent if ≥2 episodes/week. For mild and intermittent symptoms, lifestyle and dietary modifications are first-line interventions. Dietary counseling is particularly important for patients after metabolic surgery as many foods that are GERD triggers may be foods they were advised to avoid. Given the negative correlation between weight loss and GERD, continued dietary and lifestyle coaching should also be provided to patients not meeting their expected weight loss target according to procedure. Additionally, individualized elimination of dietary triggers such as caffeine, chocolate, spicy foods, high-fat-containing foods, carbonated beverages, and peppermint can be successful in some patients. Smoking and frequent alcohol use should be eliminated. Elevation of the head of the bed should be recommended for patients with nocturnal or laryngeal symptoms, as well as minimizing oral intake within 2 h of laying down. Pharmacologic therapies to consider in this setting include antiacids, surface agents (i.e., sucralfate), and alginates.

For severe or frequent symptoms and/or erosive esophagitis, therapy with PPI is often the initial intervention. Repeat endoscopy, following 2 months of therapy, is recommended for patients with Los Angeles classification grade C or D esophagitis. Patients with continued symptoms despite compliance with twice a day PPI therapy can try additional pharmacologic agents. Bedtime/evening H2RAs can be con-

sidered in patients with persistent acid reflux on pH testing. Baclofen can be prescribed in patients with non-acid reflux on MII/pH testing. Tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor, selective serotonin uptake inhibitor, or trazodone can be used for refractory GERD in patients with esophageal hypersensitivity (normal MII and pH study). Lastly, prokinetics can be tried in patients with GERD in the setting of delayed gastric emptying. When lifestyle modification and medications do not control symptoms or heal esophagitis, then a more extensive workup as described earlier can be pursued. Particular attention should be paid to the presence of hiatal hernias, large pouches, dilated fundus, and kinks/twists/stenosis within the sleeve.

Procedural Management

Refractory GERD after metabolic surgery poses a unique challenge. Conventional procedural options for addressing reflux, including surgical or transoral incisionless fundoplication, are not technically feasible given the removal or exclusion of the fundus in SG and RYGB. Ideally, the spectrum of indicated procedural therapies, endoscopic and surgical, should be offered based on available expertise prioritizing shared decision-making through a discussion of the risks/benefit profile of each therapeutic option tailored to the individual patient. We will first review the endoscopic procedures.

Marketed as Stretta, endoluminal delivery of radiofrequency energy to the GEJ, is one procedural option which may be considered for patients with refractory GERD after metabolic surgery. To date, minimal data exist, and only two small retrospective series have explored the use of Stretta in patients with GERD after SG and RYGB. In a study of seven patients with GERD after SG, Stretta did not improve GERD-HRQL and only resulted in PPI cessation in 20% at 6 months [41]. Another small series including seven patients with persistent GERD after RYGB reported symptom resolution and normalization of pH studies in five patients at 20 ± 2 months [42]. Safety and effectiveness data on Stretta are more robust on the non-metabolic surgery patient population. The procedure has a favorable safety profile with rare incidence of complications including gastroparesis and ulcerative esophagitis and infrequent side effects involving transient epigastric or chest pain, low-grade fever, dyspepsia, mucosal bleeding, dysphagia, and odynophagia [43]. Twenty-eight studies (4 randomized controlled trials, 23 cohort studies, and 1 registry) representing 2468 unique patients undergoing Stretta at an unweighted mean follow-up time of 25.4 months were included in a meta-analysis. The authors concluded that Stretta results in improvement of subjective and most objective GERD endpoints including GERD-Health Related Quality of Life (GERD-HRQL), heartburn standardized score, cessation of PPI therapy in 51% of patients, and reduced mean esophageal acid exposure [44] (Fig. 60.1). Long-term outcomes at 8 and 10 years show persistent improvement in GERD-HRQL, satisfaction, and reduction or cessation of PPI use in up to 72% of patients though the objective effects on esophageal acid exposure may wear off [45, 46]. The proposed mechanisms whereby Stretta improves GERD include increased LES pressure, increased gastric yield pressure defined as the difference between the cardia opening and resting gastric pressures, decreased GEJ compliance, and reduction of TLESR frequency [47–49]. The primary mechanisms by which this procedure works are primarily reducing TLESRs and some augmentation of the LES resulting from collagen deposition. Though additional evidence on the use of radiofrequency energy delivery to the GEJ in patients with refractory GERD after SG and RYGB is needed, this modality is safe and can be considered in this patient population. Therefore, this intervention works best in those patients with normal sleeve morphology and fairly normal pressures within the LES. Obviously, this comprises a small group of patients.

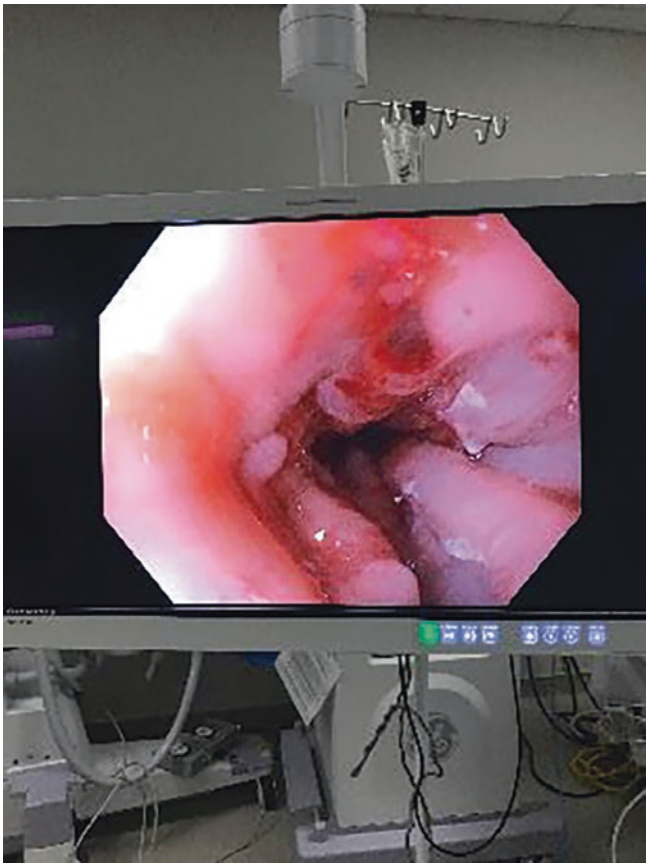

Fig. 60.1 View of LES after radiofrequency energy delivery

Anti-reflux mucosectomy (ARMS) is another novel endoscopic technique recently investigated in patients with refractory GERD. This modality is technically feasible following

metabolic surgery. The procedure involves a 240°–270° endoscopic mucosal resection (EMR) of the gastric cardia around the GEJ usually sparing portions of the lesser and greater curves. Several approaches can be employed to accomplished EMR including banding, cap-assisted, or endoscopic submucosal dissection (ESD). The exact mechanisms through which ARMS results in GERD improvement have not been studied, but narrowing of the GEJ via scarring has been proposed. Several small studies have investigated ARMS in patients with GERD. At a mean follow-up of 10 ± 5 months in 21 patients treated with ARMS, one patient required surgical fundoplication, and adverse events included bleeding needing no treatment in one and dysphagia managed endoscopically in three patients. PPI reduction/discontinuation was 76% at 3 months and 72% at 6 months accompanied by improvements in GERD-HRQL [50]. In a series of 62 patients, DeMeester score normalization was 72.5%, and GERD-Q scores improved at 2 months. PPI cessation was 69.4% at 2 and 61.3% at 12 months. Dysphagia needing endoscopic dilation was the main complication reported, occurring in 8% of patients [51]. Similar results have been described by others [52–54]. One study investigated ARMS in patients with refractory GERD after SG. It reported technical feasibility in all six patients and >50% reduction in GERD-HRQL score in 5 patients at 3 months. Complications included one patient with esophageal stricture and one with bleeding [55]. It is not known which subset of patients with GERD may experience the most benefit from this technique though smoking and Hill grade I or II versus III or IV have been proposed as factors perhaps associated with failure of ARMS [56].

Surgical procedures to manage GERD after metabolic surgery are aimed at improving drainage or augmenting the LES. The RYGB procedure has been considered the "ultimate" procedure for the management of reflux disease [57]. For patients with high pressure in the sleeve leading to severe reflux, conversion to RYGB works very well as a decompression procedure. In addition, HH noted after any of the metabolic procedures will contribute to GERD symptoms. HH should be fixed. The greatest challenge in managing reflux after metabolic surgery is how to augment the LES. In these metabolic operations, as stated earlier, the fundus of the stomach is either removed or excluded. Following RYGB, although the fundus is still present, it is in the remnant stomach which is no longer in the pathway of food. Therefore, the fundus does not distend with eating and therefore will not function as a neovalve as it does in a proper Nissen with intact gastric anatomy. LES augmentation with falciform ligament has also been described but again is not a dynamic valve as a Nissen or Toupet would be.

