Kevin M. Reavis
Editor

Per Oral Endoscopic Myotomy (POEM)

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Introduction by Haruhiro Inoue MD, PhD

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Preface

Evolution in the surgical approach to esophageal disease has occurred with enthusiastic acceleration over the past few decades. How we address achalasia and other related esophageal motility disorders in terms of myotomy has transformed from open transthoracic or transabdominal approaches to thoracoscopic and laparoscopic approaches on to an endoscopic approach devoid of external incisions and with minimal post procedural convalescence. Peroral endoscopic myotomy (POEM) is the first widespread clinically accepted application of Natural Orifice Translumenal Endoscopic Surgery (NOTES) for the treatment of esophageal disease. This now serves as a bellwether for the evolution of surgical innovation in the gastrointestinal tract. Following its emergence from endoscopic submucosal dissection techniques and initial clinical description in 2008 to the tens of thousands of patients who have benefitted from POEM over the past several years, the procedure has received plenty of praise and criticism via hundreds of peer-reviewed publications. POEM has been discussed in numerous surgical textbook chapters and now deserves a comprehensive assessment of its origin, clinical evolution, and current clinical and future applications.

The concept of *Peroral Endoscopic Myotomy: POEM* as a reference text emerged following several panel discussions in 2014 at which time the technique was just gaining a foothold of acceptance outside of select esophageal surgical programs. I am truly excited to have gathered several of the brightest pioneering minds as well as rising stars in the field of surgical endoscopy and interventional gastroenterology who have graciously contributed their very personal insights, investigations, and experiences with POEM to this text. This reference provides the background and evolution of POEM as well as current outcomes along with recommendations for initiating a clinical program and a glimpse into the future of what is yet to come for students, physicians, and affiliate staff who have a passion for the treatment of esophageal diseases.

I would like to thank the contributing authors for their selfless dedication and Springer publishing for helping to make this text a reality. I hope that the knowledge shared here inspires the next generation to dream big and advance our surgical treatment of gastrointestinal disease.

Portland, OR — Kevin M. Reavis, M.D., F.A.C.S.

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1 Introduction: Endoscopic Submucosal Dissection to Per Oral Endoscopic Myotomy (POEM)

Kevin L. Grimes and Haruhiro Inoue

Introduction

The development of Per Oral Endoscopic Myotomy (POEM) for esophageal achalasia is, in large part, the result of large-population screening for GI malignancy. While screening for colorectal cancer in average-risk patients over the age of 50 is well-accepted in America, there is no equivalent screening protocol to address esophageal or gastric cancer. In Japan, on the other hand, the rates of both gastric adenocarcinoma and squamous carcinoma of the esophagus are much higher than those observed in Western countries. As a result, screening upper endoscopy is not only more widespread, but also more sophisticated, involving adjuncts such as chromoendoscopy, narrow band imaging, magnification endoscopy, and more recently endocytoscopy. A large number of lesions are detected (the National Cancer Center in Tokyo alone treats more than 10,000 gastric lesions per year) and some form of resection is recommended for the vast majority. This is partly the result of differences in the pathologic interpretation between Japanese and Western pathologists (a lesion with "high grade dysplasia" or "carcinoma in situ" in the West may be considered "cancer" in Japan). Based on the observation that early lesions have a very low rate of lymph node metastasis, local resection is often preferable to surgery and a number of endoscopic techniques have evolved for this purpose.

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This chapter will trace the development of the POEM procedure from its roots in the endoscopic resection of esophageal and gastric lesions. We will follow the progression of the technical components, from simple colorectal polypectomy to *en bloc* resection of "strips" of tissue, and finally to dissection of the submucosal space and submucosal tunneling. We will also examine the evolution of the equipment necessary for the procedure, including the creation of distal caps and the development of specialized knives.

Endoscopic Mucosal Resection (EMR)

Strip Biopsy

In 1955, two years before the development of the fiberoptic endoscope, Rosenberg reported the "saline lift" technique, in which he injected saline into the submucosal space to increase the distance between the mucosa and the muscle layer, thereby reducing the risk of perforation during polypectomy in the rectum and distal colon [1, 2]. In Germany, Deyhle et al. developed a similar technique for the resection of sessile colon polyps in 1973, and they reported the first true *en bloc* EMR of a small gastric lesion using a wire snare in 1974 [3–5]. In Japan, Tada et al. also applied the saline lift to the resection of early gastric lesions. They utilized submucosal saline injection followed by resection of the mucosal bleb with a wire snare. Their technique was initially published in Japanese in 1984, and ultimately they published a large series in English in 1993 [6].

An alternate technique, dubbed the "lift and cut biopsy," was originally described by Martin et al. in 1976 [7]. Rather than pushing the mucosa away from the muscle layer with saline, they utilized a double-snare technique, using one snare to grasp and elevate the mucosa, and the other snare to resect the specimen. Takekoshi et al. applied this to early gastric cancer in Japan beginning in 1978 [8]. They used a grasper to elevate the mucosa and an electrocautery wire snare to resect the lesion. In their series of 308 lesions over 15 years, they noted that the size, depth, location, and differentiation of the lesion affected their ability to completely excise lesions. The rates of incomplete resection were as high as 57% for undifferentiated carcinomas, lesions larger than 1–2 cm, and lesions on the anterior or posterior wall. The technique was most useful for small, well-differentiated lesions on the lesser curve.

The original "strip biopsy" merged the "saline lift" with the "lift and cut biopsy," beginning with a submucosal saline injection, then elevating the mucosa with a grasper, and finally resecting the specimen with a wire snare.

Monma et al. and Makuuchi et al. applied the "strip biopsy" (injection, lifting, and snaring) to lesions of the esophagus and published reports in Japanese in 1990 [9, 10].

Band Ligation

Publications in Japanese by Masuda et al. in 1993 and in English by Chaves et al. in 1994 reported use of a variceal ligating device, similar to the technique of Van

Stiegmann, in which flat lesions were converted into "polyps" by grasping tissue and strangulating it at the base with a ligating band [11, 12]. The "polyp" could then be resected in the usual fashion with a wire electrocautery snare. The technique eventually became known as the "EMR-L." While beginning in the colon, EMR-L was applied to lesions of the esophagus by Fleischer et al. who published their series in 1996 [13].

Evolution of the Distal Cap

Inoue and Endo modified the "lift and cut biopsy," adding a transparent overtube to improve their ability to control and resect esophageal mucosa by grasping and snaring. In 1990, they reported a series of 11 cases, including resection of a small focus of adenocarcinoma in a short segment of Barrett's esophagus, and they found that it was possible to resect both large and near-circumferential segments of mucosa in piecemeal fashion, leaving the underlying muscle layer intact [14].

Makuuchi developed a special overtube, which he combined with submucosal saline injection, suction (rather than grasping), and snaring to resect larger fragments of esophageal mucosa than had previously been possible [15]. Kawano et al. modified the so-called "Makuuchi tube" to include a lateral window, which served as a mucosal trap [16]. The main limitation of the tube technique, however, was that it could only be applied to lesions of the esophagus.

To address the shortcomings of the transparent overtube, Inoue et al. developed a transparent plastic cap that attached to the distal tip of the endoscope in 1992 and published their initial series in 1993, calling their technique the "EMR-C" [17]. A refinement published by Inoue et al. in 1994 added a small ridge to allow for easy seating of the snare at the distal end of the cap [18]. The basic idea of grasping, strangulating, and resecting tissue was the same as with EMR-L, but the EMR-C procedure combined strangulation and resection into a single step. The technique was applied to a series of colonic lesions published by Tada et al. in 1996 and to resection of the duodenal ampulla by Izumi et al. in 1998 [19, 20]. In effect, the EMR cap served as a portable tube that traveled with the endoscope and allowed for the injection, suction, and snare technique to be applied to lesions anywhere in the gastrointestinal tract that could be reached with the endoscope.

Large-Volume Injection

The main complication associated with both the EMR-L and EMR-C techniques is involvement of the muscle layer within the resected specimen, causing full-thickness perforation. Anticipating this, early ex vivo pilot studies conducted in Japan involved resected surgical specimens, including human esophagus, stomach, and colon. EMR-C was performed at various locations and with various volumes of injected saline (ranging from 0 to 20 mL), while simultaneously examining the bowel wall under ultrasound guidance. The purpose at the time was to determine safety parameters regarding the size of the distal cap, volume of submucosal saline injection, strength of the suction, and ideal location within the bleb for placement of the wire snare; however, of particular interest is the finding that large-volume saline injection in the esophagus caused semi-circumferential submucosal dissection, creating a space of approximately 1 cm (the diameter of a standard gastroscope) between the mucosa and the muscle layer without any apparent disruption of the mucosa itself.

Endoscopic Submucosal Dissection (ESD)

From EMR to ESD

Beginning in 1982, Hirao et al. added a "pre-cutting" step to the original "strip biopsy." They began with submucosal injection with a solution of hypertonic saline and epinephrine, and followed this by cutting the mucosa circumferentially around the lesion using a needle knife. In doing this, the intended specimen retracts, effectively increasing the size of the lesion that can safely be resected with the cutting snare. They utilized the technique in 106 patients with lesions of the stomach ($n = 101$) and esophagus ($n = 5$) and published their series in 1988 [21]. The step of pre-cutting anticipated what would later become a critical step in ESD.

Hosokawa and Yoshida added a triangular plate protected by a ceramic tip to the end of a needle knife in 1995, developing the first insulated tip (IT) knife, which they published in Japanese in 1998. The following year, Gotoda et al. modified the "pre-cutting" technique of Hirao et al. using the IT knife rather than the needle knife to resect two rectosigmoid lesions [22]. They felt that the IT knife was easy to use and that the insulated tip minimized the risk of perforation. The upper limit of lesions that could be resected with pre-cutting and snaring, however, remained approximately 3 cm.

The group of Yamamoto et al. developed a technique that utilized submucosal injection and pre-cutting, but did not require use of a snare. They used an insulated, single-tooth forceps attached to electrocautery that could both grasp and cut tissue, along with a modified transparent cap that was flat at the distal end to maintain the orientation of the forceps. An added benefit of the cap was to maintain visualization during retraction and dissection of the tissue. In 1998, they resected a 4 cm flat lesion in the rectum by injecting, pre-cutting circumferentially, and dividing the submucosal fibers under direct vision; and in 2000, they presented the *en bloc* resection of a 6 cm gastric lesion at the ASGE meeting in San Diego, CA [23, 24]. Further modifications included use of a tapered cylindrical (rather than flat) hood and a needle knife to more precisely control the location and depth of the electrocautery. In 2002, the group published a series of 70 cases using this refined technique [25].

Evolution of Knives

In 2004, Rösch et al. reported their initial experience using the IT knife (rather than the needle knife) in 37 patients with admittedly poor results, but as this modified *en bloc* form of EMR (eventually renamed ESD) became more popular, the equipment and procedural techniques evolved quickly [26].

Oyama et al. published a series in 2005 with improved rates of *en bloc* resection using a "hook knife" (initially reported in Japanese in 2002), which consisted of a right-angle modification of the needle knife [27]. The knife could be rotated to the optimal direction and then used to hook and retract the tissue prior to cutting, resulting in improved precision and safety.

In 2004, Yahagi et al. reported (in Japanese) the use of a "flex knife." Created from a twisted snare and a flexible sheath, the knife was soft and flexible with a bumper on the end to easily control the depth of incision, reducing the risk of disruption of the muscle layer. In the same year, Inoue et al. reported (also in Japanese) an ESD using the triangle-tipped (TT) knife, which essentially removed the ceramic tip from the IT knife, exposing the multidirectional triangular tip.

As equipment continued to evolve, the "flush knife" was developed, combining a cutting needle tip with a water jet to reduce the number of instrument exchanges and aid in the development of the submucosal space. In 2007, Toyonaga et al. published (in Japanese) their initial experience using the flush knife for resection of gastric lesions.

Submucosal Tunneling

One of the technical challenges of ESD is control of the specimen as it is being dissected off the underlying muscle layer. The standard technique involves submucosal injection, followed by mucosal pre-cutting, and then division of the submucosal fibers; in the final step, the endoscopist must simultaneously retract the specimen to provide visualization, while at the same time developing the submucosal space to dissect and divide the fibers. As a possible solution to this difficulty, von Delius et al. reported "endoscopy of the submucosal space" in 2007 [28]. In a pig esophagus model, they essentially reversed the last two steps. They performed a submucosal injection and then entered the submucosal space through a mucosotomy, dividing the submucosal fibers and creating a tunnel under the lesion without any pre-cutting. Once the mucosa containing the lesion had been completely dissected off the underlying muscle layer, they completed the resection by "post-" cutting the mucosa. With this technique, they were able to demonstrate successful resection of lesions of various sizes, including complete *en bloc* circumferential donuts, which are particularly difficult (though still possible) using the standard ESD technique. Although submucosal tunneling was never widely adopted for ESD, it was a critical innovation for the development of the POEM procedure.

POEM

Experimental Endoscopic Myotomy

The first reported endoscopic esophageal myotomy actually predates the initial EMR techniques. In 1980, Ortega et al. reported the outcomes of six dogs followed by 17 patients who underwent an endoscopic myotomy procedure for achalasia in a hospital in Venezuela [29]. Based on their dog experiments, they determined an optimal depth of 3 mm for their hand-made wire needle knife, and then applied this to human patients, performing two blind 1 cm incisions through the mucosa just above the squamo-columnar junction. Surprisingly, they reported at least partial improvement in all patients, no cases of full-thickness perforation, and only a 17.6% (3/17) rate of procedural bleeding. Their procedure, of course, was not widely adopted, and the endoscopic options for the next three decades were limited to esophageal dilation or Botox injection.

In 2004, Kalloo et al. reported their experience with endoscopic transgastric peritoneoscopy (and liver biopsy) in a pig model, suggesting this as a possible alternative to laparoscopy [30]. This generated renewed interest in performing surgical procedures endoscopically and led to the development of a field known as natural orifice transluminal endoscopic surgery (NOTES). The bulk of research generated during the NOTES era involved the (now rarely performed) transgastric or transvaginal approaches to appendectomy or cholecystectomy. In September of 2007, however, Pasricha et al. published a refined version of the endoscopic myotomy for achalasia [31]. In four pigs, they performed a submucosal injection followed by mucosal incision and entered the submucosal space, developing a tunnel with a pneumatic balloon (rather than by directly dissecting the submucosal fibers as reported by von Delius earlier in the same year). Following this, they directly cut the circular muscle with a needle knife under direct vision, proceeding from distal to proximal and providing a significant improvement in safety when compared to Ortega's initial description.

Early Experience with Human POEM

The first human POEM was performed by Haruhiro Inoue in Yokohama, Japan, in September of 2008 [32]. The technique incorporated several important refinements to make Pasricha's porcine model suitable for clinical application.

Patients were anesthetized with a cuffed endotracheal tube to help protect against pulmonary aspiration, and positive pressure ventilation was applied to overcome any potential mediastinal or pleural pressures that might be generated by endoscopic insufflation. In addition, carbon dioxide rather than air insufflation was used based on theoretical concerns for the possible development of mediastinal emphysema or air embolization. In the initial series of 17 patients, postprocedure CT scans did reveal some small collections of mediastinal or pleural gas; however, these did not appear to be clinically significant. Of interest, one patient unexpectedly developed capnoperitoneum, which resulted in elevated peak pulmonary pressures; this resolved with simple needle decompression of the peritoneal space, but reinforced the importance of using CO_2 and limiting the volume of insufflation to the lowest level possible.

Initially, an oblique distal attachment, similar to one of the early EMR-C caps, was used to aid in visualization and to protect the mucosa from inadvertent thermal injury. In later iterations of the procedure, a straight, tapered ESD cap allowed more precise control during entry into the submucosal space. Following submucosal injection and longitudinal mucosal incision (horizontal incision resulted in an easier entry, but a much more difficult closure), the submucosal tunnel was created. In the porcine model, this was done with blind inflation of a pneumatic balloon; however, there is potential for misplacement of the balloon and inadvertent damage to the esophageal mucosa or blood vessels. In clinical practice, the submucosal fibers were divided under direct vision, similar to ESD or the submucosal endoscopy described by von Delius, providing more precise control and better hemostasis [28].

Division of the circular muscle layer also differed from the experimental model. While Pasricha et al. performed a retrograde myotomy with the needle knife, the first POEM cases were done in an anterograde direction with the TT knife, which was initially developed for ESD. In doing this, it was possible to dissect the circular muscle, layer by layer, to identify the intermuscular space, and then to use the TT knife to hook the circular muscle bundles away from the longitudinal fibers, maintaining direct vision and protecting the longitudinal layer for the entire length of the dissection.