The addition of a variety of anti-reflux procedures to SG has also been studied. Cruroplasty and 180° cardioplication at the time of SG or SG and transit bipartition were studied in 88 patients and compared to unmatched controls. At a mean follow-up of 22 months, the authors reported resolution of GERD symptoms in 61.4% and cessation of PPI use in 63.7% of patients in the intervention group compared to 6% symptom resolution and 12% PPI discontinuation in controls [58]. Completion of a fundoplication at the time of SG has also been explored. Morbidity from this approach has been described as 9.4% overall complication rate including gastric perforation (3.1%), bleeding (1.8%), and gastric stenosis (1.2%) following the review of seven studies totaling 487 patients [59]. In a series of 70 patients with documented esophagitis undergoing Nissen fundoplication plus SG, resolution of GERD symptoms was reported in 98% and 70% of patients who experienced endoscopic resolution of esophagitis without compromising weight loss outcomes at 1 year [60]. At this time the authors do not recommend fundoplication with SG.

One prospective study of 18 patients undergoing SG and ligamentum Teres cardiopexy (LTC) for prevention of GERD reported no GERD symptoms at 6 moths. Notably, most of the patients in these series underwent HH repair (HHR) [61]. Four small studies totaling 46 patients with GERD after SG undergoing LTC with variable follow-up at 6–36 months reported symptom resolution in 67–100% [62]. Similarly, in a series of ten patients with GERD after SG, LTC resulted in 80% symptom resolution at a median follow-up of 7 ± 3 months. Of note, five patients had HHR and fundoplication plus SG as their index operation, and four patients had undergone multiple operations for reflux predating their index SG. Interestingly, 90% of patients also presented with HH which was repaired at the time of LTC. Only one readmission for dehydration was reported [63]. Though short-term GERD-related outcomes for some of these operations appear encouraging, the low quality of the evidence and the lack of data on their long-term effectiveness limit their implementation in clinical practice.

Magnetic sphincter augmentation (MSA), marketed as LINX Reflux Management System, is a novel and technically feasible procedure for LES augmentation in patients with refractory GERD following metabolic surgery. The device is made of a series of magnets arranged in a dynamic ring with sufficient attraction to augment LES pressure but also permit food passage during swallowing. MSA has been associated with increases in the median LES resting and residual pressures and distal esophageal contraction amplitude without significantly affecting peristalsis [64]. At this time, limited data exist on the effectiveness of this procedure in patients after metabolic surgery. Short-term improvements in GERD scores following MSA were reported in a series of seven patients with GERD following SG [65]. When 13 patients with GERD after metabolic surgery (8 SG, 4 RYGB, and 1 duodenal switch) were retrospectively studied, all reported at least PPI use reduction and GERD-HRQL

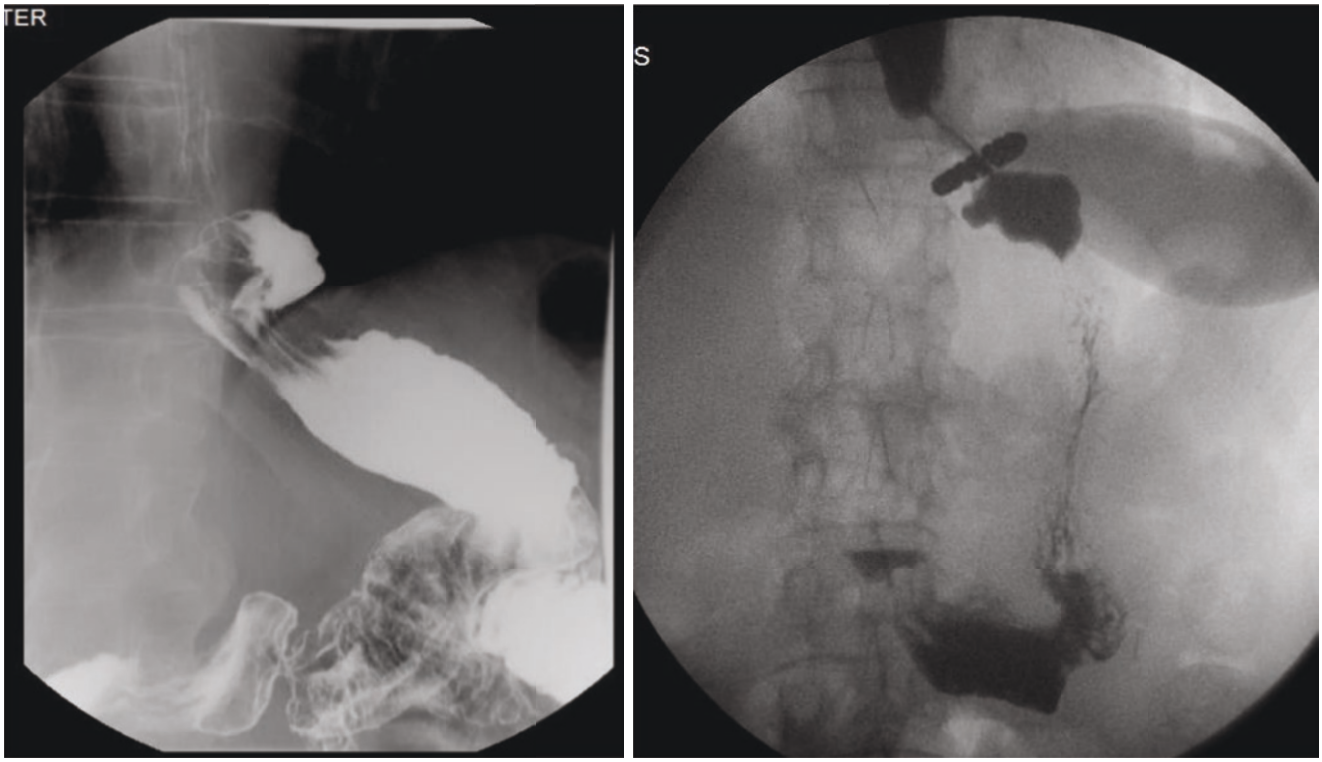

Fig. 60.2 Hiatal hernia in a patient who underwent prior sleeve gastrectomy on the left. On the right the same patient with the hiatal hernia repaired and LES augmentation with MSA

improvement with 9 patients experiencing cessation of PPI use at an average follow-up time of 20.8 months [66]. Another study of 13 patients undergoing MSA for GERD after SG also noted reduction in GERD-HRQL scores at 26 ± 12 months [67]. When MSA outcomes were compared between ten patients with GERD after metabolic surgery (8 SG and 2 RYGB) and a group of patients undergoing sphincter augmentation for standard indications, the authors reported no differences in QoL and medication cessation, 90% for the metabolic surgery group, at a median follow-up of 14.9 months [68] (Figs. 60.2 and 60.3).

Other studies have reported on the safety and effectiveness of MSA in patients with GERD in the absence of metabolic surgery. MSA has a favorable safety profile. When 1000 patients from 82 institutions were studied at a median implant duration of 274 days, the following event rates were reported: intra/perioperative complications (0.1%), hospital readmissions (1.3%), endoscopic dilations (5.6%), laparoscopic device removals primarily due to dysphagia (3.4%), and erosion of the device in one patient (0.1%) [69]. MSA is also effective. Outcomes from a single-arm prospective trial including 100 patients undergoing MSA reported PPI use reduction and QoL improvement in 93% and 92% of patients and a reduction of at least 50% esophageal acid exposure in 64% of patients [70]. Data from a prospective, single-arm

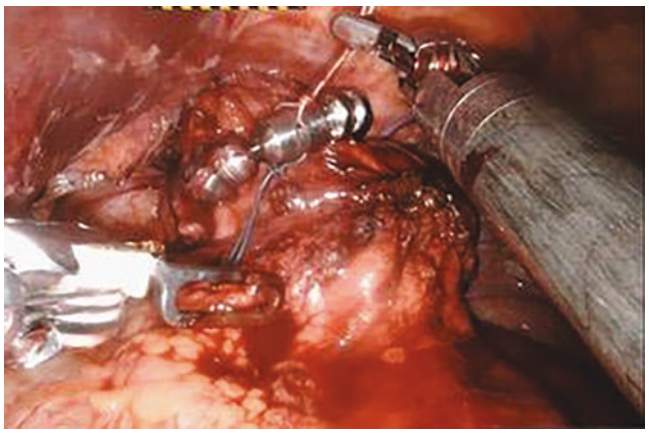

Fig. 60.3 Placement of the LINX magnetic sphincter augmentation device after prior sleeve gastrectomy due to persistent severe GERD

trial of 44 patients showed that at 1 and 2 years, 77% and 90% of patients had normal esophageal acid exposure. Cessation of PPI use was reported by 90% and 86% of patients at 1 and 2 years. This was accompanied by a reduction in GERD-HRQL scores in 85% and 90% of the sample at 1 and 2 years [71]. Four-year follow-up of 52% of the initial sample showed pH normalization (≤5.3%), GERD-HRQL improvement, and cessation of PPIs use in 80%,