In addition to the technical performance of the procedure, there were several open questions at the beginning of the clinical experience: which o'clock location to choose for the myotomy; whether to perform a selective (circular) or full-thickness (circular and longitudinal) myotomy; how to identify the esophagogastric junction (EGJ) from within the submucosal tunnel and ensure adequate gastric myotomy length; and the optimal length of the esophageal myotomy. Each of these remains an open question to some extent.

The initial o'clock location was chosen to mimic the surgical cardiomyotomy; that is, the anterior position. One of the main concerns was the inability to perform a concurrent anti-reflux procedure (such as a partial fundoplication in the case of a surgical myotomy). Care was therefore taken to avoid damage to the angle of His, which may form a natural anti-reflux barrier. At the 2 o'clock position, which endoscopically leads to the lesser curve of the stomach, the angle of His (located in the 8 o'clock position) is theoretically preserved. In two cases, a posterior (5 o'clock) myotomy was attempted, but this was found to be technically challenging due to the interference of the spine in maintaining accurate positioning of the endoscope tip. The 2 o'clock position was therefore chosen as the default location.

In regard to the thickness of the myotomy, all procedures were started with the intention of performing a selective (circular) myotomy in order to avoid damage to mediastinal structures. In doing this, the longitudinal muscle fibers were found to be thin enough to spread apart widely simply from the pressure of the endoscope, and postprocedure lower esophageal sphincter pressures decreased to the normal range without division of the longtitudinal fibers.

Several anatomic landmarks of the EGJ were noted during the first few cases: narrowing followed by widening of the submucosal space; pallisade vessels in the submucosal layer, which are located in the distal esophagus; and increased submucosal vasculature upon reaching the gastric space. Markers that were identified later include blue discoloration of the mucosa on retroflexed view of the gastric cardia and identification of a spindle vein in the submucosal space.

The total length of the endoscopic myotomy began with the length of its surgical counterpart. In the first seven cases, the mean total myotomy length was 4.9 cm. In the next ten cases, the myotomy was extended to a total length of 10.4 cm, resulting in better symptom relief and demonstrating one of the main advantages of POEM over the surgical myotomy: the ability to endoscopically perform an extended esophageal myotomy.

Summary and Future Trends

The first endoscopic myotomy for achalasia, performed in Venezuela in 1980, involved two cuts through the esophageal mucosa and into the circular muscle, with the blind hope of cutting only circular muscle fibers and avoiding a full-thickness esophageal perforation. Due to obvious safety concerns, the idea was abandoned. In subsequent years, several parallel advancements in equipment and endoscopic techniques provided the tools necessary for the first POEM procedure nearly 30 years later.

Beginning in the 1950s, submucosal saline injection was utilized to increase the distance between the mucosa and the underlying muscle layer to improve the safety of colorectal polyp resection. In the 1970s and 1980s in Germany and Japan, this was applied to early lesions of the stomach and esophagus. Endoscopists created an artificial saline “polyp” that could be resected in the usual fashion with a wire snare. An alternate technique around the same time utilized a grasper to lift the mucosa, which was then resected with the wire snare. A combination of the “saline lift” and the “lift and cut” biopsy produced the “strip biopsy” (saline injection, lift, and cut), which became a standard EMR technique.

To increase the size of lesions that could be resected with EMR, one group in Japan developed a “pre-cutting” technique, in which the mucosa was incised circumferentially around the lesion, resulting in contraction of the intended specimen. Clear plastic overtubes were utilized to better control the specimens during the “lift and cut” technique; eventually, clear plastic caps were developed to overcome the limitations of the bulky overtubes, and the technique of cap EMR (“EMR-C”) emerged. Pilot experiments on ex vivo surgical specimens to determine safety parameters for EMR-C (including the size of the cap, volume of injection, and amount of suction) revealed that large-volume submucosal saline injection could develop the submucosal plane without damaging the overlying mucosa.

As time progressed, the submucosal injection, pre-cutting of the mucosa, and a modified dissection cap were combined (again in Japan) to allow for dissection of the submucosal space under direct vision, significantly increasing the size of specimens that could be resected *en bloc*, and later being renamed to ESD. This advancement led to the rapid evolution of caps and knives, including the creation of the TT knife. Equipment originally intended for ESD was later applied to the first POEM procedures.

Despite the advancements with caps and knives, the ability to retract the specimen with the endoscope while dissecting the submucosal space under direct visualization remained difficult. Fortunately, a group in Germany reported "submucosal endoscopy" to reduce the need for retraction. They pioneered the technique of tunneling under a lesion, completing the dissection before incising the mucosa. Meanwhile, a group in Texas reported an endoscopic myotomy in a porcine model. They used a balloon to blindly develop the submucosal space and then cut the circular muscle from distal to proximal. Finally, refinements by Inoue et al. applied the principles of ESD (including large-volume injection, CO_2 insufflation, and submucosal tunneling under direct vision) in order to safely perform the procedure in human patients. The first POEM procedures sought to mimic the surgical myotomy; the esophageal portion of the myotomy was later extended to take full advantage of the endoscopic approach.

Several controversies remain regarding the POEM procedure, such as the ideal location, length, and thickness of the myotomy. It is also difficult to ensure adequate dissection has been carried out on the gastric side, and several adjuncts have been developed, including use of a second endoscope, radio-opaque clips, or intraprocedure esophageal distensibility measurements [33–35]. Future research may determine the optimal patient populations that benefit from POEM and help to answer the open questions regarding the technique.

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POEM: Concept to Research Laboratory

2

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Introduction

Given that the first experiments involving submucosal endoscopic esophageal myotomy in a porcine model were published in 2007, the interval uptake of peroral endoscopic myotomy (POEM) into clinical practice has been impressively swift. While the procedure remains limited to specialized practitioners and centers, it has become a valuable therapeutic option for the management of achalasia with outcomes that rival benchmarks established by more conventional surgical alternatives. Historical perspective helps to contextualize POEM as the conceptual outgrowth of a much longer therapeutic lineage rather than a de novo innovation to be added to the proceduralist's armamentarium. Reflecting on the specific differences between submucosal endoscopic myotomy and the interventions (both experimental and established) that preceded it allows for a clearer understanding of the ways in which POEM represents a novel therapeutic paradigm, for spastic esophageal disorders in particular and for endoscopy in general. Looking ahead, distant milestones in this conceptual evolution might include technical elaboration made possible by novel endoscopic devices or, intriguingly, molecular therapies that might render endoscopic therapy for achalasia obsolete.

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History of Achalasia Therapy

Discussing the conceptual origins of POEM merits a brief historical review of achalasia therapy in general. This chronology begins in the late seventeenth century, when English physician Thomas Willis (1621–1675) described the successful use of whalebone dilatation in a case of dysphagia. In his treatise on the subject, Willis speculated that the patient's symptoms were due to an obstruction at the level of the proximal stomach. "Cardiospasm" was formalized as a clinical entity in 1821, corresponding with classically reported symptoms of dysphagia and regurgitation and anatomical findings of a diffusely dilated esophagus in the absence of any discernible structural blockage [1].

Etiological hypotheses regarding this process were wide-ranging through the nineteenth century, including congenital muscular hyperactivity, extrinsic compression from nearby viscera, and nervous degeneration [1]. The term "achalasia" was coined at the turn of the twentieth century, favored by certain practitioners over "cardiospasm" on a mechanistic basis. The newer word was derived from Greek and suggested more explicitly a presumed failure of the lower esophageal sphincter (LES) to relax [2]. A semantic debate between these two disease models continued over the next few decades, though both attended to the LES as the primary site of pathology [3, 4]. Mechanical dilatation remained a frequently employed therapy, with pneumatic dilators by and large supplanting their hydrostatic predecessors in the latter part of the twentieth century [5, 6].

The advent of surgical therapy for achalasia also occurred in the early 1900s. The first such procedure was described in 1910 and involved a small vertical incision over the cardia that was then closed with transverse sutures. The German surgeon Ernest Heller (1877–1964) revised the cardioplasty 4 years later, using a transabdominal approach, to perform longer, extramucosal incisions on both the anterior and posterior aspects of the cardia [7]. Other surgical procedures were devised for achalasia therapy that did not address the lower esophageal sphincter directly (e.g. megaesophageal plication or side-to-side esophagogastrostomy) but abandoned relatively quickly in the face of poor outcomes [8].

Pathophysiology

Research from bench to bedside has continued to reinforce attention to the lower esophageal sphincter as the essential site of physiological dysfunction in achalasia. Early manometric analyses clarified abnormal LES relaxation as a hallmark feature of this clinical entity, and esophageal outflow obstruction remains a necessary but not sufficient criterion for making the diagnosis [9]. Clinical achalasia subtypes have since been further defined by variable manometric abnormalities of the esophageal body, ranging from absent contractility to panesophageal pressurization to premature contractile sequences consistent with spasm [10].

Muscular dysfunction was in turn tied to aberrancies in neural control, as inhibitory signaling by nitric oxide was recognized as the primary mediator of appropriate LES relaxation. Histopathological evaluation of resected specimens from patients with both early-stage and late-stage achalasia has demonstrated chronic inflammation leading to progressive injury of nervous tissue with eventual depletion of myenteric ganglion cells [11, 12]. Several investigators have conjectured that this process represents an autoimmune phenomenon, possibly tied to an infectious trigger [13]. Significant variations within this histological pattern by clinical achalasia subtype, however, suggest that achalasia pathogenesis may be marked by significant heterogeneity that is not yet fully appreciated [14].

Directed attention toward lowering LES resting pressure has led to other interventions that are not exclusively mechanical in approach. Intrasphincteric injection of botulinum toxin in patients with achalasia, for example, has been shown to result in symptomatic, manometric, and radiological improvement, albeit on a temporary timescale [15]. This intervention remains clinically relevant for its limited harm profile, well suited to individuals concerned about long-term postoperative side effects or in whom more aggressive surgical intervention is deemed prohibitively high-risk. Therapeutic inquiry has continued to explore novel means of intervening on the LES that might optimize the balance among convenience, safety, and permanence.

Early Endoscopic Myotomy

Efforts to mitigate the invasiveness of transabdominal Heller myotomy corresponded with a more general rise of interest in minimally invasive surgical techniques. The first laparoscopic and thoracoscopic cardiomyotomy procedures were successfully performed in the early 1990s [16, 17]. A logical extension of these developments was to consider endoscopic rather than surgical approaches to myotomy. Earlier, more straightforward attempts at treating achalasia with flexible endoscopy had been made but were met with limitations. The first example of endoscopic myotomy for achalasia was described by Ortega et al. in 1980, well before the first reports of laparoscopic surgical myotomy were published. Using an independently designed electrosurgical knife introduced through the biopsy channel of the endoscope, Ortega et al. performed an intraluminal myotomy procedure on six dogs, optimizing their technique through the course of these animal experiments. The authors then performed the procedure on a series of 17 patients with achalasia. Improvement was reported along all relevant dimensions, including subjective symptomatic reports as well as posttreatment radiographic and manometric evaluation [18].

This technique received little published attention in the intervening years, however, and its uptake was likely limited by concerns surrounding both efficacy and safety. Myotomy length, for instance, was limited to 1 cm through this prototypical endoscopic approach, as compared with the long or extended myotomy allowed by a conventional surgical approach with correspondingly better symptomatic outcomes [19]. Additionally, myotomy depth as reported by Ortega et al. was limited to 3 mm, with more aggressive incisions presumably increasing the risk of bleeding and perforation. Finally, this remained a blind procedure, and so clearly not for the faint-hearted.

Third Space Endoscopy

With percutaneous and intraluminal access perceived as the only two available modes for performing therapeutic incision of the LES, surgery remained the definitive option for achalasia therapy, with endoscopic dilatation maintaining relevance as an intermediate approach, a compromise between invasiveness and efficacy [20]. However, in parallel with the experiments performed under the Natural Orifice Tranluminal Endoscopic Surgery (NOTES) paradigm, which was at the forefront of attention within the therapeutic endoscopy community at the time, another novel initiative, led by Christopher J. Gostout at the Mayo Clinic, was gathering steam. A desire to perform en bloc resection of larger lesions drove interest in the development of submucosal fluid cushions that could be used to delaminate the mucosa from the submucosa [21]. The creation of a submucosal tunnel, establishing distance between points of entry and exit into the working space, constituted a novel innovation with the added benefit of protecting against leaking intraluminal contents in the event of perforation [22].

In 2007, the first practical therapeutic exploitation of this space was made using a novel experimental approach to myotomy described in a porcine model. In the experiments performed by Pasricha et al., the circular muscle of the LES could be incised under direct visualization through an endoscopic approach without disruption of the esophageal adventitia in a procedure called “submucosal endoscopic esophageal myotomy” [23]. Specifically, a dilating balloon was used to separate the mucosa from the muscularis propria in order to create a novel working space for endoscopic therapy at the esophagogastric junction. Technical success was achieved in each of four animal experiments, with significant reductions in LES pressure reliably observed after the procedure.

As with many notable events in medicine, the clinical translation of this technique might have languished were it not for serendipity. During a visit to Australia, Dr. Pasricha was giving a lecture on endoscopic myotomy attended by, among others, Haru Inoue. As a master surgeon and endoscopist, Inoue expressed his interest to Pasricha and advised that he would attempt the technique in patients over the next several months. In 2010, the first clinical report by Inoue et al. appeared, in which the procedure was renamed “POEM.” The technique was modified for therapeutic use in humans, replacing balloon-mediated separation of submucosal tissue planes with an endoscopic submucosal dissection (ESD) technique and, using a triangle-tip knife, extension of the incision at least 2 cm below the esophagogastric junction. In their series of 17 consecutive patients, the authors reported complete technical success and no serious short-term complications. Significant post-treatment reductions in both LES pressure and clinical dysphagia scores were observed [24].

Technical Maturation

Several critical questions remained unanswered in the early days of endoscopic myotomy via submucosal approach. In contrast to the conventional surgical approach, for example, the boundaries of incised muscle were not kept physically separated after submucosal myotomy, raising theoretical concern for tissue healing leading to recurrent elevations in LES tone over time. The risk of gastroesophageal reflux as a function of LES disruption (particularly in the absence of partial fundoplication, which had become a standard prophylactic adjunct to surgical myotomy) was also uncertain. More generally, the extent to which the apparent success of POEM in experimental contexts could be recapitulated in clinical settings and preserved over long-term follow-up intervals would necessarily take time to understand.

The strength of early reports, however, allowed for long-term data to accrue. The first author of the first clinical application of POEM, Dr. Inoue, has recently noted the completion of the thousandth such procedure at his center, marking this milestone as senior author of a manuscript, detailing technical insights gained as function of this experience [25]. Elsewhere as well, retrospective data sets of increasing size have suggested that the procedure's technical and clinical efficacy remain robust, that severe complications are rare, and that side effects such as reflux can be well managed medically [26]. Attention is now oriented toward particular clinical scenarios in which POEM may offer an advantage over laparoscopic surgery, such as the spastic achalasia subtype, in which a relatively long myotomy may be endoscopically performed, extending as needed to the proximal boundary of contractile dysfunction [27].

It is interesting to reflect upon the fact that POEM seems to have changed the dialog surrounding the currently moribund NOTES paradigm by virtue of its successful example. A clear distinction should be made, however, between traditional NOTES, involving largely hypothetical transvisceral approaches to organs extrinsic to the gastrointestinal lumen, and third space endoscopy, referring to procedures that use submucosal tunneling along with the skills required for endoscopic mucosal resection and, in certain cases, endoscopic ultrasound [28]. Aside from POEM, procedures falling under the rubric of third space endoscopy include, for example, peroral pyloromyotomy and submucosal tunneling with endoscopic tumor resection [29, 30]. In addition to therapeutic intervention, potential applications of these techniques include specialized drug or device delivery and deep tissue sampling for various other neurogastroenterological diagnoses that are as yet poorly characterized [31].

Future Trends

As POEM becomes steadily more entrenched within the suite of available treatments for patients with achalasia and other esophageal motor disorders, new challenges and opportunities will arise to help determine its ultimate position within the therapeutic landscape. Most basically, definitive evidence at the level of randomized controlled trials comparing outcomes of endoscopic versus surgical myotomy is still forthcoming and will clarify the logic of the procedure's wider dissemination. Accumulating data on postprocedural outcomes may also eventually facilitate building predictive models identifying which patient populations are best positioned to undergo one particular therapeutic intervention over another.

Existing as it does at the crossroads of surgery and endoscopy, POEM also poses challenging questions regarding which subset of clinicians should be performing the procedure in the future. As with other endoscopic skills that are shared between gastroenterologists and surgeons, POEM might remain a shared territory for practitioners from diverse training backgrounds, particularly as its technical description becomes more streamlined and widespread. Incentives built into the contemporary healthcare environment tend to favor low-cost alternatives, in which case, all else being equal, endoscopy suites may hold the advantage over operating rooms in the long run. Regardless, professional societies with vested interest in the procedure will likely soon be gathering to formalize credentialing guidelines.

Disagreement among specialty groups has been implicated in the reduction of interest over time in the traditional NOTES concept, in light of which active collaboration between interest groups seems vital to the practical advancement of third space endoscopy moving forward [32]. As opposed to NOTES, however, the sustainability of third space endoscopy is bolstered by its offer of a viable and robust solution to an unmet need (over and above an incremental improvement in cosmesis). In general, techniques requiring an increase in overall complexity and required skill sets to a degree that is out of proportion with the need they purport to meet will stand as poor examples of disruptive technology over time.

Given the significant amount of time and energy that has been devoted to POEM's technical refinement, it is somewhat surprising to consider that the endoscopic tools with which the procedure is performed have not yet been customized to the task. While commentators have discussed the strengths and weaknesses of various existing accessories, the endoscopic design area has not yet manufactured instruments specifically tailored to the purpose of POEM. As subtle and effortless as the procedure might become in progressively experienced hands, it retains an improvisatory, ad hoc quality in light of this hardware legacy. Engineering investments in new devices for third space endoscopy could help to flatten the procedural learning curve and perhaps even facilitate further technical innovation within the submucosal tunneling paradigm.

Finally, it is worth considering the hypothetical impact of novel approaches to achalasia and related processes that might, in the far future, subvert the relevance of even minimally invasive procedures such as POEM. Relatively recent population-level analyses have identified potential loci of genetic susceptibility to the development of idiopathic achalasia as well as a relative frequency of comorbid allergic and autoimmune disorders within this population [33, 34]. Ongoing investigation into the pathogenesis of these disorders might one day yield molecular insights into restoring lost neurons at the lower esophageal sphincter, or perhaps preventing their deterioration in the first place [35]. Understanding endoscopic myotomy as a fundamentally palliative procedure places added emphasis on pathophysiological investigation as the primary point of departure for new conceptual models in managing gastrointestinal dysmotility.

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Current and Emerging Instruments and Energy

3

James P. Villamere and Matthew D. Kroh

Introduction

Technological advancements and innovative techniques in endoscopic surgery have permitted peroral endoscopic myotomy (POEM), first described by Ortega [1] in 1980 and first performed on humans in a submucosal fashion by Inoue in 2008 [2], to become a more widely adopted and utilized technique in the treatment for esophageal motility disorders. The endoscopic technique and technology utilized for POEM were developed from the principles of endoscopic submucosal dissection (ESD), first described in 1988 as a nonoperative approach for the treatment of early gastric cancer [3]. The technique and equipment used for ESD have evolved continuously in this time. Similarly, device and instrument advancements have already been seen with POEM, and they are expected to continue with further adoption of POEM and other surgical endoscopic procedures. This chapter will highlight the current and emerging instruments and energy sources utilized for safe and efficient performance of POEM based on existing experiences.

Devices for POEM

The fundamental characteristics of instruments used for POEM must result in their ability to perform submucosal dissection and myotomy. The endoscope and electrosurgical unit (ESU) are similar to those utilized during standard interventional endoscopy. However, it is important to highlight that high-definition units are essential to optimize tissue

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differentiation for safety and efficacy during the submucosal dissection and myotomy. The electrosurgical knife is the device that performs the majority of the procedure during POEM. Other adjuvant tools are also required at various stages to optimize performance, given the complexity of this procedure. The instruments utilized for POEM are of single use, with diameters compatible with a 2.8 mm endoscopic instrument channel.

Endoscopes

Endoscopes with high-definition (HD) imaging contribute to safe performance of POEM. To obtain true HD image resolution, all components of the system including the video chip, processor, monitor, and transmission cables must be HD-compatible [4, 5]. HD endoscopes produce images with 850,000 to over one million pixels compared to 100,000–400,000 pixels on a standard endoscope [4]. During POEM procedures in particular, HD endoscopes permit optimal recognition of the anatomy in the submucosal plane, muscular layers, and potentially extramural thoracic and abdominal structures. Accurate identification of the mucosa, areolar tissue, circular, and longitudinal muscular layers is required for successful performance of POEM. Additionally, submucosal vessels must be adequately visualized and coagulated or avoided to prevent bleeding. The endoscope utilized by our group and the majority of groups is a forward-viewing HD gastroscope (GIF-H180, Olympus, Tokyo, Japan or GIF HQ190, Olympus Center Valley PA, USA) [6–10] (Fig. 3.1). This 103 cm long gastroscope has a 9.8 mm outside diameter and contains a single 2.8 mm instrument channel. It is compatible with CV-180/160/140/93 image processors [5]. The list price for this endoscope is $35,700 [5]. Others have described a single-channel GIF-H260 (Olympus, Tokyo, Japan) gastroscope for use during POEM [2, 11]. Although not described for POEM, a high-definition therapeutic gastroscope with a single large 3.7 mm instrument channel (eg, GIF-1TH190, Olympus America) has been used for ESD which combines the dual benefits of ideal optics and superior suctioning capacity, especially when a device is in the instrument channel [12]. Inoue has described benefit in using a gastroscope with a larger 3.2 mm working channel with water-jet function during POEM [13].

Fig. 3.1 GI endoscope used for POEM

Overtubes

Overtubes have the ability to facilitate luminal access during POEM and potentially limit oropharyngeal trauma with repeated esophageal intubation throughout a procedure. An overtube is a semirigid plastic sleeve-like conduit device with a soft, tapered, distal tip. The inner diameter is larger than the endoscope, with the distal end tapering to closely match the diameter of the endoscope to minimize the likelihood of mucosal entrapment between the two devices during exchanges [14]. Overtubes vary in length and caliber depending on the indication and route of access. To protect the cricopharyngeal area or airway, such as in POEM, the length needs to be 20–25 cm [14]. Overtubes are intended to facilitate endoscopy by protecting the mucosa from trauma during scope insertion, maintaining linear stability, and reducing the risk of aspiration [14]. Additionally, the sealed distal end may limit proximal gas loss (CO_2 or air) and maintain better insufflation during the procedure. We utilize a 25 cm Guardus overtube (US Endoscopy) (Fig. 3.2a) during POEM and secure it to the patient with umbilical tape (Fig. 3.2b).

Specifically for POEM, the overtube acts to stabilize the endoscope and maintain consistent access for repeated reinsertions. This limits transmission of pushing forces applied to the mucosa and may limit mucosal laceration and gaping, especially at the esophageal mucosotomy site during POEM [7, 13]. During POEM, a diagnostic upper endoscopy is first performed without the device to ensure that the overtube does not interfere with the initial insertion and obscure markings on the endoscope [14]. The overtube can be preloaded onto the endoscope, and once the diagnostic exam is complete, it is advanced over the endoscope to promote procedural efficiency and avoidance of reinsertion. Liberal use of lubricant to the endoscope and inner and outer surfaces of

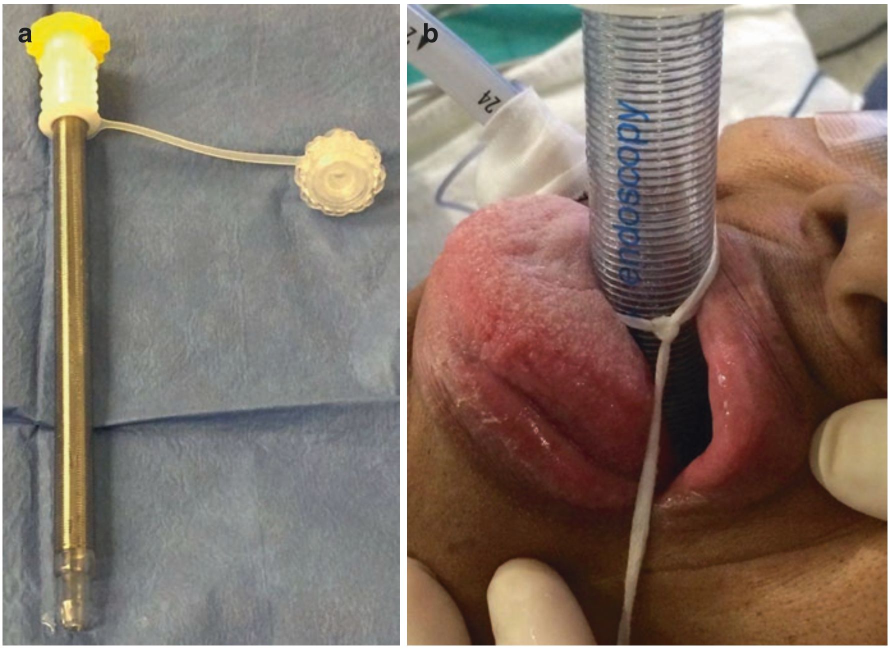

Fig. 3.2 (**a**) Guardus overtube (US Endoscopy) (**b**) Overtube secured with umbilical tape

the overtube prior to insertion is helpful, and any resistance during passage necessitates reassessment [14]. Although water-based lubricants are commonly used, they can desiccate during the extended time required to complete the POEM procedure in many cases. Medical grade olive or vegetable oils are available alternatives and maintain lubricant features for prolonged periods, thus facilitating device movement. Complications such as mucosal abrasion and tears have been reported, with overtube use secondary to the large diameter or pinching of the mucosa between the overtube and endoscope. Proper insertion techniques over a bougie or endoscope reduce this risk [14].

Gas Insufflation

Carbon dioxide (CO_2) gas insufflation is utilized during the procedure with a CO_2 insufflator CO_2MPACT™ (Bracco Diagnostics, USA) (Fig. 3.3) at our institution, or Olympus UCR (Olympus, USA) [2, 9, 11], and a standard low-flow insufflation

Fig. 3.3 CO_2 insufflation unit (CO_2MPACT™, Bracco Diagnostics, USA)

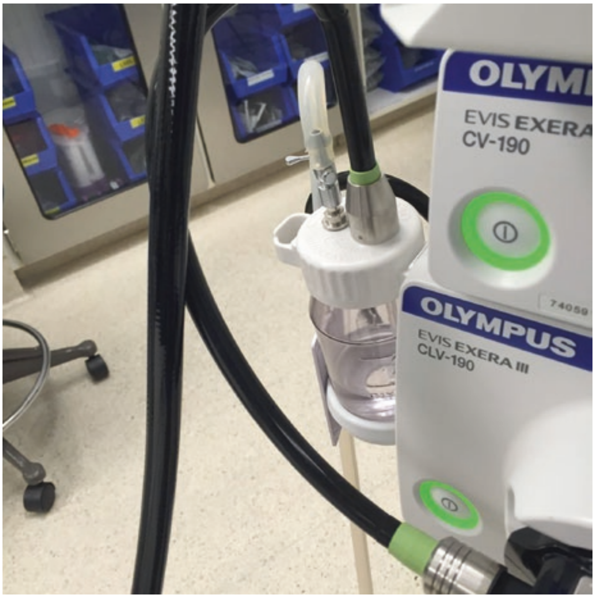

Fig. 3.4 Insufflation tube (MAJ-1742, Olympus America) with valve for precision flow

Fig. 3.5 Standard room air insufflator tuned off

tube (MAJ-1742, Olympus America) [2] (Fig. 3.4). The use of a CO_2 gas insufflation unit is preferred for performance of POEM as regular room air insufflation may lead to unique complications. Utilizing CO_2 insufflation with a low controlled gas flow of 1.2 L/min is beneficial for decreasing the risk of the gas dissecting through small holes in the longitudinal muscle causing pneumomediastinum, pneumoperitoneum, and air embolism [13, 15]. If dissection does occur, however, CO_2 is rapidly absorbed [15]. It is important to ensure that the standard endoscopic room air pump is turned off (Fig. 3.5) during the entire procedure to avoid room air being supplied in conjunction with CO_2 insufflation, thus eliminating the safety advantage of CO_2

utilization [16]. This differs from ESD where it may not be essential to turn the room airflow off, as the muscular layers are kept intact limiting mediastinal emphysema and pneumoperitoneum [13]. The abdomen should be exposed during the procedure to allow periodic examination to ensure no excessive distension is present, potentially representing capnoperitoneum. Large volumes of intraperitoneal CO_2 may result in abdominal compartment syndrome and potential hemodynamic collapse if left untreated. A decompression needle (typically large-gauge angiocatheter with cannula or Veress needle) should be readily available to perform abdominal wall puncture and aspiration if significant capnoperitoneum is present [13]. When needed, needle decompression is performed on either side of the abdomen in the subcostal area. Once successful decompression has been performed, the cannula or Veress needle is often left in place for the remainder of the procedure to evacuate any further accumulated gas.

Knives

There are two main monopolar knives utilized during POEM. Depending on endoscopist preference, either of these knives can be used alone for both the initial mucosotomy, submucosal dissection and myotomy. The most commonly used endoscopic knives are the triangle-tip electrosurgical knife (KD-640 L, Olympus, USA) and the HybridKnife® (ERBE USA) Table 3.1.

The triangle-tip electrosurgical knife (Fig. 3.6) is a monopolar energy device with a noninsulated 1.6 mm triangular electrode plate at the tip of a 4.5 mm long cutting knife. The three sharp angulations at the tip permit smooth spraying of monopolar energy over a wide circumferential range [13]. This enables submucosal dissection and myotomy to be carried out without any direct contact of the knife with the tissue, which makes the dissection more efficient with less bleeding [13, 16]. This technique also minimizes tissue accumulation on the knife, thus decreasing the number of instrument exchanges needed for cleaning, and overall improving the visual field during dissection and muscle division. The triangle-tip electrosurgical knife was the knife used in the original description of POEM [2]. Care must be taken to avoid perforation due to the relatively large distal electrode. Additional knife tip shapes,

Table 3.1 Function comparison of the two most commonly used knives for POEM and list prices[a]

Manufacturer	Device	Injection	Mucosotomy	Submucosal dissection	Myotomy	Hemostasis	Price US$
Olympus[b]	Triangle-tip electrosurgical knife		●	●	●	●	709
ERBE[c]	HybridKnife T type	●	●	●	●	●	488

[a]Modified from [12]
[b]Olympus USA
[c]ERBE USA

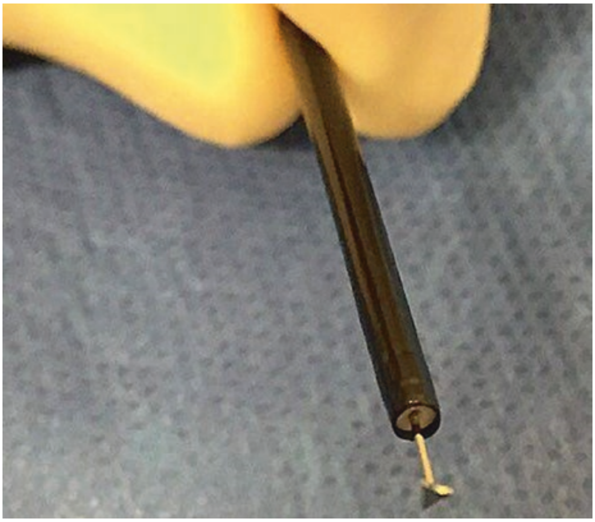

Fig. 3.6 Triangle-tip electrosurgical knife (KD-640 L, Olympus, USA)

Fig. 3.7 HybridKnife® (ERBE USA) T-type (erbe-med.com)

including L shape and ceramic-insulated triangle tip, are alternative options which can be selected based on operator preference.

The HybridKnife® has the potential ability to singularly accomplish all aspects of POEM including initial mucosal lift and dye injection during the submucosal dissection owing to its central capillary within the cutting knife. This feature allows the knife to function as an ultrafine 120-μm water jet that is powered by a foot pedal-activated, jet lavage unit: the ERBEJET®2 system (ERBE USA). The pressurized water jet has the ability to diffuse within the mucosal layer in a needleless fashion to create a submucosal lift [12]. There are three different tip configurations of the HybridKnife®, all with a 5 mm long cutting knife. The I-type is straight without an additional tip. The T-type has a noninsulated 1.6-mm diameter disk-shaped electrode at the tip. Finally, the O-type has an insulated, hemispherical, domelike tip. Only the I-type and T-type knives are approved by the US Food and Drug Administration and currently available in the United States [12], and the T-type has been the model described for use in POEM [10] (Fig. 3.7).

Bleeding during POEM is not uncommon and can significantly obscure visualization during dissection. Normally, minor bleeding can be controlled with the application of coagulation current from the triangle-tip electrosurgical knife or HybridKnife®. More significant bleeding may require management with an endoscopic coagulation forceps. Small vessels identified during submucosal dissection can also be coagulated prophylactically with the knife [12].