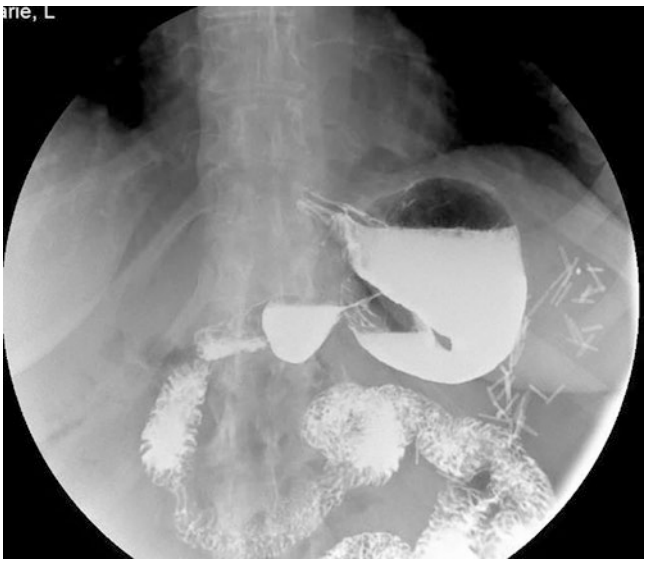

Fig. 60.4 Retained fundus seen on radiologic study after a sleeve gastrectomy

100%, and 80% of patients [72]. Of note, allergies to titanium, stainless steel, nickel, or iron may preclude patients from undergoing MSA. Patients undergoing MSA should also be counseled on the compatibility of the implant with magnetic resonance imaging.

The senior author notes that MSA should primarily be used for LES augmentation in those who have had a thorough evaluation with endoscopy, manometry, and radiographic evaluation. Patients should have proper workup to confirm proper esophageal motility to avoid dysphagia after the procedure. In addition, SG patients should have normal sleeve morphology. If the sleeve has a kink, twist, retained fundus (Fig. 60.4), or narrowing at the incisura, MSA is unlikely to be effective in the management of GERD in those patients. Results from the RELIEF trial, a large multicenter study looking at the use of MSA after SG, will be published soon.

Hiatal Hernia

GERD and obesity are prominently associated with the coexistence of a HH. The true prevalence of HH in patients with obesity is unknown but could be as high as 50% [73]. In patients undergoing metabolic surgery, the presence of a HH has been estimated at approximately 20% [74]. Interestingly, intraoperative perception of what constitutes a HH may vary by surgeon [75]. Several studies have reported on GERD outcomes when a HH is repaired at the time of index SG. A recent meta-analysis including 18 studies and 937 patients concluded that the addition of a HHR to SG was superior to SG alone in GERD remission resulting in significant reduction in GERD symptoms, improvement in esophagitis, and decrease in GERD-HRQL though no differences in de novo GERD were noted between the two approaches [76]. Compared to SG alone, concurrent HHR was found to be safe with no increase in mortality and just slight increases in readmission, re-operation, and postoperative intervention according to a large 1:1 propensity-matched cohort of 50,951 patient pairs [77]. Similar methodology has shown no difference in major complications at 30 days between the two approaches [78]. The incidence of de novo HH after SG is unknown. In a series of 51 patients undergoing intraabdominal operations for several indications and with a history of SG and no HH noted at index operation, the incidence of de novo HH was reported at 72.5% [79]. Outcomes for HHR in the setting of GERD after index SG are limited to a small series of nine patients with note of self-reported improvement of GERD symptoms in this sample [80] (Fig. 60.2).

Though no study to date has reported on GERD-related outcomes when a HHR is done during index RYGB, when undertaken this approach appears to be safe. Matched comparison of 412 patients undergoing concurrent HHR and RYGB to 1070 patients undergoing RYGB alone reported no differences in re-operations at 90 days and 1 year though patients undergoing HHR underwent more endoscopic procedures [81]. Interestingly, analysis of 130,772 patients revealed that concurrent HHR occurs in 21.0% of SG compared to only 10.8% of RYGB despite lower incidence of GERD in the SG and HHR group [82]. De novo HH may be uncommon in asymptomatic patients after RYGB with a reported incidence of 1.7% at 1 year in a series of 715 patients [83]. Alternatively, HH may be a common entity appreciated in up to 53% of patients with persistent GERD following RYGB [84]. Currently, there are no data on safety and effectiveness of HHR in patients with GERD after RYGB. However, anecdotally, the authors consider a hiatal hernia after a bypass similar to a paraesophageal hernia. Even a herniation of 1–2 cm is 30–50% of the gastric pouch and can be symptomatic. Therefore repair is recommended if symptomatic (Fig. 60.5).

In appropriately selected patients, conversion to RYGB is considered the gold standard for the treatment of refractory GERD after a SG, particularly if obesity and/or metabolic comorbidities persist. BMI is also a tipping point when considering interventions such as LES augmentation or a durable HHR as these are generally considered futile above the 35.0 kg/m^2. Moreover, it is important to consider GERD when contemplating a revision from SG for weight loss failure, weight regain, or severe metabolic comorbidities. As an example, when a duodenal switch is employed in this situation, de novo GERD can develop in as many as 26% of patients [27]. The rate of SG to RYGB conversion ranges from 1.8% to 8.9% [8]. A recently published meta-analysis of 17 studies including 556 patients undergoing conversion to RYGB from SG of which 30.4% carried the

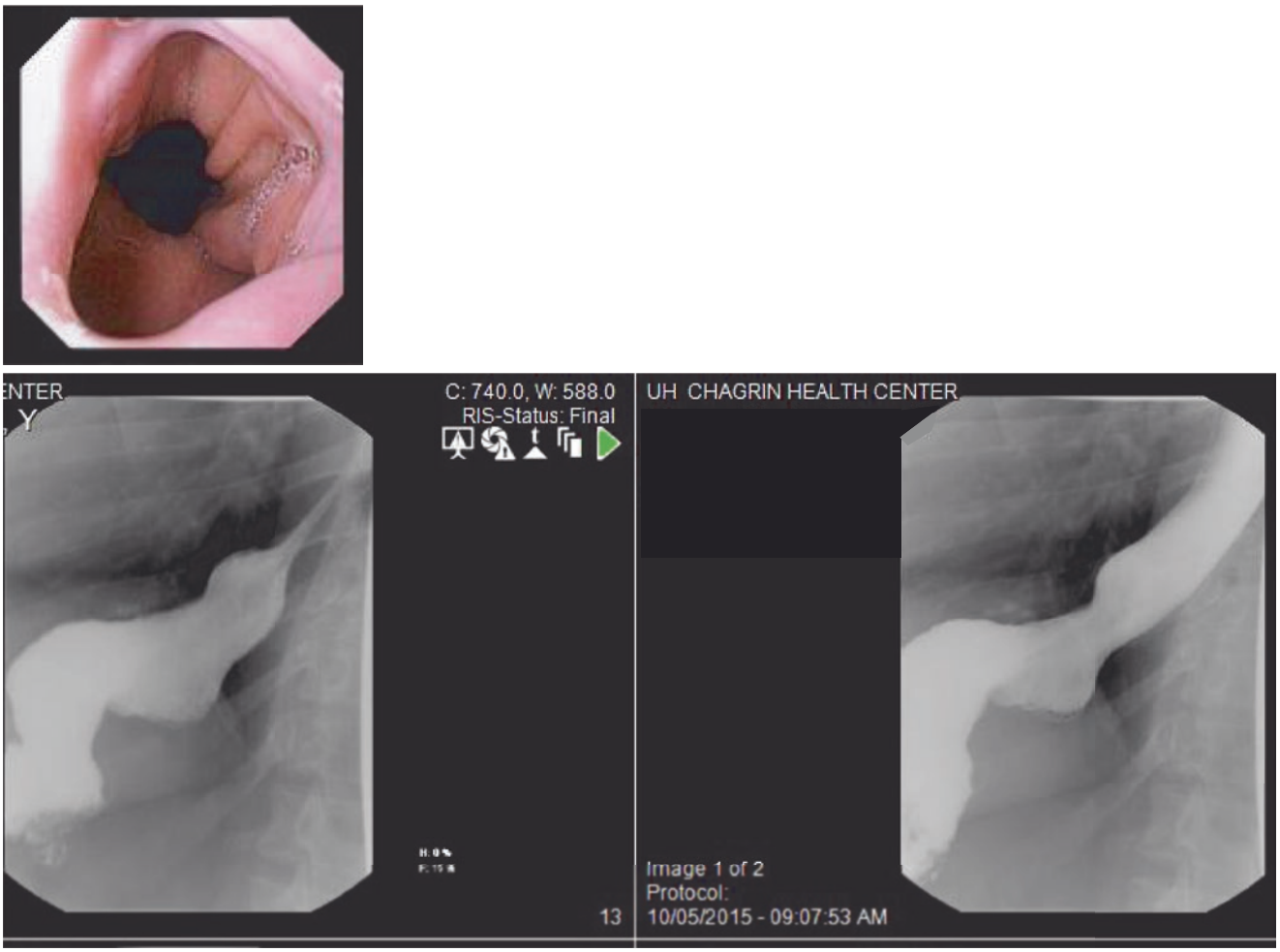

Fig. 60.5 Hiatal hernia after gastric bypass seen endoscopically and fluoroscopically (half of gastric pouch seen above the diaphragm)