Electrosurgical Units (ESU)

The electrosurgical generator unit (ESU) facilitates therapeutic endoscopy by delivering high-frequency electrical current to the endoscopic device. The ESU transfers electrical current through the endoscopic device to thermal energy for use within the tissue [17]. Currently available ESUs contain sophisticated microprocessors and software that allow them to generate multiple different electrosurgical waveforms and settings based on the application specific to various endoscopic procedures, including POEM.

The electrosurgical generator utilized for POEM at our institution is the ERBE VIO 300D (ERBE USA) (Fig. 3.8). This is a radiofrequency surgical energy system, which supports spray-coagulation mode for noncontact tissue dissection during both the submucosal dissection and myotomy [13]. This unit is compatible with both the triangle-tip electrosurgical knife and the HybridKnife. The settings can be adjusted as needed during the procedure. The most frequently reported settings for the various stages of POEM are depicted in Tables 3.2 and 3.3. In general,

Fig. 3.8 ERBE VIO® 300D (Olympus, Germany)

Table 3.2 Settings reported for ERBE VIO® 300D (ERBE USA) utilizing triangle-tip electrosurgical knife (TT knife) (KD-640 L, Olympus, USA) for different stages of POEM [2, 6, 11, 13, 16]

POEM stage	Device	ESU mode	ESU setting	ESU power
Mucosal incision	TT Knife	ENDO CUT® Q	E2	Cutting duration 1, cutting interval 4
Submucosal dissection	TT Knife	SPRAY COAG	E2	50 W
Hemostasis	TT Knife for vessels <1.5 mm or hemostatic forceps for vessels >1.5 mm	FORCED COAG or SOFT COAG	E2 or E5	50–80 W
Myotomy	TT Knife	SPRAY COAG	E2	40–50 W

Table 3.3 Settings reported for ERBE VIO® 300D (ERBE USA) utilizing the HybridKnife® (ERBE USA) for different stages of POEM

POEM stage	Device	ESU mode	ESU setting	ESU power
Mucosal elevation	HybridKnife	ERBEJET® 2	Effect 30–60	
Mucosal incision	HybridKnife	ENDO CUT® Q	E2	Cutting duration 3, cutting interval 3
Submucosal dissection	HybridKnife	ENDO CUT® Q, or SWIFT COAG®	E3	Cutting duration 2–3, cutting interval 3–4
			E3–E4	70 W
Hemostasis	HybridKnife for vessles <1.5 mm or hemostatic forceps for vessels >1.5 mm	FORCED COAG® or SOFT COAG®	E2	50–60 W
Myotomy	HybridKnife	ENDO CUT Q or SWIFT COAG	E3	Cutting duration 2, cutting interval 4
			E3, E4	70 W

Fig. 3.9 ERBEJET®2 system (ERBE USA) (erbe-med.com)

low-voltage (>200 V) settings are used for tissue coagulation, medium-voltage settings (200–600 V) are used for tissue cutting, and high-voltage settings (>600 V) are used for tissue ablation.

When the multifunctional HybridKnife is used for POEM, the integrated electrosurgical and waterjet ERBEJET®2 (Fig. 3.9) functions can improve procedural efficiency. A recently published study comparing the triangle-tip electrosurgical knife and the HybridKnife® during POEM found the HybridKnife to significantly shorten procedural time and decrease device exchanges, while achieving similar treatment success [18].

The use of electrosurgical energy facilitates therapeutic endoscopy, and ESUs possess features that augment patient safety and ease of use. Knowledge of the basic principles of electrosurgical energy and the various settings and applications of the ESU is critical for safe and effective performance of POEM and other advanced endoscopic procedures.

Fig. 3.10 Coagrasper (FD-411QR, Olympus America) hemostatic forceps

Hemostatic Forceps

Bleeding in the submucosal space during POEM is typically from the muscular layers and occurs during the development of the submucosal plane, or more often, during the myotomy. The muscular layers of the esophagus contain an abundance of blood vessels and collateral circulation that may be encountered during the procedure [11]. Monopolar and bipolar hemostatic forceps may be used for hemostasis of submucosal vessels during POEM through coaptive thermoregulation [6, 8, 12]. The Coagrasper (FD-411QR, Olympus America) (Fig. 3.10), commercially available in the United States, is a monopolar hemostatic forceps that comes in a length of 165 cm for the purpose of gastroscopy, and has been used for POEM [2, 9, 12, 16]. It features serrated jaws that open to a width of 5 mm [12]. During submucosal dissection, minor bleeding is generally treated by forced coagulation with the knife, while pulsating bleeding from larger vessels may require hemostatic forceps to grasp and coagulate the vessel using the soft coagulation mode [11]. If larger vessels are identified in the submucosal space during dissection, it is advantageous to precoagulate these vessels with hemostatic forceps [11]. Generally, vessels <1.5 mm can be successfully coagulated with the tip of the knife using FORCED COAG E2, 60 W, while vessels >1.5 mm are best treated with coagulation forceps using FORCED COAG E2, 50 W [11]. Others have described coagulation of larger vessels with Coagrasper in soft coagulation mode (E5, 80 W) [2, 9, 16] and (E2, 80 W) [13]. Use of endoscopic clipping devices are rarely used in the submucosal space, secondary to the small working space and the potential deleterious effects of leaving a foreign body within the layers of the esophageal wall [11].

Adjuvant Tools for Tissue Retraction and Enhanced Visualization

A transparent distal attachment cap fitted to the end of the gastroscope is utilized in POEM to facilitate submucosal tissue dissection and exposure similar to the principles with ESD [10, 15]. Caps come in many different shapes and configuration, tailored to the needs of specific parts of any procedure. During POEM procedures, one or more caps may be utilized during the procedure, and change of caps occurs at a specific step of the operation. The purpose and benefit of the cap are in maintaining improved visualization during dissection in the submucosal tunnel as it keeps the flap of mucosa off of the endoscope lens, thus reducing the "red out" effect [12]. During initial access of the submucosal plane, we prefer a softer, smaller, and tapered cap. This design facilitates entrance into this plane with less maneuvering and potential tissue damage. Once the submucosal tunnel is established and progressed, we prefer to change caps to a larger diameter oblique cap. The cap affords radial tension that assists with submucosal dissection [6] and also protects the mucosa from the knife coagulation spray. The majority of caps have drainage holes, which may need to be fashioned, that permit an outlet for water, tissue debris, and blood to clear from the endoscopic lens, therefore optimizing visualization [12].

Caps are available from a variety of manufacturers. The caps typically utilized for POEM are the 4-mm long and 12.4-mm diameter soft straight distal attachment (D201-11804, Olympus America) [9, 10] (Fig. 3.11), tapered ST hood (Fujifilm, Tokyo, Japan) [13] (Fig. 3.12a), and the oblique distal attachment MH-588 (Olympus) (Fig. 3.12b).

We utilize both the tapered ST hood (Fujifilm, Tokyo, Japan) and the oblique distal attachment cap. The tapered orifice promotes an easier insertion of the endoscope into the submucosa space with a smaller mucosal incision and helps maintain endoscopic visualization in this space [7, 16, 19]. We then switch to the oblique design, which has an orifice with the longer end of the bevel posterior and extends a distance of 1 cm beyond the distal end of the endoscope. It can be helpful for widening the submucosal tunnel to aid dissection and it also effectively effaces the lumen for assistance with clipping the esophageal opening [13]. Dislodgement of the cap within the submucosal tunnel during POEM has been described, and therefore a highly adhesive water-resistant tape to secure the cap to the end of the endoscope is recommended [10]. Our group utilizes standard electrical tape for this purpose (Fig. 3.13).

Fig. 3.11 Olympus (D201-11804, Olympus America) soft straight distal attachment

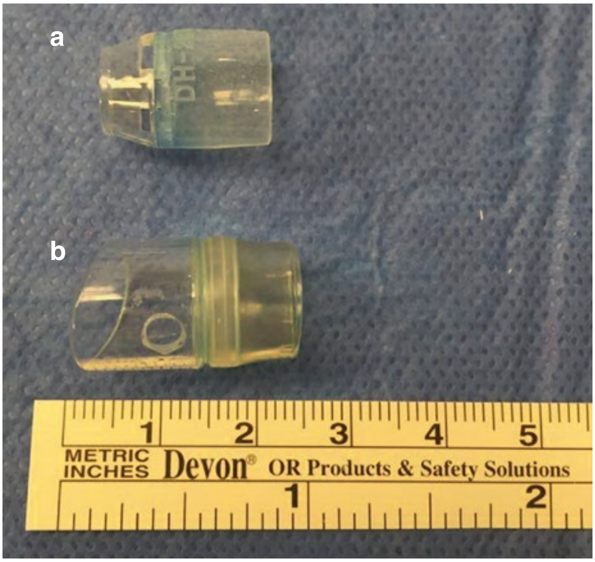

Fig. 3.12 Tapered ST hood (Fujifilm, Tokyo, Japan) and oblique distal attachment caps utilized at our institution. Upper cap is (**a**) and is the oblique cap, Lower cap is (**b**) and oblique cap

Injection Agents and Devices

Injection agents are utilized in the submucosa plane at the site of planned mucosotomy to create an elevated wheel. This separates the mucosa from the submucosa, which provides a margin of safety when performing the mucosotomy [12]. The

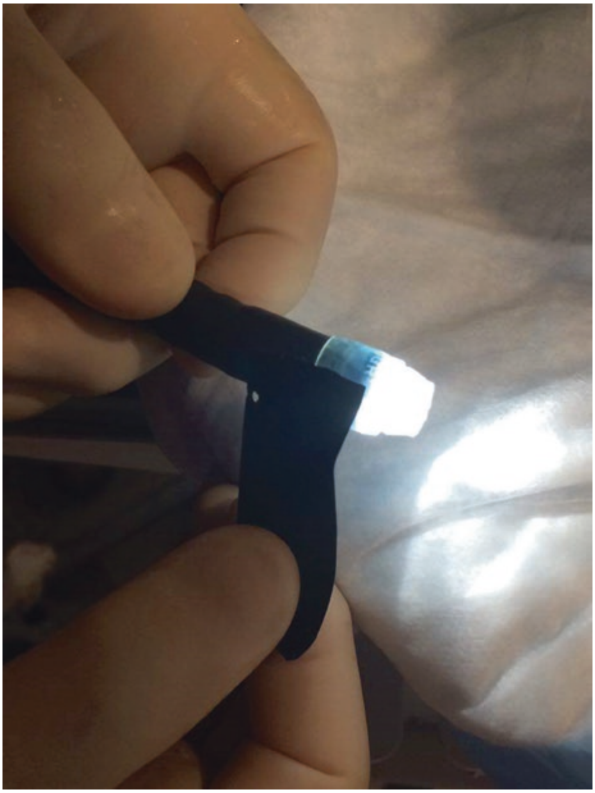

Fig. 3.13 Standard electrical tape to secure the cap to the end of the endoscope

initial submucosal injection is typically delivered with a 21–25 gauge endoscopic needle injection catheter [12].

An Olympus InjectorForce Max™ (Olympus America) single-use disposable 4-mm, 23-gauge injection needle has been described for use with POEM [10, 11]. We utilize the Articulator™ (US Endoscopy) injection needle at our institution (Fig. 3.14). The HybridKnife® is unique in that it features an ultrafine 120-μm water jet that is powered by a foot pedal-activated, jet lavage ERBEJET®2 unit that has the ability to penetrate the mucosal layer in a needleless fashion to create the submucosal wheel and facilitate the initial incision [12].

Dyes such as Indigo Carmine and Methylene Blue are often used for POEM. Differential uptake by mucosal, submucosal, and muscular layers during submucosal injection allows for better tissue plane recognition during dissection. Injection agent mixtures that have been utilized for POEM include 10 mL of saline with 0.3% Indigo Carmine dye [13, 16] or a solution of 250 mL saline, 3 mL Indigo Carmine, with and without the addition of dilute epinephrine, which may aid in

Fig. 3.14 Articulator™ (US Endoscopy) injection needle

hemostasis (1:250,000) [11]. We use a mixture of 500 mL saline with 2 amps of Methylene Blue and 2.5 amps of dilute (1:10,000) epinephrine.

Repeated injection in the submucosal tunnel during dissection is beneficial whenever the submucosal layer and muscular layer demarcation becomes unclear. Differential uptake of the blue dye facilitates identification of the mucosa and orientation as well as enhances the demarcation between tissue layers [16, 19] (Fig. 3.15). During initial endoscopic inspection of the patient's anatomy at the beginning of the POEM procedure, a small volume (1 mL) of full concentration dye is commonly

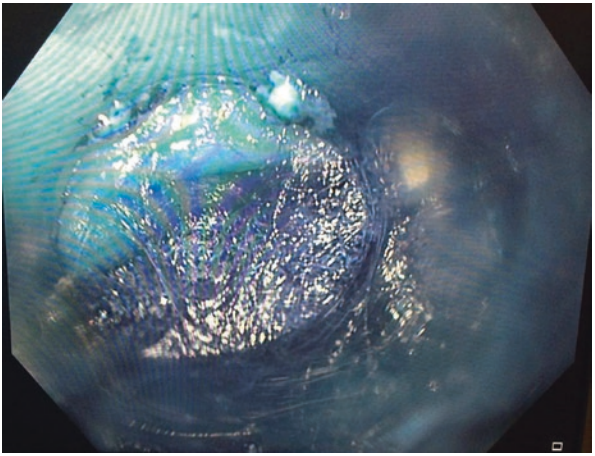

Fig. 3.15 Differential uptake of injection agent by mucosal, submucosal, and muscular layers during submucosal injection for tissue differentiation

injected in the submucosal space of the target endpoint of dissection within the gastric cardia. This is done using a retroflexed position. Later in the procedure, the deep blue discoloration of the gastric cardiac mucosa and submucosa aids in confirming the adequacy of extension of the submucosal tunnel beyond the lower esophageal sphincter [9].

We also inject a mixture of 250 mL saline with 250,000 units of bacitracin into the submucosal space prior to mucosal closure.

Biliary Extraction Balloon

Gentle submucosal balloon dilatation with a 12 mm biliary extraction balloon can facilitate initial entry to the submucosal space [8, 15]. (This is an off-label use of this product.) Care must be employed when inserting the balloon catheter bluntly to avoid mucosal or muscular injury [10]. The balloon is carefully inserted into the submucosal space parallel to the true lumen after the mucosotomy, and dilated up to 12–15 mm to initiate the creation of the submucosal tunnel [10]. Our group utilizes the Olympus V-System single-use stone-extraction balloon (Olympus America) (Fig. 3.16), while others have described the use of a Boston Scientific (Natick, MA, US) controlled radial expansion balloon dilator (12 mm) [10]. Previously, some Western groups utilized the submucosal balloon dilation technique for completion of the submucosal tunnel, but due to the risk of bleeding, have since adopted and become proficient using the knife for submucosal dissection [10, 11, 20].

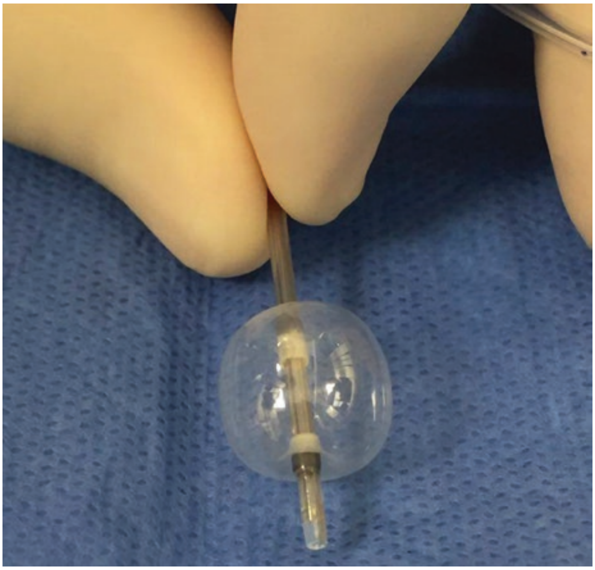

Fig. 3.16 Stone extraction balloon (V-System, Olympus America)

Mucosal Closure Devices

Adequate closure of the initial mucosal entry site during POEM is important to prevent passage of esophageal contents into the submucosal plane, peritoneal cavity, and mediastinum [7, 16]. The optimal closure device is safe, efficient, inexpensive, reliable, and durable [21].

Most centers, including our institution, utilize standard hemostatic clips such as the EZ Clip™ (HX-110QR, Olympus) or Resolution™ Clip (Boston Scientific, Natick, MA, USA (Fig. 3.17) [9, 10, 15, 16]. Several through-the-scope hemostatic clips are currently available in the United States. Typically 5–10 clips are necessary [16, 19], and an average of seven clips has been described during POEM [6]. The total number of clips used varies based on the initial mucosotomy size, and an appropriate amount should be used to completely close the defect, when possible. Our preferred technique for closure commences by placing the first clip in a vertical orientation at the distalmost portion of the mucosal incision. This aligns the mucosal edges to facilitate subsequent proximal clip placement [15]. This approach for mucosal closure is efficient and has been described taking 6 min when performed by an experienced endoscopist [8].