indication of GERD reported GERD resolution rates of 79.7% and 91.3% at 1 and 2 years. Complication rates within 30 days were 16.4% and 11.4% after 30 days with an overall re-operation rate of 3.9% [85]. Altogether, SG to RYGB conversion is a highly effective procedure for patients with refractory GERD at the cost of slightly higher re-operative morbidity.

Alternative surgical approaches have been studied in patients with GERD in the setting of metabolic surgery. Redo-SG has been considered when residual fundus and/or diffuse dilatation of the sleeve coincides with refractory GERD. Improvement in GERD and PPI cessation in all patients at 24 months was reported in a series of 19 patients. Five postoperative complications were reported including two cases of bleeding, one mid-gastric stenosis, and two leaks [86]. Follow-up at 52 months revealed recurrent GERD or conversion to RYGB in 87.5% of the available sample [87]. Based on the limited available evidence, Redo-SG is not a durable, nor recommended, strategy for the treatment of refractory GERD after SG.

Conclusion

Reaching pandemic proportions, the prevalence of obesity and related diseases continues to rise. Level 1 evidence now supports metabolic surgery as a safe and the most effective treatment for obesity and associated metabolic conditions. As a result, more metabolic procedures, of which 77.2% is accounted for by SG and RYGB, are performed each year. The association between GERD, obesity, and metabolic surgery is complex. There is a large body of literature supporting a differential impact of SG and RYGB on GERD with the former operation comparatively associated with higher risk of persistent, worsened, and de novo GERD. The management of refractory GERD after these procedures presents a unique challenge as the absence or exclusion of the fundus precludes fundoplication. Moreover, any operative approach following index SG or RYGB may likely incur in the increased morbidity related to revision. Currently, several endoscopic and surgical procedures appear technically feasible for the management of refrac-

tory GERD after the most commonly performed metabolic operations. However, substantial evidence gaps in areas such as patient selection, indications for each procedure, comparative outcomes, and short- and long-term safety and effectiveness in patients with refractory GERD after metabolic operations preclude the standardization of procedural management. In addition, better standardization in creation of SG may also minimize the reflux post procedure that is currently being realized. Despite these limitations, the following guiding principles should be considered. Lifestyle modifications and pharmacology are first-line strategies in the management of GERD after metabolic procedures. GERD refractory to these interventions should be thoroughly investigated with UGI series, upper endoscopy, pH study, and manometry. Though the indications, safety, and effectiveness of Stretta and ARMS have not been defined in patients with refractory GERD after metabolic operations, these novel endoscopic therapies are technically feasible in this population. Evidence on the use of MSA to treat refractory GERD in carefully selected patients after metabolic procedures is encouraging. The presence of a HH in patients with refractory GERD after metabolic surgery should be addressed. In appropriately selected patients, SG to RYGB conversion is the gold standard for treatment of refractory GERD, especially if the BMI remains above 35 kg/m^2. Ultimately, additional investigative efforts are most needed before a comprehensive evidence-based strategy for the management of refractory GERD after metabolic surgery can be put forth.

Questions

1. What is the gold standard procedure for GERD after Sleeve gastrectomy?
   A. Duodenal switch
   B. Single Anastomosis Duodeno-ileostomy
   C. RYGB

Answer: C. RYGB.

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Part VIII

Specific Considerations

Health Advocacy

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V. Raman Muthusamy and Sushrut Sujan Thiruvengadam

Introduction

Health advocacy is defined as activities related to ensuring timely access to modern evidence-based care, addressing health inequities, influencing health policy, and creating fundamental system changes [1]. Physicians have a unique role to play as health advocates. One important distinction for physicians to make is health promotion versus health advocacy. Health promotion refers to changing patient behaviors to reduce disease [1]. One common example is a physician encouraging his/her patients to quit smoking to prevent lung cancer and emphysema. Health advocacy, on the other hand, involves addressing the role of systems and social determinants of health in patient outcomes [1]. The goal of health advocacy is not to change patient behaviors but to change the systems which play a key role in their health [1].

Health advocacy can be further subclassified as shared or directed advocacy. Shared health advocacy refers to physicians advocating together with an individual, group, community, or population [1]. In this scenario, the physician works with others to advocate for health systems change. With directed advocacy, the physician uses his/her expertise and understanding of the health needs of the patient population in order to advocate for appropriate health system changes [1]. In this way, the physician is working to directly implement change based on an understanding of his/her patients' challenges.

In this chapter, we will also classify health advocacy efforts by physicians as either legislative or payer advocacy. With legislative advocacy, the physician advocates for legislative change to improve access for care and to address health inequities. With payer advocacy, the physician advocates for changes in the payment model to determine fairer reimbursement for existing services or establishing coverage for newer diagnostic tests and treatments provided by physicians. We will discuss the different ways gastroenterologists and general surgeons can be involved in legislative and payer advocacy, with specific focus on the role of local and national societies. We will highlight several examples of successful advocacy and ongoing efforts. Finally, we will discuss how individual physicians can become involved in health advocacy and be effective advocates for their patients.

Legislative Advocacy

For gastroenterologists and general surgeons, legislative advocacy can require changes at the national level. Often, this is best accomplished by national societies, who commonly pursue legislative advocacy in one of two ways.

First, societies can support individual politicians who share common interests. For example, national gastroenterology societies have political action committees (PAC) specifically dedicated to gastroenterology [2]. The stated goal of these PACs is to support legislators who protect the needs of patients with digestive health issues and the healthcare professionals who treat these conditions [2]. Similarly, surgical societies have developed a political action committee to "ensure surgical advocacy remains a top priority in Washington, DC and across the country" [3].

National societies can also play a more direct role by supporting specific legislation. One example of gastroenterology societies pursuing legislative advocacy was in reversing an important loophole in colorectal cancer screening known as the "post-polypectomy surprise." While the 2010 Affordable Care Act waived cost-sharing for screening colonoscopy, there was an important exception. If, during the colonoscopy, a polyp was removed, the procedure would be converted from "screening" to "therapeutic," and cost-sharing would no longer be valid [4]. This resulted in many unexpected bills, which were commonly referred to as the "post-polypectomy surprise" [4]. Furthermore, this shifting

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of cost burden to patients was counterintuitive as the goal of screening colonoscopy is to find and remove polyps and thus prevent future colon cancer. To address this situation, the Centers of Medicare and Medicaid Services (CMS) proposed that physicians notify patients of the cost-sharing implications prior to the colonoscopy [5]. Major national gastroenterology societies voiced joint criticism of this proposal as this did not address the actual loophole [5]. To address this problem, a coalition of national GI organizations advocated for the Removing Barriers to Colorectal Cancer Screening Act. This bill eliminated coinsurance requirement with regard to colorectal cancer screening tests regardless of the code billed for a resulting diagnosis or procedure (such as polypectomy) [6]. This bill was passed in December 2020 as part of the COVID relief package and will be implemented over the next 8 years [6]. Through well-organized advocacy efforts on the part of physicians in national societies, legislation was passed to close this loophole which placed unfair cost burdens on patients seeking colorectal cancer screening.

Other similar legislative efforts by national societies are ongoing. For instance, one priority for national gastroenterology and surgical societies is to change how the congressional budget office "scores" budget effects of preventative care. Currently, the CBO scores legislation based on cost and cost-savings within a 10-year period [7]. However, interventions such as screening colonoscopy and bariatric surgery have benefits that are often seen after 10 years. Therefore, there is a concern that CBO scoring underestimates the true cost-saving potentials of these preventative measures and therefore affects relevant legislation [7]. To address this, national gastroenterology [7] and bariatric surgery [8] societies have together advocated for the Preventive Savings Act. This allows the CBO to determine if legislation would reduce spending outside the 10-year window through preventative health care [9]. This improved CBO score would make key legislation important to the long-term interests of patients easier to pass. This bill was introduced in 2017 but has not yet been passed [9]. Advocacy efforts to address this significant issue are ongoing.