Some have described mucosal closure during POEM with an endoscopic suture device, the OverStitch™ Endoscopic Suturing System (Apollo Endosurgery, USA) (Fig. 3.18). In experienced groups, this technique has good results and no significant difference in mean closure time and cost when compared to standard endoscopic

Fig. 3.17 Resolution™ clip (Boston Scientific, USA)

Fig. 3.18 OverStitch™ endoscopic suturing system (Apollo Endosurgery, USA)

clipping technique [20]. The OverStitch™ Endoscopic Suturing System is a disposable, single-use device that is affixed to a double-channel therapeutic endoscope. It permits placement of either running or interrupted full-thickness sutures. A limitation of this device is that it is only compatible with a single endoscope, the Olympus

Fig. 3.19 OTSC® Clip (Ovesco Endoscopy)

GIF-2T160 gastroscope (Olympus America) [21]. Use of the OverStitch™ suturing device has also been successful in closing inadvertent full-thickness esophagotomy in a two-layered fashion by approximating the muscular layer and then the mucosa separately [22].

Some have also reported mucosal closure with an over-the-scope clipping device, OTSC® clip (Ovesco Endoscopy) [7] (Fig. 3.19) or fibrin sealant [23]. Saxena et al. described an alternative method of mucosal flap closure during POEM, when closure was unsuccessful with hemostatic clips alone. In these case reports, the proximal portion of the mucosa was successfully approximated utilizing a OTSC® Twin Grasper® (Ovesco Endoscopy) followed by placement of OTSC® clip [7]. The OTSC® clip may provide a more durable mucosal closure than standard hemoclips owing to its wider mouth span, capacity to grasp larger amounts of tissue, and ability to apply greater compressive force [24].

Summary

As with all advanced endoscopic and surgical procedures, familiarity with and expertise of use of tools and equipment are important components to the success of the intervention. POEM procedures utilize both commonly and relatively less frequently used devices. Mastering these techniques, including POEM, is incumbent upon understanding of the spectrum of tools available and appropriate and skilled implementation (Table 3.4).

Table 3.4 POEM: OR equipment checklist

Device	Brand
EGD Videoscope (1)	GIF-HQ190 (OLYMPUS)[a]
Overtube (1)	Guardus overtube for esophagus—25 cm (US Endoscopy)[a]
Umbilical tape (1)	
CO_2 insufflator (1)	CO_2MPACT™ (Bracco Diagnostics, USA)[a] or UCR (OLYMPUS)
Low-flow tube for UCR (1)	MAJ-1742 (OLYMPUS)
Needle for removal of excessive CO_2 pressure (1)	Veress needle[a] or 14G IV catheter
Endotherapy (ET) knife (2)	Triangle-tip knife [KD-640L] (OLYMPUS)[a] or HybridKnife® (ERBE)
Endoscopy tower (1)	EVIS EXERA III CV-190 (OLYMPUS)[a]
Electrogenerator (1)	ERBE VIO® 300D (ERBE)[a]
Endotherapy (ET) grasper (1)	Coagrasper [FD-411QR] (OLYMPUS)[a]
Distal attachment (cap) (1, 2)	Tapered ST hood (FUJIFILM)[a] and/or oblique distal attachment MH-588 (OLYMPUS)[a]
Adhesive tape (1)	
Injection needle (1)	Articulator™ (US Endoscopy)[a] or Olympus InjectorForce Max™ (OLYMPUS) (23 G or 25 G)
Saline (1) plus Indigo Carmine or Methylene Blue (1) +/− Epinephrine (1)	
Bowl (2)	
Disposable hemostatic clips (5+)	Resolution clip [M00522610] (BOSTON)[a] or EZ Clip™ [HX-110QR] (OLYMPUS)
Syringe (30 mL) (2)	
Antifog solution (1)	
Alcohol swab (1)	
Water/oil-based lubricant	

[a]Used at our institution

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Indications and Preoperative Workup for Peroral Endoscopic Myotomy

4

Ashwin A. Kurian

Peroral Endoscopic Myotomy

The Per Oral Endoscopic Myotomy (POEM) technique popular today and first described by Inoue et al. in 2008 [1] was preceded by nearly 30 years via a simple albeit blunt approach. The first flexible endoscopic myotomy for the treatment of esophageal motility disorders was described by Ortega in 1980 using a 3 mm thick and 1 cm long esophagotomy technique in a blinded fashion [2]. This technique was not widely adopted at the time due to concerns of both safety and efficacy. However, the enthusiasm generated by the potential of NOTES in the mid-2000s and advancements in the field of flexible endoscopy facilitated an interest in endoscopic myotomy using mucosal tunneling techniques. The technique of performing a POEM is addressed in accompanying chapters, however briefly; it involves creating a distal esophageal mucosotomy, longitudinal submucosal tunneling across the gastroesophageal junction, esophageal myotomy, and closure of the mucosal defect. Both anterior and posterior myotomies have been described as primary procedures. However, most commonly, anterior myotomy is employed for patients who have not undergone a prior myotomy, while posterior myotomy is reserved for revising patients who have undergone a prior Heller myotomy or indeed a prior POEM. Patients are usually discharged home on postoperative day 1.

Achalasia

Esophageal achalasia is the most common surgically treated primary esophageal motility disorder. It is characterized by the absence of esophageal peristalsis and impaired relaxation of the lower esophageal sphincter (LES) on swallowing.

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The term achalasia originates from the Greek language meaning "nonrelaxing." This results in esophageal outflow obstruction, presenting as dysphagia, regurgitation, aspiration and pulmonary complications, chest pain, heartburn, and weight loss.

Symptom Evaluation

Dysphagia

Dysphagia is the most common presenting symptom, with most patients reporting difficulty with swallowing both solids and liquids. Patients often gradually alter their diet to accommodate for this issue.

Regurgitation

Regurgitation is the second most common symptom of achalasia. Again, due to changes in dietary habits, most patients learn to swallow while minimizing regurgitation. Regurgitation is often associated with aspiration and subsequent laryngeal and pulmonary complications.

Chest Pain

Approximately 50% of patients with achalasia will report chest pain which usually occurs postprandially. The etiology of chest pain is poorly understood. This symptom does improve after myotomy suggesting that it is likely multimodal in its etiology including the pathophysiology of esophageal stasis and fermentation.

Heartburn

Heartburn is a fairly common confounding symptom and is seen in about 40% of patients with achalasia. Heartburn often leads to an evaluation for gastroesophageal reflux disease (GERD). The heartburn described by achalasia patients possibly again is partly due to stasis and fermentation.

Weight Loss

Weight loss is fortunately an uncommon occurrence in achalasia patients. Diet modification, emphasizing soft and liquid foods, is utilized to achieve adequate caloric intake. Weight loss usually suggests severe disease. Significant and rapid weight loss should be thoroughly evaluated to address the risk of pseudoachalasia secondary to an obstructing malignancy.

Table 4.1 Scoring system to determine Eckardt Score

Score	Dysphagia	Regurgitation	Retrosternal pain	Weight loss (kg)
0	None	None	None	None
1	Occasional	Occasional	Occasional	<5
2	Daily	Daily	Daily	5–10
3	Each meal	Each meal	Each meal	>10

Symptom Scores

Various symptom scores have been devised for achalasia; however, the Eckardt scoring system is the most commonly used. It is the sum of the four cardinal symptoms of achalasia—dysphagia, regurgitation, chest pain, and weight loss. Total scores range from 0 to 12 (Table 4.1). A postoperative Eckardt score > 3 is consistent with disease recurrence. The Eckardt score has been shown to correlate with objective testing such as a timed barium swallow in the evaluation of postoperative outcomes [3].

Past Medical History

A detailed past medical history is important in the preoperative workup of a POEM patient. Knowledge of prior endoscopic treatments of achalasia such as Botulinum toxin injection or pneumatic dilation is important in determining the relative hostility of the submucosal plane during dissection. A prior esophageal perforation at the time of pneumatic dilation may effectively obliterate the submucosal plane. Prior exposure to mediastinal radiation also results in fibrosis of the esophageal layers. Cardiovascular or pulmonary comorbidities must also be considered during preoperative planning.

Diagnostic Evaluation

All patients, in whom POEM is being considered should undergo the following diagnostic tests to confirm the diagnosis, aid in patient selection as well as operative planning.

Upper Endoscopy

An upper endoscopy is usually the first test that was performed in the evaluation of a patient with dysphagia. Upper endoscopy might reveal a tortuous, dilated, sigmoid esophagus with retained saliva, fluid, or even food. Esophagitis might be seen due to stasis, especially of pills. Stasis might lead to esophageal candidiasis, commonly presenting with signs of esophagitis and overlying white exudate. Biopsies should always be performed to confirm Candida esophagitis in order to facilitate preoperative antifungal treatment.

Although rare, a preoperative upper endoscopy is essential to rule out a diagnosis of pseudoachalasia in which an infiltrating gastroesophageal junction tumor causes esophageal outflow obstruction mimicking achalasia. A high index of suspicion for pseudoachalasia should be maintained for patients older than 60 with a rapid progression of symptoms and excessive weight loss. Another rare but serious condition which can be detected endoscopically is the presence of esophageal varices. Computerized tomography or endoscopic ultrasound are helpful adjuncts to help confirm the diagnosis of pseudoachalasia and/or varices when suspected. The presence of either pseudoachalasia or esophageal varices is a contraindication to POEM and likely the completion of esophageal myotomy regardless of approach.

Contrast Esophagram

Although an esophagram can be normal in patients with early stages of achalasia, classically it reveals a tight narrowing at the gastroesophageal junction with a *bird beak* appearance, impaired LES relaxation, esophageal dilation, esophageal tertiary contractions, and poor esophageal emptying. A Timed Barium Swallow (TBS) provides information not only on esophageal anatomy but also on emptying. The TBS includes spot images that are performed at 1 min, 2 min, and 5 min after a barium bolus of 200 cm^3. The contrast column height and width reported in centimeters indicate the relative severity of the esophagogastric outlet obstruction. This test is also useful to evaluate postoperative improvements in esophageal emptying.

A sigmoid esophagus (dilated and tortuous with a sigmoid shape) that suggests difficulty with navigation through the submucosal tunnel during POEM can be expected. Although some practitioners have published outcomes in patients with end-stage achalasia/sigmoid esophagus, they suggest that these patients should ideally be approached after the learning curve of this procedure has been surmounted [4]. Outcomes in these patients are less predictable due to their end-stage disease when compared with patients who present with early achalasia.

Associated pathology such as a hiatal hernia or an epiphrenic diverticulum can also be detected on barium swallow. An unaddressed hiatal hernia will likely result in excessive gastroesophageal reflux following POEM. Hence, these patients are more appropriately approached laparoscopically with a hiatal hernia repair, myotomy, and partial fundoplication. A coexistent epiphrenic diverticulum will need to be excised or involuted to prevent postoperative stasis, dysphagia, and regurgitation. These patients are also best approached laparoscopically.

Esophageal Manometry

High-resolution manometry is the confirmatory test and serves as the goal standard for the diagnosis of achalasia. The advent of high-resolution impedance manometry, compared with standard resolution manometry, has enabled a classification of achalasia variants. High-resolution impedance manometry (HRIM) is performed with a solid-state catheter and has supplanted the use of water perfusion catheters. Thirty-two circumferential sensors spaced 1 cm apart give high-definition information of esophageal motility. Information on LES relaxation is obtained as long as passage through the LES and into the stomach is achieved. This has resulted in the Chicago classification basing the definition of achalasia on LES relaxation. Once impaired LES relaxation is identified on HRIM, three subtypes of achalasia are defined based on peristaltic data in the esophageal body.

Type 1 achalasia is associated with minimal esophageal body pressurization; type 2 achalasia with pan-esophageal pressurization, and type 3 is the spastic variant (Fig. 4.1). POEM is considered to have a significant advantage over either laparoscopic cardiomyotomy or pneumatic dilation for type 3 patients. The spastic variant may benefit from a long myotomy encompassing the entire length of the high-pressure zone which is often 10–15 cm [5]. As the proximal extent of the myotomy is not limited in POEM by the esophageal hiatus, as compared with a laparoscopic myotomy, POEM is rapidly becoming the procedure of choice in spastic achalasia patients.

Ambulatory pH Monitoring

Esophageal pH monitoring is performed either with catheter-based or wireless capsule-based Bravo pH testing systems. The pH tracing in achalasia shows a gradual downward slide in pH consistent with esophageal outflow obstruction and fermentation as compared with the intermittent drops of pH with normalization as seen in GERD.

Patients with nonrelaxing LES with esophageal peristalsis and prolonged episodic reflux events have a combination of both esophageal outflow obstruction and gastroesophageal reflux disease (GERD). These patients are not ideal POEM candidates, but should be treated with laparoscopic myotomy and fundoplication to address both issues.

Ambulatory pH testing is also useful in the postoperative period to diagnose GERD resulting from the myotomy. It is important to objectively look for GERD, as symptoms of heartburn and regurgitation are often not present in these patients due to compromised sensory innervation of the involved anatomy.

Expanded Indications

POEM has been utilized in the management of nonachalasia hypercontractility disorders of the esophagus. These disorders can be categorized into nonrelaxing LES disorders and esophageal body spastic disorders. The spastic disorders such as nutcracker esophagus and diffuse esophageal spasm are generally treated with extended myotomy akin to type 3 achalasia. The nonrelaxing LES disorders are approached like type 1 and type 2 achalasia by performing a 6–8 cm myotomy of the LES (2–4 cm) with a 2 cm margin proximally and distally as long as the condition treated is not associated with a mixed GERD/esophageal outflow presentation as mentioned above.

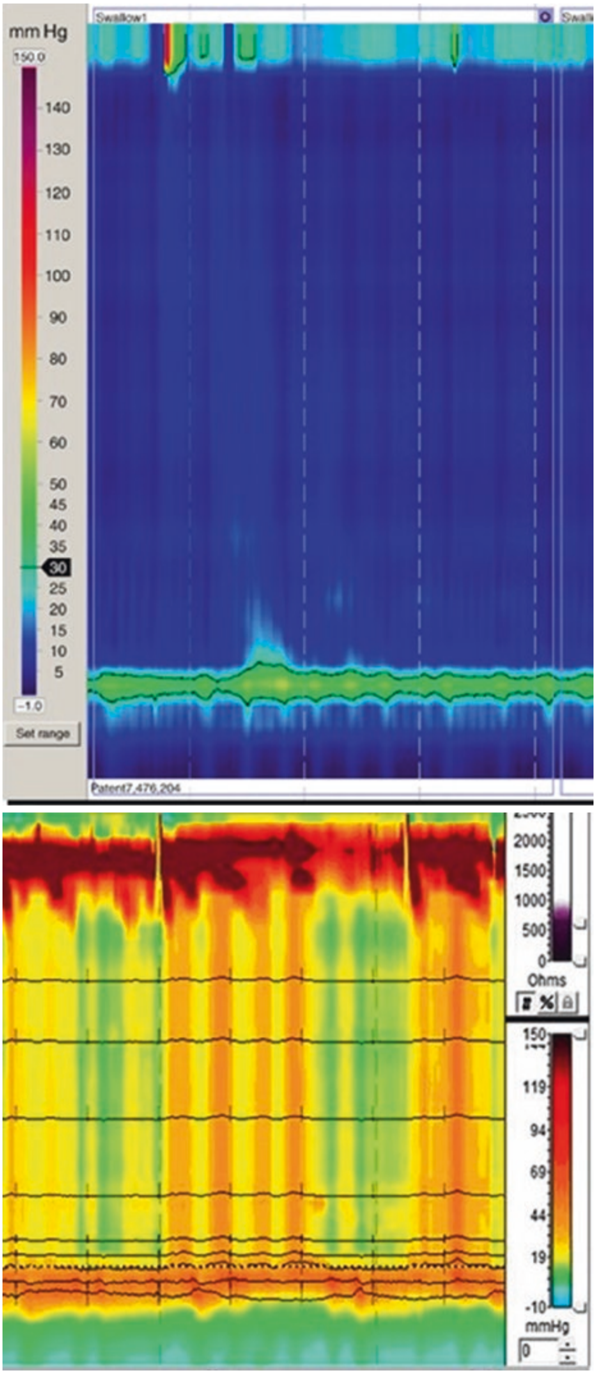

Fig. 4.1 Manometric topography of achalasia types 1, 2, and 3

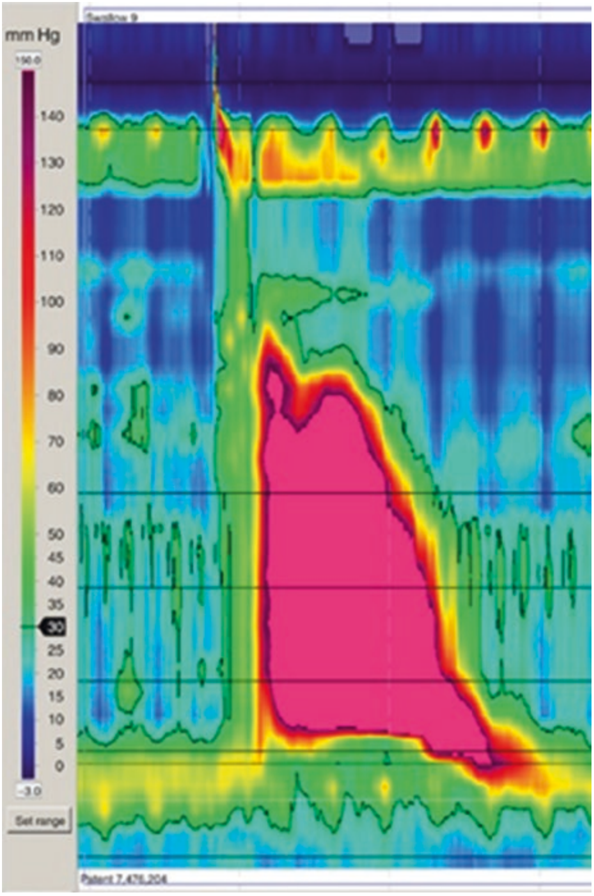

Fig. 4.1 (continued)