At the state and local level, regional societies also play an important role in physician advocacy. One of the best examples of an effective state medical society is the Ohio Gastroenterology Society (OGS). The OGS began in 2009 as a private society but in 2013 merged with the Ohio State Medical Associations (OSMA) [10]. The OGS advocates for clear legislative goals at the state level. One example is reforming non-medical switching. This refers to a practice in Ohio where insurers can force patients to switch to a less expensive treatment in the middle of a plan year for no medical reason which disrupts the physician's and patient's medical plans [11]. The OGS has come out in support of House Bill 153 which would prohibit insurers in Ohio from engaging in non-medical switching [12]. The OGS is currently planning on meeting with legislators to discuss this and other legislation during their annual Virtual Legislative Day [11].

Through such efforts, both at the national and state levels, gastroenterologists and surgeons can help effectively advocate for their patients through important legislation.

Payer Advocacy

Beyond advocating for legislative changes which improve patient access to care, physicians can also play a key role in ensuring fair reimbursement for services provided. This payer advocacy usually focuses around Medicare reimbursement, as most commercial payers tie their fee schedule to the Medicare Physician Fee Schedule (MPFS) [13].

Payer advocacy sometimes requires direct advocacy with Medicare. One example of this is advocating for certain Merit-Based Incentive Payment System (MIPS). MIPS is an important determinant of Medicare payment adjustments. In 2019, Medicare released a proposed 2020 MPFS which planned to remove certain MIPS relevant to GI, including incentives for adenoma detection rates [5]. National gastroenterology societies submitted joint comment letters opposing the removal of these MIPS as there were no adequate incentives to replace these measures [5]. In this way, gastroenterologists have ensured that appropriate markers of performance influence Medicare reimbursement.

In some cases, national societies respond directly to the MPFS. For instance, in December 2020, surgical societies voiced their disapproval over the proposed 2021 MPFS which cut Medicare payments up to 9% for some surgical subspecialties [14]. These societies argued that these cuts would affect patient care by forcing doctors to reduce Medicare patient intake, laying off administrative staff and not investing in new technology [14]. In response, surgical societies advocated for the Holding Providers Harmless From Medicare Cuts During COVID-19 Act of 2020, which would prevent Medicare payment cuts from taking place [15]. This bill was introduced, but no action has been taken at the time of the drafting of this chapter [15].

Another way physicians can advocate for appropriate reimbursement is through participation in the AMA/Specialty Society Relative Value Scale Update Committee (RUC) [13]. At this time, payment for physicians is mainly fee for service. Each procedure is given a Relative Value Unit (RVU) which depends on physician work, practice expense, and professional liability [13]. In 1991, the AMA formed the RUC as an expert panel developing recommendations to CMS regarding appropriate RVU/reimbursement rates for each procedure or service. The RUC is an important committee as the CMS generally accepts about 90% of recommendations made by the RUC [13].

In order to make recommendations, advisory committee members in the RUC work with other members of their specialty to generate recommendations using a survey method. The RUC survey collects information on how practicing physicians view a specific service relative to other services. Using results from this survey, value updates are proposed by specialty societies within the RUC, and the majority of these updates are approved by the RUC [13].

The RUC is extremely important to gastroenterologists and surgeons. As part of the ACA, physician services that are misvalued require constant re-evaluation. This involves over 100 endoscopic procedures. In order to determine adequate representation in this process, national gastroenterology societies nominated a member gastroenterologist to the AMA RUC panel which met in April 2021 [16]. National gastroenterology and surgical societies also encourage physicians in their respective specialties to participate in RUC surveys and thus give a realistic view of procedures and operations performed. This in turn allows for fair reimbursement for services provided.

Beyond advocating for specific legislation, developing guidelines, and making recommendations within the RUC, national societies can also present relevant evidence to payers to help reform or expand coverage via several other methods. These include setting up meetings and conferences that address new technologies and provide updates on the existing evidence surrounding these advancements. These meetings can include payers and regulators and can therefore serve to address the concerns these parties have regarding coverage of new diagnostic tests and therapies. National societies can also directly have leadership, or society members make presentations during payer evidence review boards. Finally, gastroenterology and surgical societies can create registries of patients who underwent procedures or operations using new technologies. Data from these registries can help show real-world outcomes and effectiveness which may help spur more widespread coverage and appropriate reimbursement. In this way, gastroenterologists and surgeons can provide robust evidence directly to payers and regulators showing the potential benefits of expanding coverage for new technologies.

Physicians as Effective Advocates

Regardless of whether a physician is pursuing legislative or payer advocacy or whether these efforts are done at the national or state level, certain principles are important for effective advocacy. These mainly center around how a physician can conduct effective legislative visits.

The first step to effective advocacy when visiting state or national legislature is preparation. It is important to fact-check the topics prior to contacting elected officials. The proposed bill in question should be read with clear reasons for the physician's support or opposition discussed or written down. Furthermore, research should be done on the legislator whose office is being visited, and it is important to understand how this person voted on prior similar bills. Importantly, political party affiliation should not stand in the way of communicating with a legislator when considering bills of interest [17]. Furthermore, the physician advocate must be prepared to come up with alterations to a proposed bill to potentially correct problems. Simply asking a legislator to vote or not vote for a bill will be inadequate, and preparation should be made to have a deep discussion about the relevant issues and to aim for an ongoing collaboration with the legislator and their staff.

The next step in a legislative visit is the initial contact with the legislator. It is often most useful to employ a personalized approach with a phone call or an email to the office [17]. For many physicians in a busy practice, it may be difficult to find the time to craft such a message. Fortunately, national gastroenterology [18] and surgical [19] societies have online tools where a physician can enter basic information, and a templated email to send to the appropriate legislator (based on entered zip code) can be generated in a process that takes less than 5 minutes. When contacting a representative or senator, it is important that the physician gives background information, including general information about the physician and his/her specialty. Many legislators may not know the specifics of what a gastroenterologist or surgeon does on a daily basis, so a simple overview of this is useful. When making an appointment, it is often useful to interact with the office scheduler or legislative staff in charge of healthcare legislation. In general, in-person meetings are the best way to connect personally with legislators.

Once a meeting is arranged, either in-person or virtually, the actual message delivered is the most important part of effective advocacy. The message to the legislator should resemble an "elevator speech" where the physician advocate is able to convince the legislator in 2 min that their issue is important. After this, the physician must succinctly discuss the important points in 15–20 min. Simple handouts can be drafted to help with this. It is important not to "overstack" the agenda and to instead keep the conversation centered around a few simple, but important points. It is also useful to keep the discussion patient-centered with use of local patient stories and narratives to explain complex situations of coverage denial or lack of access to care. Even when discussing topics like reimbursement, it is essential to discuss how decreased reimbursement may result in loss of services to patients and an overall negative impact on the health system. The conversation should not focus on how reimbursement affects the physician's bottom line except as to describe how practices may adapt to such reimbursement changes and how those changes could adversely impact access to or the quality of care delivered.

Personal examples from physicians can also be very useful. Statistics should be given, but it is important to end with a compelling argument relating back to patient care.

Finally, after a legislative meeting, it is important to forge a working relationship for future advocacy efforts. After the meeting, thanking the representative or senator by email or handwritten note is important and keeps the lines of communication open. It is important for a physician advocate to make themselves available to the legislator for future questions. It is also a good idea to offer to have the legislator visit a physician's practice. This allows for the opportunity for the legislator to experience and better understand the everyday challenges physicians and their patients face and how appropriate legislation can make a difference. Finally, as time passes, intermittently emailing the legislator's office to check in on ongoing legislative efforts is useful to maintaining a productive relationship moving forward.

Conclusion

For gastroenterologists and surgeons, health advocacy is becoming increasingly important. While physicians recommend interventions to patients on a daily basis to improve their health and well-being, correcting larger systemic issues which affect patient care through health advocacy requires a different set of skills. In order to address gaps in access to care and health inequities, effective legislative advocacy at both the state and national level is important. Historically, national or state societies have been useful in helping organize these legislative efforts. In order to determine fair physician reimbursement, thus ensuring a high standard of care for patients, effective payer advocacy is also needed, with both legislation, appropriate recommendations from the RUC, and direct advocacy efforts with payers and regulators. For both legislative and payer advocacy, it is important for physicians to advocate in the "front lines" whether it be in Washington, DC, in various state capitals, or locally. These legislative visits require adequate preparation; appropriate initial contact with elected officials; a succinct, powerful message; and an ongoing strong relationship after the visit. In this way, gastroenterologists and surgeons can ensure that the needs of their patients are heard and addressed, not only in the clinic, endoscopy suite, and operating room but also in the offices of state and local legislators, regulators, health plan administrators, and even in the halls of Congress.

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Robotic Foregut Surgery

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Tanuja Damani, Caitlin Houghton, and Ryan C. Broderick

Since the introduction of the robotic platform in 2000, there has been wide adoption with a significant increase in both the variety and the volume of cases performed robotically. Robotic surgery has significant advantages in a narrow interior field with the benefits of stable camera platform, added length and wristed movements of the instruments, three-dimensional magnification, motion scaling, and tremor filtration. These features facilitate better visualization, greater access to superior portions of the mediastinum from the abdomen, as well as meticulous and circumferential dissection of the esophagus in the mediastinum, which is one of the most inaccessible compartments of the human body. Robotic compared to laparoscopic foregut surgery has been demonstrated to be associated with increased costs. However, with advances in the learning curve, decreased operative times, decreased conversion rates in redo foregut surgery, decreased rate of esophageal lengthening procedures, and potentially shorter LOS, some of these costs may be offset. Robotics also has a potential disadvantage of a lack of haptic feedback which may lead to inadvertent injury to surrounding organs or tissues, especially early in the learning curve.

This chapter describes robotic approaches to benign esophageal conditions including achalasia, gastroesophageal reflux disease, hiatal and paraesophageal hernias, as well as revisional surgery for these conditions.

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Robotic Heller Myotomy

Introduction

Achalasia is a rare esophageal motility disorder characterized by failure of lower esophageal sphincter relaxation and an absence of distal esophageal peristalsis. It is caused by destruction of the ganglion cells of Auerbach myenteric plexus and is a slowly progressive disease with a primary symptom of dysphagia. Additional symptoms may include regurgitation, chest pain, heartburn, weight loss, aspiration, chronic cough, and recurrent pneumonia. A thorough diagnostic evaluation for achalasia includes upper endoscopy, timed barium esophagram, and high-resolution manometry. Recently functional lumen imaging probe (FL IP) has shown promise in the work-up of esophageal motility disorders. Current durable treatment options include pneumatic dilation, Heller myotomy, and per oral endoscopic myotomy (POEM). Both POEM and Heller myotomy have been described to be equally efficacious at relief of dysphagia for type I and II achalasia. Generally a partial anterior or posterior fundoplication is performed with a Heller myotomy to avoid postoperative reflux. Longer-term studies are needed to assess incidence of postoperative reflux after a POEM. POEM is the preferred approach for spastic or type III achalasia due to the ability to perform a longer myotomy.

Robotic Heller Myotomy

Robotic Heller myotomy was first reported by Melvin and colleagues in 2001. Since then multiple studies in the literature have confirmed the safety and efficacy of a robotic Heller myotomy, with comparable relief of dysphagia, estimated blood loss, conversion to open surgery, and operative times. The robotic approach has been shown to be associated with a statistically significant lower rate of intraoperative esophageal perforations. Esophageal mucosal injury with

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laparoscopic myotomy in most studies has been reported to vary between 5% and 15%. More than a dozen studies have shown a significantly lower incidence, close to zero, of esophageal perforation with robotic approach, attributed generally to high definition, three-dimensional stereoptic visualization, tremor filtration, and motion scaling provided by the robotic platform allowing meticulous visualization and division of each muscle fiber, in addition to comfortable surgeon ergonomics.

Surgical Technique

Patients are placed on a liquid diet for 2 days before the surgery to prevent aspiration during induction from any retained food in the esophagus. A rapid sequence intubation is performed, and the patient is position in a 30° reverse Trendelenburg position with arms tucked.

The port placement using daVinci Xi is shown in Fig. 62.1. The left lateral segment of the liver can be elevated using a "Dima" hammock stitch or a subxiphoid Nathanson liver retractor. The first step involves division of the gastrohepatic ligament to expose the right crus of the diaphragm. The dissection between the right crus and the esophagus is performed and taken over anteriorly to the left crus. Anterior mediastinal dissection is performed to expose anterior esophagus about 8 cm proximally. Short gastric vessels are divided using the vessel sealer if the plan is for a concurrent fundoplication. If a partial posterior fundoplication is planned, the retroesophageal dissection is completed. The anterior vagus nerve is clearly identified, and the gastroesophageal junction (GEJ) fat pad removed to clearly expose the GEJ. The myotomy is begun just above the gastroesophageal junction, usually between 11:00 and 1:00 anteriorly. It is very important to maintain caudad and lateral traction on the esophagus during the myotomy. The longitudinal and circular muscle fibers are divided using the hook electrocautery, with bulging of the esophageal submucosa noted. The myotomy is extended proximally to about 6 cm and then continued retrograde toward the GEJ and onto the cardia of the stomach. The oblique sling fibers of the cardia are clearly identified, and these are divided for another 2–3 cm onto the cardia.

A completion upper endoscopy is performed to make sure that the lower esophageal sphincter is wide open and patulous on completion of the myotomy as well as to confirm that there is no inadvertent full-thickness perforation. An intraoperative FLIP can be performed both before and after the myotomy to ensure adequate improvement in distensibility index. Partial anterior or posterior fundoplication is then performed. The authors' preference is for a Toupet fundoplication, which tends to separate the edges of the myotomy, preventing delayed refibrosis. With a robotic approach, the concern for an inadvertent esophageal perforation or micro-

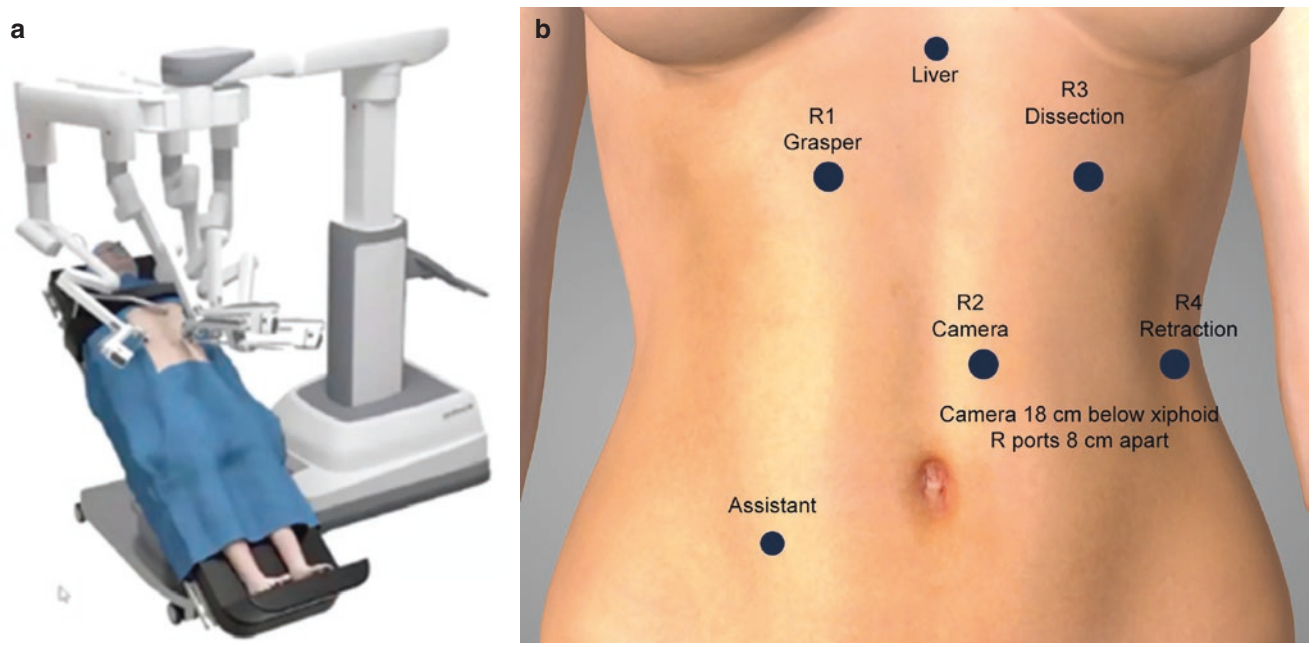

Fig. 62.1 (**a**) Patient positioning. (**b**) Trocar positioning

perforation is very low, which is often the reason to consider an anterior fundoplication to cover the area of the myotomy. The fundoplication can be anchored to the left and the right crura or posteriorly to the hiatus.