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Clinical Introduction of POEM for Achalasia: Technique

5

Hannah Y. Zhou and Jeffrey A. Marks

Abbreviations

CO_2	Carbon dioxide
EGD	Esophagogastroduodenoscopy
ERCP	Endoscopic retrograde cholangiopancreatography
GE	Gastroesophageal
LES	Lower esophageal sphincter
POEM	Peroral endoscopic myotomy

Introduction

This chapter details the technical aspects of the peroral endoscopic myotomy (POEM), including patient positioning, equipment setup, operative technique, and perioperative management. The equipment and setup were developed with the assistance of Dr. Haruhiro Inoue [1] and modified over the last several years during our experience at University Hospitals Cleveland Medical Center. Given the relatively recent development of the procedure, there are no evidence-based guidelines for the individual steps of the procedure. It should be disclosed that this chapter is presenting one suggested approach to the POEM, understanding that there are multiple varying techniques that have been successfully utilized around the world.

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Preoperative Patient Preparation

After a patient has undergone evaluation for achalasia and is deemed an appropriate candidate for the POEM, he/she undergoes preadmission testing if needed. The patient is placed on a clear liquid diet for 48 hours prior to the operation to minimize intraluminal debris at the time of POEM. There is usually some retained fluid and food in the esophagus that will require clearing prior to proceeding with POEM. Due to the higher incidence of esophageal candidiasis in patients with achalasia [2], the patient is given fluconazole 200 mg daily for 2 days preoperatively. Some institutions use nystatin in the preoperative setting [3, 4]. The patient is made nil per os at midnight before the operation.

Preoperative Operating Room Preparation

Before the patient is taken to the operating room, it should be verified that the required equipment is available and functioning properly. A high-definition single-channel diagnostic gastroscope with an instrument channel of 2.8 mm (GIF-H180, Olympus, Tokyo, Japan) is recommended for the case. The diagnostic gastroscope and a therapeutic Guardus overtube (US Endoscopy, Mentor, OH, USA) are adequate for the procedure, as shown in Fig. 5.1. Occasionally, when there is significant food debris in the esophagus, a single-channel or double-channel therapeutic gastroscope (GIF-2TH180, Olympus, Tokyo, Japan) can be used to facilitate removal. A carbon dioxide (CO_2) insufflator with a valve is obtained. The procedure strictly requires CO_2 because of the risk of causing prolonged pneumothorax, pneumomediastinum, and pneumoperitoneum with standard air insufflation.

The required supplies for each step are listed in Table 5.1 with ancillary equipment described in Table 5.2. A clear endoscopic cap that contains a hole is used to aid in dissection. It is fixed to the end of the gastroscope with tape—we use black electrical tape to prevent the cap from becoming dislodged in the submucosal tunnel. Methylene Blue is used to aid in visualizing and enhancing the tissue planes. We previously used Indigo Carmine, but that has since been discontinued at our institution. We currently use 125 mg of Methylene Blue with 2.5 mg of epinephrine in 500 cm^3 of 0.9% sodium chloride, used in 10 cm^3 increments. The dye is injected via an Articulator injection needle (US Endoscopy, Mentor, OH, USA) into the submucosa prior to creation of the longitudinal mucosotomy. Subsequent dye injections utilize a blunt-tipped endoscopic retrograde cholangiopancreatography (ERCP) cannula (G22093, Cook Medical, Bloomington, IN, USA) for the remainder of the case. The dissection in the submucosal plane is carried out with a triangle-tip knife (KD-640L, Olympus, Tokyo, Japan). The energy source for the knife is ERBE set on coag spray, effect 2, 60 W, cut effect 3 (ERBE, Marietta, GA, USA). A solution of 25,000 units of bacitracin in 250 cm^3 of 0.9% sodium chloride is made, and 60 cm^3 is used at the conclusion of the case to irrigate the submucosal space. Twenty standard endoscopic clips (Resolution Clip, Boston Scientific, Marlborough, MA, USA) are available to close the mucosotomy.

Fig. 5.1 Gastroscope with overtube (*arrow*) placed

Table 5.1 Essential supplies for the peroral endoscopic myotomy (POEM)

Step	Equipment
Preoperative setup	Diagnostic gastroscope with suction and surgical lubricant
	Therapeutic overtube
	CO_2 insufflator with valve
	Monitor positioned over patient's abdomen
	Step stools at patient's head
	Gowns and gloves
Patient setup	Sequential compression devices
Mucosotomy	Methylene Blue with 12 cm^3 syringe and injection needle
	Triangle-tip knife with ERBE on cut current
Submucosal tunneling	Cap with electrical tape
	Triangle-tip knife with ERBE on coag current
	Methylene Blue with 12 cm^3 syringe and ERCP cannula
	Flashlight to check distance
Myotomy	Triangle-tip knife with ERBE on coag current
Mucosotomy closure	Bacitracin solution in 60 cm^3 syringe
	Endoscopic clips

Table 5.2 Ancillary supplies for the peroral endoscopic myotomy (POEM)

Item	Purpose
Table with cover	Storage of supplies
Towels	Cleaning as needed
Basins	Storing solutions as needed
Scissors	For electrical tape
Cotton-tipped applicators	Cleaning the cap as needed
Blunt needles—1½″ 15 gauge	Injecting the bacitracin solution
Gauze	Grasping the gastroscope
Scratch pad	Cleaning the triangle-tip knife
Cap from three-way stopcock	Occluding the ERCP cannula side port
Marking pen with labels	Labeling the syringes/solutions
12 cm^3 syringe ×4	For Methylene Blue solution
60 cm^3 syringe ×2	For bacitracin solution
Dual Knife (KD-650U, Olympus, Tokyo, Japan)	Coagulating bleeding vessels
Hook Knife (KD-620UR, Olympus, Tokyo, Japan)	Coagulating bleeding vessels
IT Knife 2 (KD-611L, Olympus, Tokyo, Japan)	Coagulating bleeding vessels
Laparoscopic tray	Accessing the abdomen
Sterile prep	Use if abdominal access is required
Veress needle or 14 gauge angiocatheter	Decompressing pneumoperitoneum

Additional supplies available in the operating room include sterile preparation materials and a minor laparoscopic tray in the event the abdomen requires access. In the first several cases completed at this institution, a laparotomy tray was kept sterile and open in the operating room. After hundreds of cases and increasing expertise with the procedure, a laparoscopic tray is now placed unopened in the operating room. A 14-gauge angiocatheter or a Veress needle (Ethicon, Somerville, NJ, USA) is available to evacuate the pneumoperitoneum if it is noted during periodic examinations. A Coagrasper (FD-411UR, Olympus, Tokyo, Japan) is available if needed for hemostasis. An extra triangle tip knife is available as well.

The operating table is positioned such that the head of the bed is rotated slightly away from the anesthesia equipment to allow the anesthetist and the endoscopists adequate space for the operation. A monitor suspended from a boom is lowered to just over the patient's abdomen for all operators. If that is not possible, a split-leg bed is used with the monitor placed between the patient's legs. The table of endoscopic equipment (Fig. 5.2) is positioned to the patient's left side, based on the typical setup of the equipment in the operating room used for this procedure.

With regard to operating room staff, either endoscopy or operating room nursing staff can be involved with the POEM. The anesthesiologist involved is asked to follow and state airway plateau pressures and peak end-tidal CO_2 values every 5 min. If there are significant increases in either value, the operation is paused and the gastroscope passed into the native esophageal lumen to desufflate the

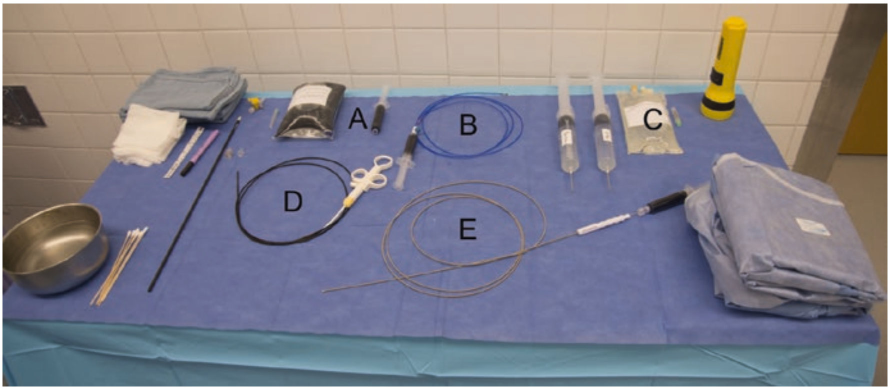

Fig. 5.2 Table with required instruments. *A*: Methylene Blue. *B*: Methylene Blue attached to endoscopic retrograde cholangiopancreatography (ERCP) cannula. *C*: bacitracin solution. *D*: triangle-tip knife. *E*: Methylene Blue attached to injection needle

stomach. Frequent communication is emphasized and is an essential aspect to a successful POEM.

Intraoperative Patient and Staff Preparation

After the patient is intubated in the operating room, the endotracheal tube is secured to the right side of the mouth. He/she will need to be under general endotracheal anesthesia for the entirety of the case. Preoperative antibiotics are used prior to mucosotomy—a second-generation cephalosporin is administered. Sequential compression devices are used for deep vein thrombosis prophylaxis. Subcutaneous heparin and urinary catheters are not routinely used, given the relatively short duration of the procedure, typically less than two hours. The left arm is tucked due to the placement of equipment on the patient's left side. The right arm can remain abducted. The patient's abdomen is exposed to periodically monitor for gastric distention and pneumoperitoneum. Figure 5.3 shows the patient on the operating room table, the position of the monitor, and the anesthesia equipment.

Step stools are placed at the head of the bed. For optimal comfort and positioning, the operating surgeon stands on the step stools a few steps away from the patient's head. The energy foot pedal is placed on one of the stools. He/she will be manipulating the gastroscope dials and instruments via the channel as well as controlling the energy foot pedal. The assistant surgeon supports and manipulates the gastroscope. He/she usually stands to the left of the operating surgeon and closer to the patient. An endoscopic assistant can stand to either side of the surgeons. We recommend the involvement of two surgeons for the procedure, generally an attending surgeon and a surgical fellow or chief resident at our institution, with additional assistants as needed.

Fig. 5.3 Patient and monitor positioning. The upper abdomen is exposed to periodically examine for distention

Operative Technique

The overtube is loaded onto the gastroscope, as shown in Fig. 1.1. The air is turned off and the CO_2 is turned on at this point. After passing the gastroscope into the esophagus, the overtube is advanced such that the end of the overtube is placed in the proximal esophagus. This allows the gastroscope to pass in and out easily with minimal trauma to the oropharynx and proximal esophagus. The esophagus is assessed and suctioned of all fluid and food debris. This may require the assistance of a double-channel therapeutic gastroscope. The stomach is assessed, taking care to examine the gastroesophageal (GE) junction on retroflexion to exclude neoplasms as a source for pseudoachalasia. The distance from the incisors to the GE junction is measured several times with the overtube in place. A flashlight is used to aid in seeing the marks on the gastroscope while the operating room lights are dimmed.

The gastroscope is removed, and the cap is secured to the end with an electrical tape. The hole in the cap is positioned at 6 o'clock to facilitate drainage of the water used to wash the lens. We found that electrical tape works well in keeping the cap firmly secured. The gastroscope is advanced again until it is approximately 14 cm from the GE junction. The distance from the GE junction and the anterior/posterior position on which to create the mucosotomy varies among operators. Some groups begin the mucosotomy at 6 cm from the GE junction [5], some use 7–10 cm [6], and some use 10–15 cm [7]. We choose to use 14 cm from the GE junction in the event

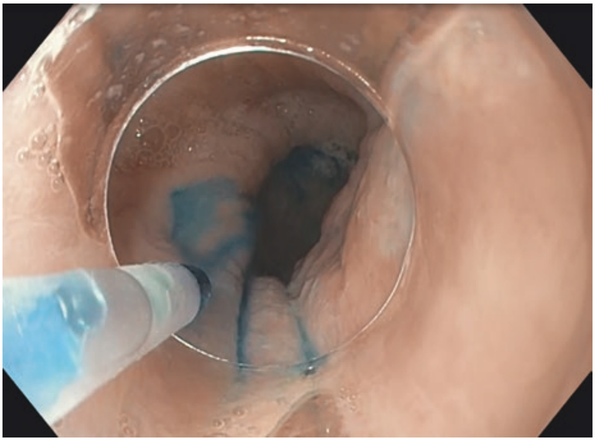

Fig. 5.4 Determining the orientation of the esophagus using the injection needle and Methylene Blue

there is mucosal damage while creating the proximal submucosal tunnel. To determine the anterior and posterior esophageal walls, a small volume of Methylene Blue is injected in the lumen with the Articulator injection needle, and the orientation is determined by gravity, as shown in Fig. 5.4. The anterior approach is thought to be technically easier than the posterior approach [1]. For patients who have not previously undergone myotomy for achalasia, we use a strictly anterior approach at the 12 o'clock position. Some groups create the submucosal tunnel at the 2 o'clock [1] or 3 o'clock [7] position in order to be aligned with the lesser curvature of the stomach. The angle of His, which is at approximately 8 o'clock with the patient supine, is avoided to prevent disturbance of natural antireflux mechanisms. For patients who have previously undergone Heller myotomy with fundoplication for achalasia, the patient is routinely positioned with several blankets under the right side, so that the adjusted 12 o'clock position is aligned with the lesser curvature of the stomach. However, another consideration for those who have undergone anterior myotomies via Heller or POEM is a posterior approach [8]. There are groups that routinely utilize the posterior approach for the POEM, with results similar to those using the anterior approach [9, 10]. There currently is no clear evidence that one approach is more effective for first-time myotomies. Once the position of the mucosotomy is determined, the Articulator injector needle is used to inject 8–10 cm^3 of the Methylene Blue solution into the submucosal space to lift the mucosa from the muscular layers, as shown in Fig. 5.5. A 2 cm longitudinal mucosotomy is created with the triangle-tip knife on the cut current, as shown in Fig. 5.6 [10]. The length of the mucosotomy is likely not significant, provided the gastroscope with the cap affixed can easily fit into the submucosal space, and the entire length of the mucosotomy is closed securely at the conclusion of the procedure. If the mucosotomy is created and is not long enough for the cap and endoscope to easily pass, the mucosotomy may inadvertently tear, resulting in a longer mucosotomy that will require closure.