Robotic Antireflux Surgery

Introduction

Gastroesophageal reflux disease (GERD) is defined as reflux of gastric contents into the esophagus causing troublesome symptoms and/or complications. Pathophysiology of GERD is secondary to the breakdown of the antireflux barrier made of the lower esophageal sphincter, the crural diaphragm, and the anatomic flap valve. Typical symptoms of GERD include heartburn, dysphagia, and regurgitation, while the atypical symptoms can include cough, respiratory symptoms, chest pain, globus, throat clearing, and hoarseness. A comprehensive diagnostic evaluation is needed to assess candidacy for antireflux procedure as well as the type of procedure. It includes an upper endoscopy, barium esophagram, pH testing with or without impedance, high-resolution manometry, and gastric emptying study if indicated based on symptoms of early satiety, bloating, or vomiting.

Surgical options for primary antireflux procedures include Toupet (posterior 270°) or Nissen (total 360°) fundoplication or magnetic sphincter augmentation/LINX placement. Both procedures entail a hiatal hernia repair/cruroplasty, which contributes significantly to restoration of reflux barrier. Recent literature has shown Toupet and Nissen fundoplications to have comparable 5-year objective (pH testing) and subjective (symptom questionnaires) relief of GERD with Toupet fundoplication having a lower side effect profile.

Robotic Fundoplication

While robotic antireflux surgery has been shown to be safe and feasible, the proven additive value for the use of this technology for primary fundoplication is controversial due to costs with no difference in outcomes or length of stay. Several randomized control trials have reported significantly longer operative times for robotic fundoplication with no significant difference in postoperative outcomes, reflux control, complication rates, hospital stay, and conversion or reoperation rates. However it has been well shown that as the familiarity with the robotic surgery platform increases and surgeons get past the learning curve, the operating time will decrease as has been shown in many other procedures. The total operation costs are also likely to decrease with more robotic platforms entering the market leading to decreased cost of the system, maintenance, as well as instrumentation.

Surgical Technique for Robotic Fundoplication

The port placement for robotic fundoplication is similar to that for robotic Heller myotomy (Fig. 62.1). Dissection is begun by opening the pars flaccida and identifying the right crus. If a sliding hiatal hernia is present, it is reduced, and dissection is begun between the right crus and hernia. This is taken around the arch of the crus to the left crus. This dissection is carried in the mediastinum anteriorly and laterally, taking care to avoid violation of the pleura. A retroesophageal window is made with placement of an umbilical tape or Penrose drain to provide traction of the lower esophagus. With caudad traction on the tape, mediastinal dissection of the esophagus can be performed to obtain 3–3.5 cm of intraabdominal esophagus without tension. The anterior and posterior vagus nerves are clearly identified and preserved. It is easy to overestimate the length of intraabdominal esophagus due to the pneumoperitoneum pushing the diaphragm up, caudad traction on the esophagus, and robotic magnification. It is important to ensure 3–3.5 cm from the left crus to the angle of His to prevent axial traction from a short esophagus causing a recurrent hernia.

Short gastric arteries are divided using the vessel sealer, and posterior attachments of the superior fundus taken down to allow a tension-free fundoplication. Hiatal closure is then performed with non-absorbable sutures. The choice of running versus interrupted versus mattress sutures is left to surgeon's discretion. It is important to decrease pneumoperitoneum pressures to allow tension-free hiatal closure if there is wide radial separation of the crura. If a tension-free closure cannot be achieved or the crural pillars seem thin, attenuated, or deperitonealized, a synthetic biodegradable mesh reinforcement of the hiatus using Bio-A or phasix ST can be performed. Whether mesh decreases short- and long-term recurrence of hiatal hernia continues to be controversial. It is important to be mindful of the robotic magnification so the hiatal closure is not made too tight. A 50–60 French bougie can be used for calibration. Intraoperative FLIP measurements have also been shown to be helpful for calibration during hiatal closure.

A Toupet or Nissen fundoplication is performed by passing the upper greater curvature of the fundus behind the esophagus. A shoeshine maneuver is performed to confirm sufficient gastric mobility for a tension-free wrap as well as to avoid posterior redundancy of the fundus. For a total/Nissen fundoplication, a 50–60 French bougie can be used for calibration. It is important to keep the fundoplication short about 2 cm, symmetric, floppy, and situated entirely on the distal esophagus above the GE junction. A tight of excessively long fundoplication will cause dysphagia and other functional problems. An incorrectly positioned wrap will not sufficiently prevent pathologic reflux. An asymmetric wrap with long sling formation will create dysphagia, early satiety, or gas bloat. The wrap is then anchored to the crura either as

collar stitches to the left or right crura or posteriorly to the hiatal closure to prevent acute transthoracic herniation of the fundoplication. A completion endoscopy can be performed to ensure that the hiatal closure is not too tight and there is no angulation of the esophagus and to assess the adequacy of the wrap and Hill grade valve on retroflexion.

Robotic Paraesophageal Hernia

Introduction

Hiatal hernias are a common finding especially in the aging population. Some figures report 50% of the population will develop a hiatal hernia by the age of 60. Hiatal hernias are classified into four types. A sliding hiatal hernia that displaces the GEJ upward accounts for 95% of all hiatal hernias. Types II–IV are considered paraesophageal hernias. Type II hernias have GEJ in the normal position with fundus herniating into the chest. Type III hernias have a displaced GEJ and fundus residing above the diaphragm, and type IV hiatal hernias have adjacent organs also herniating into the chest such as small bowel or spleen. Ninety percent of paraesophageal hernias are type III morphology.

Patients with paraesophageal hernias are often symptomatic presenting with either typical GERD symptoms of regurgitation or dysphagia; other symptoms include atypical chest pain, exertional dyspnea, or fatigue from anemia from Cameron's ulcers. In rare cases, these patients present emergently with ischemia, obstruction, or volvulus. Others are asymptomatic and found incidentally. In the past incidental hernias were often left alone, but now, with minimally invasive techniques having excellent perioperative outcomes and shorter length of stays, even asymptomatic hernias are often repaired in patients to avoid future complications.

Robotic Paraesophageal Hernia Repair

Similar to robotic fundoplications, robotic paraesophageal hernia repairs are safe and feasible, but the literature has not shown a clear benefit. The benefits often reported by frequent users of the robotic platform include better delineation of the natural tissue planes to aid in reduction of the sac and mobilization of the esophagus. This, paired with enhanced optics and a stable camera high in the mediastinum, makes complete reduction of the hernia sac and its contents less strenuous. Several single institution studies show a decreased recurrence rate for experienced users after robotic reduction and repair, while other studies show no benefit and potentially increased complication rates, especially early in the learning curve. Although the benefit has not been clearly shown to date, 40% of all paraesophageal hernias performed are done robotically.

Pre-operative work-up for paraesophageal hernias should entail an upper endoscopy and an esophagram. High-resolution manometry is often inaccurate due to distorted anatomy with an intrathoracic LES and EGJ outflow obstruction noted from extrinsic compression of the esophagus from the herniated stomach, presenting as dysphagia. There is also real indication for pH testing since the repair is performed due to the paraesophageal herniation and not primary GERD.

Surgical Technique for Robotic Paraesophageal Hernia Repair

The trocar placement for robotic paraesophageal hernia repair is similar to previously mentioned foregut procedures (Fig. 62.1). The patient is placed in steep reverse Trendelenburg (30°) and the robot is docked. Authors prefer a no touch technique to start the case. This means that the stomach and herniated contents are not attempted to be reduced prior to starting dissection. The dissection starts similarly to the fundoplication at the pars flaccida of the gastrohepatic ligament. The ligament is then divided to reveal the edge of the right crus. One caveat is that the left gastric vessels are often pulled up into the mediastinum and must be identified and preserved. The right crus is then scored down to the muscle fibers, and the peritoneal covering of the crura is opened along the length of the right crus. This ensures the dissection is started outside the hernia sac and will aid in reduction. With tension on the hernia sac, blunt dissection is used to find the avascular plane between the hernia sac and the mediastinal structures. This avascular plane can then be utilized to reduce the hernia sac anteriorly. Care must be taken to preserve the pleura to avoid billowing and distorted visualization. If there is pleural violation, decreasing pneumoperitoneum pressures is helpful. To prevent the tension physiology, the pleural opening can be extended; the resulting capnothorax can also help with decreasing tension during crural closure by causing a flaccid diaphragm. The anterior vagus nerve is identified and preserved prior to dividing tissue anteriorly. The dissection continues to the left crus. The peritoneal covering is then scored down to the muscle fibers and opened along the left crus. Continued dissection of the avascular planes will lead to reduction of the hernia sac and its contents. Anteriorly, once the hernia sac is reduced, the esophagus will come into view. The GEJ is most often found in the mediastinum, and therefore the posterior window may be made in the mediastinum so the penrose will encircle the esophagus and not herniated contents.

Circumferential mobilization of the esophagus is then pursued. Turning the camera 30° up can aid in the posterior

dissection of the esophagus. The anterior and posterior vagus nerves are identified and preserved during this dissection whenever possible. In some cases, the anterior vagus nerve may need to be mobilized or divided in order to achieve adequate intraabdominal esophageal length. Dissection is often continued to the level of the inferior pulmonary veins to achieve 3 cm of intraabdominal esophageal length. Collis gastroplasty is uncommon among surgeons using the robotic platform due to the increased ability to mobilize high in the mediastinum but may be considered if adequate length is not achieved. Once the hernia is reduced, the crura is closed. It is up to surgeon's discretion to use a running 2-0 non-absorbable barbed suture or interrupted 2-0 Ethibond stitches. With signifiacnt radial separation or attenuated crura, the barbed suture can potentially cut through the muscle. The crural closure starts posteriorly. In patients with widely displaced crura, lateral stitches may be required as well to effectively close the crura around the esophagus. The crural muscle should approximate but not impinge the esophagus in the resting position. An absorbable mesh may be placed in the posterior or reverse C position to reinforce the crural closure and sutured into place. Large hernia sacs often have to be resected off the esophagus prior to creating the fundoplication in paraesophageal hernia repair cases. A partial fundoplication (Toupet, Dor, Watson) can be performed per surgeon's discretion.

Robotic Revisional Foregut Surgery

Introduction

Failures of paraesophageal hernias are most frequently migration, disruption, or slippage of the wrap. Radiographic recurrence after paraesophageal hernia repair is quoted as high as 50%. Failure rates of laparoscopic antireflux surgery are between 5% and 15%, with the most frequent symptoms being recurrent heartburn/regurgitation and persistent or new-onset dysphagia. After a full diagnostic, objective reassessment (endoscopy, dynamic radiographic swallow, high-resolution manometry, pH testing, gastric emptying study), the patient can be considered for re-operation. Particularly complicated patients should be discussed in a multidisciplinary conference with a panel of foregut surgeons and gastroenterology/motility specialists.

Indications and Pre-operative Preparation for Re-operative Foregut Surgery

Insufficient diagnostic work-up can lead to an incorrect diagnosis and, as a consequence, to an incorrect indication for antireflux surgery, occurring still in 2–3% of cases. As a consequence, these patients may present with a second failure or third failure lacking any information about their primary functional status. While redo foregut surgery is often due to an anatomic problem or recurrence, motility issues and other causes of symptoms must be ruled out. Therefore, a full diagnostic evaluation is required to inform the indication for surgery, even if all tests were performed prior to the first foregut operation.

Often in a "hostile" re-operative surgical field, the anatomy of the hiatus becomes blurred. The modern minimally invasive surgeon has multiple tools to combat this. ICG can help delineate vascular structures. An intraoperative EGD can confirm the level of the GE junction and help guide the surgeon away from an incidental enterotomy. Adhesions can be significant and at times result in a frozen hiatus especially if permanent mesh had been used previously. Therefore, the surgical team must be prepared for any potential option during surgery. The expertise or team available for a potential thoracic approach is also necessary. It is important that redo surgery be performed in expert, high-volume foregut centers with the available resources.

Robotic approach in redo foregut surgery allows for enhanced 3D visualization and meticulous wristed dissection in the mediastinum and improved ergonomics which may contribute to lower conversion to open rates and improved functional outcomes. Many surgeons therefore value a robotic approach as highly desired especially in the redo foregut operation.

Surgical Technique of Redo Foregut Surgery

Adhesions in a re-operative hiatal dissection can be extensive, even more so in cases where non-absorbable mesh was used for crura reinforcement. With the intimate proximity of the vena cava, aorta, pericardium, pleura, and intraabdominal solid organs, a re-operative field can be highly technical and fraught with danger.

Redo foregut surgery is an area of advantage for the robotic approach. Ports are placed as described for primary foregut surgery (Fig. 62.1). Early in the operation, it is crucial to delineate planes of dissection to avoid injury and enterotomy. A bloody, non-delineated plane leads to inaccurate and potentially harmful dissection. The initial and most important step in redo surgery is the complete dissection of the hiatus to fully define the anatomy as if performing a primary foregut operation. Adhesions often occur between the anterior gastric wall and the left lobe of the liver, in addition to significant scarring of the hiatus. First, the left lobe of the liver is dissected from the stomach to begin establishing anatomic landmarks. Following the liver assists with finding the hiatal arch and subsequently the crura. Care is taken to preserve the gastric serosa as well as liver capsule, where pos-

sible. Once these landmarks are established, dissection can be directed to the lower mediastinum.

Crura dissection may be started on either the left or right, depending on intraoperative anatomy/adhesions. When dissecting the right side, the groove between the liver and the right crus contains the vena cava. The IVC may be covered by adhesions or appear to be the right crus, which is a dangerous site of dissection. Care is required to avoid catastrophic injury to the vena cava while completely dissecting the right crus for appropriate hiatal repair later. On the left side, the surgeon can take down the short gastric vessels and adhesions with an energy device. Special care is taken to avoid damaging the splenic vessels, spleen, and pancreas. The left crus must also be completely dissected for later crura approximation.

Next, mobilizing and takedown of the prior wrap can be performed. Wrap takedown can vary from thin adhesions separated with scissors versus difficult dissection and potential need for stapled separation and/or repair of unavoidable enterotomies to the fundus. Posterior fundus and hiatal dissection often have dense adhesions to prior sutures and/or mesh. Alternating between right- and left-sided dissection is often necessary until a retro-esophageal window can be created safely. Robotic wristed instruments provide an advantage along the posterior hiatus and into the lower mediastinum as there is limited space for instrument manipulation. The esophagus must be circumferentially mobilized in the lower mediastinum to allow for 3 cm of intraabdominal, tension-free esophagus. Shortened esophagus from prior scar or baseline patient anatomy may need to be dealt with by an esophageal lengthening procedure; however proximal dissection into the mediastinum can often provide adequate esophageal length; this is another advantage of robotic dissection as higher dissection in the superior mediastinum is more easily achieved. Permanent meshes at times have to be partially or completely removed, particularly in erosion or close approximation to posterior esophagus.

As with any foregut operation, extreme care must be taken to avoid any injury to the vagus nerves. The robot allows for fine dissection and improved visualization. Introducing a gastric motility disorder on top of redo foregut surgery can lead to devastating symptomatic consequences.

Once all anatomy is fully delineated, reconstruction can be completed. Posterior cruroplasty is performed with a permanent suture of choice, is sized with a bougie in place, and is often reinforced with absorbable mesh. A new fundoplication is then shaped, again using a bougie for calibration. Careful attention is required to create an ideal fundoplication and potential identification of why the previous one failed. The wrap must be shaped with a symmetric wrap positioned appropriately at the LES.

The above principles of dissection and reconstruction can be applied for most redo foregut surgery whether it be esophageal myotomy, bariatric surgery, or hernia/antireflux surgery. Whether a foregut surgeon is consulted for conversion from a Nissen to Toupet fundoplication, the recurrence of a paraesophageal hernia, or a conversion of sleeve to gastric bypass, a robotic approach is an invaluable tool in these re-operative fields.

Outcomes

With every successive redo foregut surgery, the likelihood of a satisfactory functional result decreases, and the likelihood of major resection increases. As indicated above, re-operative foregut surgery is technically more demanding. The robot allows for meticulous dissection and restoration of primary anatomy in most cases. Compared to laparoscopic approach, the robot has shown decreased conversion to open surgery, decreased vagal injuries, and lower post-op complications. The robot has also shown advantage in regard to shorter hospital stay, lower readmission rates, and improved functional outcomes/symptom resolution. There are reports of similar functional outcomes of robotic redo-PEH to primary PEH repair despite recurrent operations historically being associated with worse outcomes. It is also significant to note that robotic PEH is safe, feasible, and with significant reduction in need for esophageal lengthening procedures. Recurrence rates are low despite significant proportion (30%) of revision cases in some robotic cohorts.

Conclusion

Robotic-assisted esophageal surgery allows improved visualization, dexterity, and precision, which are especially beneficial in a narrow mediastinal space, in addition to comfortable surgeon ergonomics leading to less mental and physical fatigue, advantages that are amplified in complex/revisional cases.

A growing number of studies have shown benefits of robotic surgery in Heller myotomy with regard to decreased esophageal perforation rates and in complex re-operative foregut surgery with respect to decreased conversion rates, lower readmission rates, and improved functional outcomes. However it has been demonstrated to be associated with increased costs. With advances in the learning curve leading to decreased operative times, decrease conversion rates for re-operative surgery, decreased need for esophageal lengthening procedures, and shorter length of stays, some of these costs may be offset. Further studies are needed to demonstrate learning curves, assess cost-effectiveness, and evaluate clinical benefit.

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