The remainder of the dissection is carried out with the triangle-tip knife on the coagulating current setting (coag). We find that using Methylene Blue is extremely useful in delineating the mucosa from the submucosa, areolar tissue, and the muscular layers, as shown in Fig. 5.7. Dissection is carried out inferiorly to the tissue

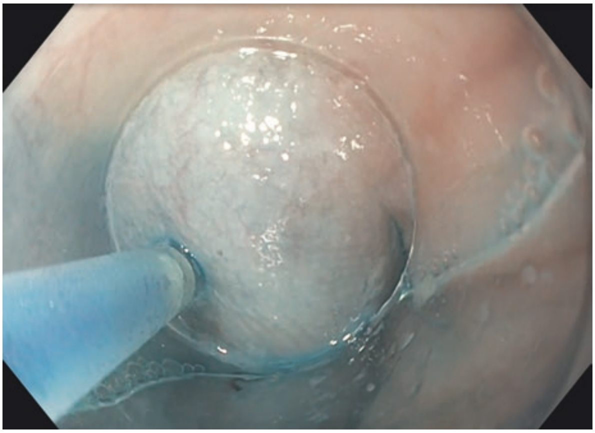

Fig. 5.5 Submucosal injection of the esophagus using the injection needle and Methylene Blue

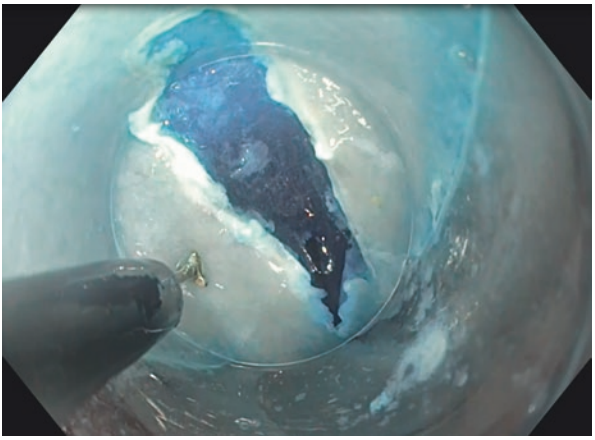

Fig. 5.6 Esophageal mucosotomy using the triangle-tip knife on the cut current

that is not stained with Methylene Blue. Approximately 5–10 cm^3 of the Methylene Blue solution is periodically injected into the submucosal space with the ERCP cannula. The gastroscope with the cap is deflected up and down to assist in separating the layers and to create tension on the areolar tissue, which is cut with the triangle-tip knife on the coag current, as shown in Fig. 5.7. Blood vessels encountered are coagulated to prevent bleeding and obstruction of view. Rarely, a Coagrasper is required to obtain hemostasis. The submucosal tunnel is created in its entirety prior to the myotomy. The stomach is periodically decompressed as some CO_2 from insufflation of the submucosal tunnel will distend the gastric lumen, resulting in respiratory changes as well as alteration in the angle of His, limiting creation of the tunnel beyond the lower esophageal sphincter (LES). Airway pressures and

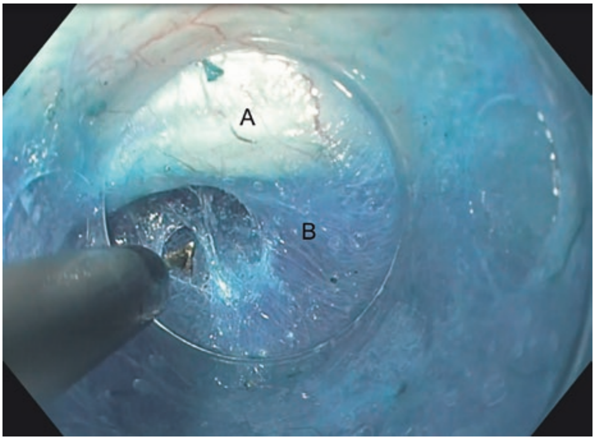

Fig. 5.7 Creation of submucosal tunnel using the triangle-tip knife on the coag current. *A*: muscle fibers. *B*: areolar fibers of the submucosa

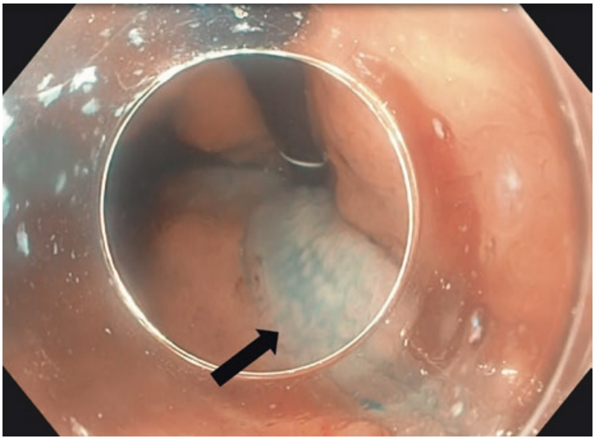

Fig. 5.8 Retroflexed view of the gastroesophageal junction. The Methylene Blue dye extends into the stomach by a few centimeters (*arrow*), indicating adequate length of the submucosal tunnel

end-tidal CO_2 are monitored, and significant changes, specifically increases, are noted and treated by periodic gastric desufflation, and rarely by peritoneal desufflation with an angiocatheter or Veress needle. The submucosal tunnel is continued caudally to an area 2–3 cm past the GE junction onto the gastric wall. During the periodic endoscopic examinations of the stomach, the dye is examined from the native esophageal lumen as well as the proximal stomach with retroflexion to determine if the dissection has been carried out past the GE junction. Most groups performing the POEM create the submucosal tunnel 2–3 cm onto the gastric cardia. A retroflexed view is shown in Fig. 5.8. Sling muscle fibers are usually noted in the transition from esophagus to stomach. Khashab et al. experimented with a new submucosal autotunneling gel, which in animal experiments decreased the total operative time to 28 min and did not result in any submucosal bleeding [11]. This may be considered for future studies in humans, although the experimental tunneling does end at the level of the LES and may not autotunnel through adhesions or areas of previous treatment.

After the submucosal tunnel has been completed, the myotomy is carried out. We typically divide the circumferential muscle layer and leave the longitudinal layer intact. A retrospective study by Li et al. showed similar intraoperative and perioperative complication rates between dividing just the circumferential layer versus dividing both the circumferential and longitudinal layers [12, 13]. Specifically, there was no increased risk of infectious complications in the patients who underwent full-thickness myotomies. The proximal border of the myotomy is offset from that of the mucosotomy to allow for fusion of the two layers after the conclusion of the procedure. The myotomy is started 2–3 cm distal to the inferior aspect of the mucosotomy. This distance can vary depending on the group performing the procedure [6]. The cap is deflected to stretch the divided circular fibers and create tension for the adjacent undivided circular fibers. The fibers are divided with the triangle-tip knife on the coag current. This is demonstrated in Figs. 5.9 and 5.10. This is continued until a few centimeters past the GE junction, onto the gastric wall and at the end of the submucosal tunnel. The sling fibers of the GE junction are divided as well. When the myotomy is complete, the native GE junction is assessed for patency. The gastroscope should very easily pass through into the stomach, and the GE junction should have a "gaping" appearance consistent with a Hill grade 2 valve. The tunnel is reassessed at this time and all bleeding is controlled with the triangle-tip knife on the coag current or the Coagrasper. There is usually minimal to no blood loss during this procedure. In our practice, 60 cm^3 of the bacitracin solution is used to irrigate the tunnel, although other investigators have performed POEMs without complications in the absence of irrigation solutions.

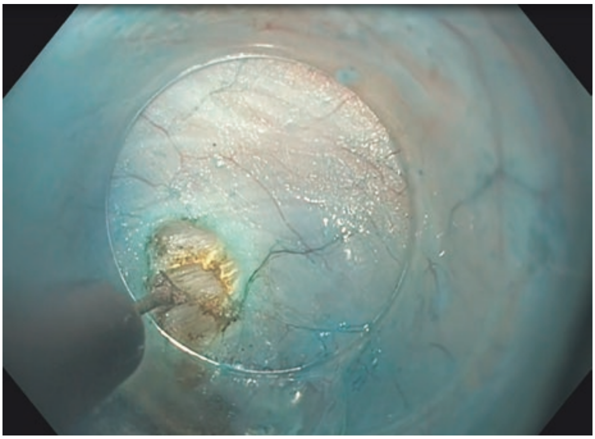

Fig. 5.9 Initiation of myotomy. The horizontally oriented muscle fibers are visible and will be divided by the triangle-tip knife on the coag current

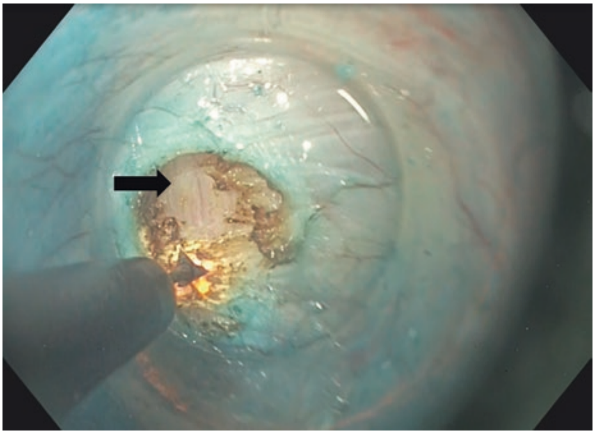

Fig. 5.10 Continuation of the myotomy. Note the vertically oriented longitudinal fibers (*arrow*), which are left intact

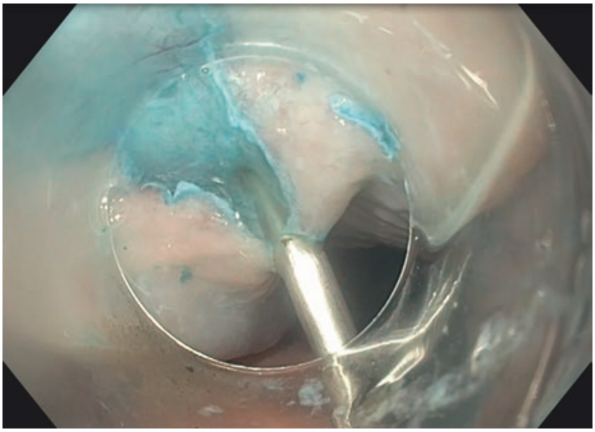

Fig. 5.11 Placement of first endoscopic clip on mucosotomy closure. The clip is placed at the distal aspect of the mucosotomy

The mucosotomy is then prepared for closure. An endoscopic clip is first placed at the distal aspect of the mucosotomy to aid subsequent clip placement (Fig. 5.11). Clips are then placed proximally using the previous clip as a tissue retractor, as shown in Figs. 5.12 and 5.13. Some groups have found better success with over-the-scope clips due to its larger jaw and ability to grasp a greater amount of tissue when compared to the clips (Ovesco, Endoscopy AG, Tübingen, Germany) [14]. Other investigators have also used endoscopic suturing devices for closure of the mucosotomy with good results (Overstitch, Apollo Endosurgery, Austin, Texas). The most important aspect of this part of the POEM is to ensure complete closure of the mucosotomy to prevent mediastinitis. After final examination of the mucosotomy, the overtube is removed while maintaining the gastroscope in the esophagus. The esophageal wall at the site of overtube placement is assessed while the gastroscope is slowly removed to assess for traumatic injury. The patient is then extubated and taken to recovery.

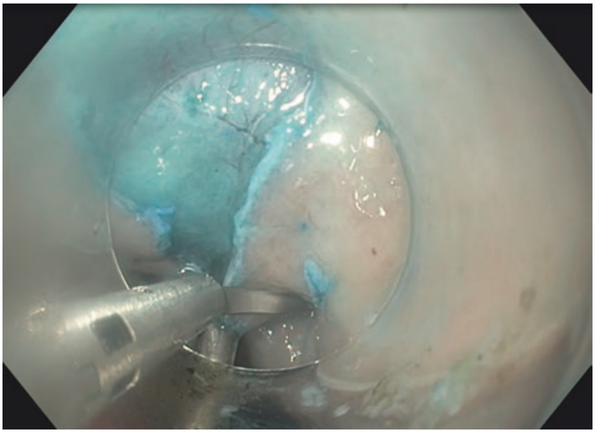

Fig. 5.12 Additional endoscopic clip placement, moving proximally with each subsequent clip

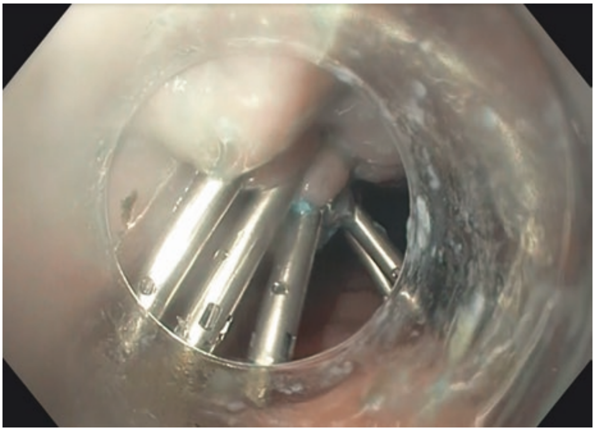

Fig. 5.13 Complete closure of the mucosotomy

In the recovery area, a chest X-ray can be obtained to assess for significant capnothorax, capnoperitoneum, or capnomediastinum. There may be a small amount of CO_2 in the thorax or abdomen. They usually do not require intervention unless the patient is symptomatic, as CO_2 should be readily absorbed. A significant capnoperitoneum can be decompressed in a sterile manner with an angiocatheter or a Veress needle. A significant and/or symptomatic capnothorax can be evacuated with a catheter or thoracostomy tube. Capnomediastinum or subcutaneous CO_2 is commonly seen but generally do not require additional intervention [15].

Mediastinitis is a rare complication and is likely prevented by a complete mucosal closure (Fig. 5.13). Bleeding complications can be evaluated with repeat emergent endoscopy and evaluation of the submucosal tunnel. Li's group reported an incidence of 0.7% of delayed bleeding, all successfully treated endoscopically with coagulation of bleeding muscular fibers as well as insertion of a Sengstaken-Blakemore tube (Fuji Systems Corporation, Tokyo, Japan) to assist with hemostasis [9].

The patient is placed on a strict nil per os diet and given intravenous analgesia and antiemetics as needed. He/she undergoes a contrast esophagram on the first postoperative day to assess for leaks and for flow of contrast across the LES. There may be slow passage through the LES due to postoperative edema. Provided the patient is not nauseated and no leak is demonstrated on imaging, clear liquids are initiated. Once he/she tolerates that well for 1–2 h, we advance the diet to full liquids. The patient is usually discharged on the first or second postoperative day on a full liquid diet for 1 week and a proton pump inhibitor. If the patient tolerates full liquids well, they advance to a soft diet after 1 week. He/she follows up with the operative endoscopist approximately 2 weeks postoperatively. The patient usually undergoes a timed barium esophagram 3 months postoperatively and an esophagogastroduodenoscopy (EGD) with a Bravo esophageal pH test (Given Imaging Ltd., Yokne'am, Israel) at 6 months postoperatively to evaluate for reflux.

Commentary

The POEM is a recently developed operation that is gaining in popularity for treatment of achalasia and other esophageal motility disorders. This can be carried out in the setting of previous botulinum toxin injections, balloon dilations, Heller myotomy, or POEM. Due to the novelty of the procedure, there are no current guidelines or data defining the number of supervised cases required before a surgeon can independently perform the POEM. At this institution, the learning curve was determined to be 15–20 cases. The fellows training to perform the POEM at our institution already have flexible endoscopy experience during training at Accreditation Council for Graduate Medical Education-approved general surgery residency programs. Additional studies confirm the 20-case learning curve for this operation [16]. Experience in laboratory and simulator settings will likely become mandatory for those interested in performing this procedure [7].

There are concerns with the POEM that should be considered when planning for an operation. There is no accompanying antireflux procedure given the endoscopic nature of the procedure. However, the extrinsic anatomy of the LES is not disturbed during a POEM. Most groups complete a pH study postoperatively to determine whether the patients have significant reflux. Patients may initially be medically managed and, in the future, be considered for an antireflux procedure. Long-term studies are necessary to determine the percentage of post-POEM patients who eventually require surgical intervention for reflux.

Additional prospective research is required to determine the optimal techniques in carrying out the procedure, including the anterior versus posterior approach, length of myotomy, and extent of myotomy. Given the low incidence of achalasia, most studies published thus far have had low patient volume [1, 7]. What is notable is that even with the variability of the procedure among different groups, most studies do show significant relief of symptoms in the short term. Recently, Inoue et al. published a series of 500 patients undergoing POEM with short-term and long-term follow-up showing that the procedure is a safe and reliable treatment option for achalasia [17].

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Technical Modifications for Motility Disorders: Dimensions of Dissection

6

Caitlin Houghton, Santiago Horgan, and Bryan Sandler

Introduction

Achalasia is an uncommon esophageal motility disorder defined as incomplete LES relaxation and aperistalsis of the esophageal body without a structural explanation (e.g., tumor, stricture) for these abnormalities [1]. The patients often present with dysphagia to solids and liquids. Symptoms may also include chest pain, heart burn, and regurgitation. There is no curative treatment that reverses the pathophysiology of achalasia and therefore treatment is geared towards optimizing the passage of solids and liquids through the gastroesophageal junction (GEJ.) [2]. Treatment options for achalasia traditionally involve both endoscopic and surgical options. Endoscopic options include injection of botulinum toxin to the GEJ and endoscopic balloon dilation [3]. Laparoscopic Heller myotomy (LHM) with partial fundoplication is the surgical gold standard for achalasia [4]. Campos et al. [3] performed a meta-analysis to look at treatment success of achalasia using 105 articles reporting on 7855 patients. Botox injections have a reported initial success in 78.7% of patients, but over time this percentage has declined to 40.6% of patients at 12 months, which correlates with the temporary effects of botox. Balloon dilation improved symptoms in 84.8% of patients at 1 month; however, by 1 year, only 58.4% of patients continued to have symptomatic improvement. Additionally, 25% of patients required repeat pneumatic balloon dilation. Treatment success with laparoscopic Heller myotomy was the highest with 89.3% of patients reporting improvement in symptoms. These patients continued to have relief at 1- and 2-year follow-up.

Peroral endoscopic myotomy (POEM) was introduced as an alternative treatment for achalasia in 2008. POEM emerged as a natural orifice transluminal endoscopic surgery (NOTES) procedure for the treatment of achalasia from a modification

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of endoscopic submucosal dissection for treatment of esophageal masses [5]. In 2007, Pasricha et al. [6] first described a novel approach for the endoscopic treatment of achalasia by creation of a submucosal tunnel followed by myotomy of the circular muscle of the lower esophageal sphincter in a porcine model. In 2008, Inoue et al. [7] performed the first successful POEM procedure in a human patient; then went on to report the first case series in 2010. Since this time, several studies have shown its efficacy and safety. Recently, several large studies have been published which confirm safety and efficacy [8–11]. In a recent meta-analysis, outcomes between POEM and laparoscopic Heller myotomy (LHM) are comparable with respect to complications, incidence of Gastroesophageal reflux, symptomatic recurrence rates, and other short-term outcomes [12], validating its use as an alternative to the current gold standard LHM.

Preoperative Evaluation

The preoperative work up of patients with achalasia is important for characterizing the disease, ruling out the presence of pseudoachalasia and to evaluate the anatomy of the esophagus and GEJ prior to surgical intervention [13, 14]. Once there is clinical suspicion for a diagnosis of achalasia, work up must include esophagogastroduodenoscopy (EGD), Barium swallow study, and manometry. The EGD is important to evaluate the esophageal anatomy and to ensure that there is no obstructive process such as a tumor near the GEJ which would lead to pseudoachalasia. Hallmarks on barium swallow include a dilated esophagus with a bird's beak appearance of the GEJ [15]. It is important, however, to recognize that the barium swallow will vary based on the type of achalasia. Manometry is the hallmark diagnostic study used to confirm failure of LES relaxation and aperistalsis of the esophageal body [16]. The Chicago classification then uses manometric measurement to classify achalasia into three subtypes, which will be discussed in the next section (Fig. 6.1).

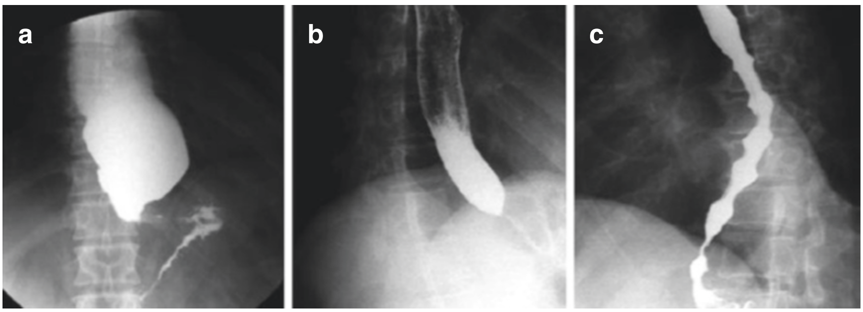

Fig. 6.1 Barium esophagram demonstrating each type of achalasia. Type 1 achalasia (**a**) with dilated esophagus and bird's beak appearance at the lower esophageal sphincter (LES). Type II achalasia (**b**) with non-dilated esophagus but narrowing at the LES. Type III achalasia (**c**) with corkscrew appearance from spasm in the esophageal body [17]

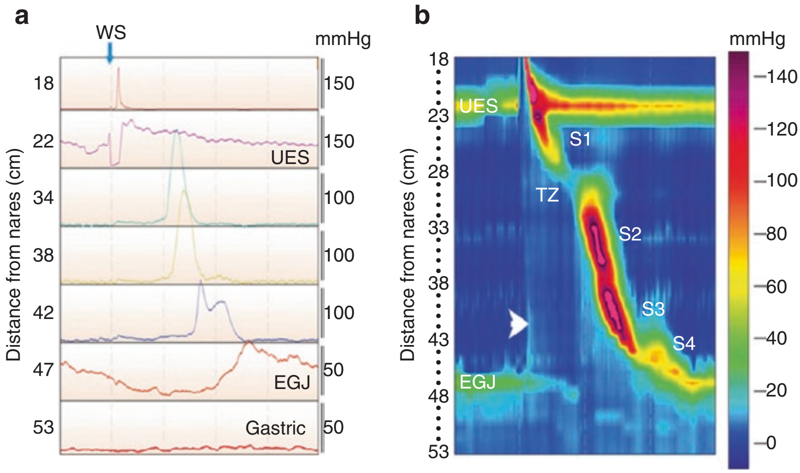

Fig. 6.2 Comparing conventional recordings of manometric pressure with the Clouse plot or esophageal pressure topography (EPT). Conventional manometry tracings came from catheters made with pressure sensors spaced at relatively wide intervals, usually at 3- to 5-cm. (**a**) Is a representation of conventional manometric recordings. (**b**) Is a representation of the widely adopted Clouse plot [20]

Manometry

While EGD and barium swallow are mandatory for the work up of achalasia, manometry is the gold standard diagnostic test [16]. Providers must have a thorough working knowledge of manometry in order to diagnose achalasia, classify patients according to the Chicago classification, and differentiate achalasia from other motility disorders such as diffuse esophageal spasm and jackhammer esophagus [18].

Manometry became possible in 1970s when Wyle Jerry Dodds and Ron Arndorger developed the first high-fidelity manometry system. In the 1990s, Ray Clouse and his colleagues developed high-resolution manometry (HRM) which included several modifications allowing for capture of the motor function from the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES) simultaneously with each swallow, giving us a complete spatial and temporal depiction of the esophageal motor function for the first time. HMR manometry also converts the pressure data to a topographical plot providing a pictoral representation of pressure waves called esophageal pressure topography (EPT) [19]. Colors are assigned to pressures, with high pressures represented by warmer colors (reds and yellows) and low pressures by cool colors (blues and greens) (Fig. 6.2).

High-Resolution Manometry Analysis

Analysis of HRM starts by noting the pressures of the upper and lower esophageal sphincters at rest. Then the pressure waves are analyzed during ten wet swallows taking note of three important characteristics: (1) The function of the lower esophageal sphincters during bolus transit, (2) Peristaltic integrity of the esophageal body, and (3) Distinguishing pressure patterns [1].

In order to evaluate the resting characteristics of the esophageal sphincters, a 30-s period during which no swallow occurs must be observed. The upper and lower esophageal sphincters are identified as zones of higher pressure depicted on the EPT as horizontal bands of color, as seen in Fig. 6.3. The location of the LES relative to the pressure inversion point (PIP) can indicate the presence of a hiatal hernia.

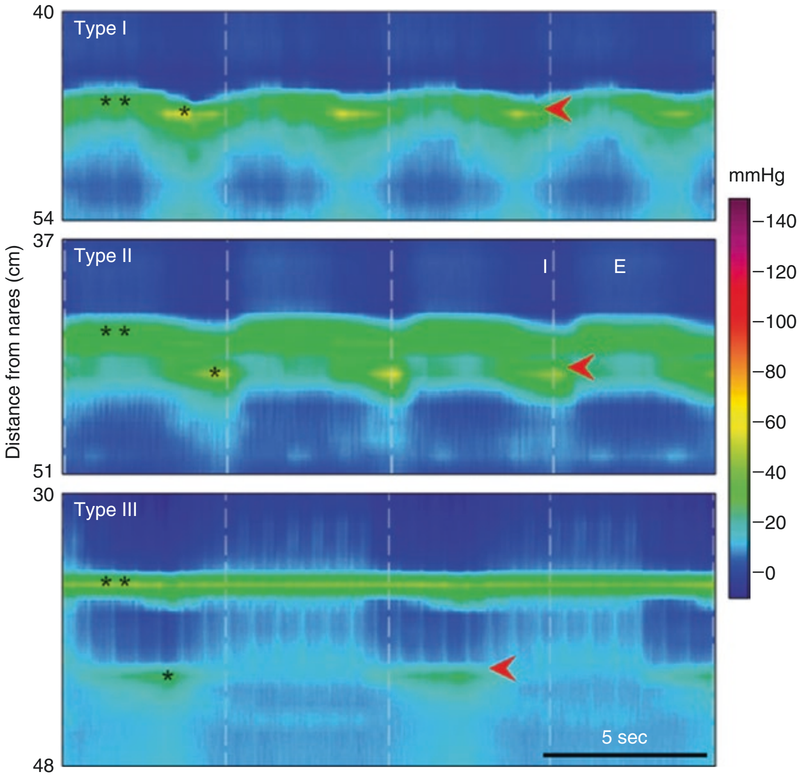

Fig. 6.3 Pressures recorded from the esophagogastric junction (EGJ) are a composite of tonic lower esophageal sphincter (LES) contraction (*double asterisks*) and cyclical crural diaphragm contraction with inspiration (*asterisk*). During inspiration, pressure decreases in the thoracic cavity, and during expiration it increases. The opposite is true in the abdominal cavity. The point at which pressure across the EGJ during inspiration becomes negative relative to intra-abdominal pressure is called the respiratory or pressure inversion point (PIP). It indicates the location of the crural diaphragm. The *red arrowhead* denotes the location of the PIP. The *top panel* is an example of a normal (Type I) EGJ in which the LES and crural diaphragm are coincident. In the *middle panel,* there is a small spatial separation (<2 cm) of the diaphragm from the LES, indicating a small hiatal hernia (Type II EGJ). In the *bottom panel,* there is a large spatial separation (>2 cm) between the crural diaphragm and LES, indicating the presence of a large hiatal hernia (Type III EGJ). *I* inspiration, *E* expiration [20]

The PIP identifies where the diaphragm separates the chest from the abdomen and usually is found close to the LES. Spatial separation of the LES and PIP in the EPT indicates a hiatal hernia [20].

Next, the manometry is evaluated during a series of at least ten wet swallows (5 mL water) to observe the function of the lower esophageal sphincter (LES). The integrated residual pressure (IRP) is a tool developed to measure the resistance to bolus movement across the EGJ. IRP greater than 15 mmHg indicates outflow obstruction at the GEJ, which can be due to achalasia or mechanical obstructions such as neoplasms or strictures [21]. Differentiation between achalasia and mechanical obstruction is determined by non-peristaltic esophageal pressurization patterns which indicate achalasia [1].

The peristaltic integrity is determined by the 20 mmHg isobaric contour line. It is a black line drawn around all parts of the EPT where the pressure is 20 mmHg. This threshold value of 20 mmHg is chosen because this is the peristaltic pressure required for normal bolus transit when the EGJ is functioning normally [1]. Peristaltic integrity is assessed by measuring gaps in the 20 mmHg contour line along the length of the esophagus.

The third step in analyzing EPT is to determine if there is a pressurization pattern. Pressurization is recognized as isobaric pressure along varying lengths of esophagus. It indicates bolus entrapment. Once all the swallows are analyzed with the tools described above, the data are used in the Chicago classification to make a diagnosis (Table 6.1).

Table 6.1 Esophageal pressure topography metrics utilized in the Chicago classification [16]

Pressure topography metrics	
Metric	Description
Integrated relaxation pressure (mmHg)	Mean EGJ pressure measured with an electronic equivalent of a sleeve sensor for four contiguous or non-contiguous seconds of relaxation in the 10-s window following deglutitive UES relaxation
Distal contractile integral (mmHg s cm)	Amplitude × duration × length (mmHg s cm) of the distal esophageal contraction >20 mmHg from proximal (P) to distal (D) pressure troughs
Contractile deceleration point [(CDP) (time, position)]	The inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating the tubular esophagus from the phrenic ampulla
Contractile front velocity (cm s^{-1})	Slope of the tangent approximating the 30 mmHg isobaric contour between P and the CDP
Distal latency (s)	Interval between UES relaxation and the CDP
Peristaltic breaks (cm)	Gaps in the 20 mmHg isobaric contour of the peristaltic contraction between the UES and EGJ, measured in axial length

All pressures referenced to atmospheric pressure except the integrated relaxation pressure (IRP), which is referenced to gastric pressure

The Chicago Classification

The Chicago classification was derived using the ManoScan™ (Sierra Scientific Instruments, Los Angeles, CA, USA) HMR system. It is important to note that measurements may vary based on HMR transducer used. The Chicago classification is indicated to classify primary motility disorders. It is not intended for post-surgical patients as procedures such as the lap band, fundoplication, and even balloon dilation alter manometry characteristics [16]. The Chicago classification uses five main metrics to classify motility disorders: (1) The integrated relaxation pressure (IRP), (2) Distal Latency (DL), (3) contractile deceleration point (CDP), (4) Peristaltic Breaks, and (5) Distal contractile Integral (DCI) [21]

1. The integrated relaxation pressure is a tool to measure the resistance to bolus movement across the EGJ. The HMR catheter is positioned to straddle the LES and measure pressures over a 6 cm segment. It calculates the maximum pressure along the 6 cm segment at each time point within a 10-s window. The 4-s IRP algorithm takes these pressures and averages the lowest pressures of any 4 s within the 10-s timeframe [21]. IRP greater than 15 mmHg indicates outflow obstruction at the GEJ [1].
2. Distal latency is a measurement of the time from start of swallow-induced UES opening to time of arrival of the esophageal contraction to the contractile deceleration point [21]. The lower limit of normal is 4.5 s.
3. The contractile deceleration point is defined as the inflection point along the 20 mmHg isobaric contour line where the propagation velocity slows demarcating the time at which esophageal peristalsis terminates and the LES begins.
4. Peristaltic breaks are gaps in the 20 mmHg isobaric contour of the peristaltic contraction between the UES and GEJ. According to the Chicago classification, small defects measure 2–5 cm and large defects are >5 cm [1]
5. Distal Contractile Integral is used to measure the robustness of peristaltic contraction in the smooth muscle esophagus. The DCI integrates pressure, distance, and time along the esophagus to describe the mean contractile amplitude of the small bowel esophagus, the length over which the contraction propagates, and the duration of the contraction. DCI >8000 is seen in symptomatic patients (Fig. 6.4).

The Chicago Classification can help classify esophageal motor abnormalities into four general groupings: Achalasia, esophageal outlet obstruction, abnormalities of esophageal motor function, and boarder line abnormalities, which are usually seen in asymptomatic patients.

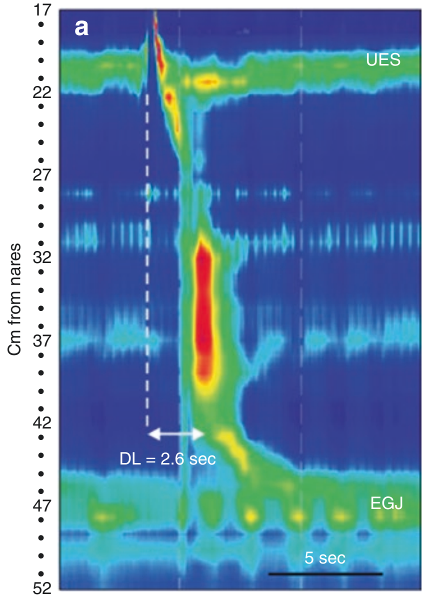

Fig. 6.4 Evaluation of peristalsis with the distal latency and contraction front velocity. (**a**) Distal esophageal spasm is characterized by normal lower esophageal sphincter relaxation and a short distal latency (<4.5 s). It is the arrival of the swallow-induced contraction in the distal esophagus too rapidly, producing a simultaneous contraction [20]

Achalasia

Achalasia is defined by failure of normal peristalsis and inadequate lower esophageal sphincter relaxation (integrated residual pressure (IRP) greater than normal 15 mmHg). This disorder is then subclassified into three subtypes based on analysis of esophageal pressure patterns, defined by the Chicago classification [21]. All types have failure of LES relaxation (IRP >15 mmHg), but have different pressurization patterns. Type I achalasia has no appreciable motor activity, type II is characterized by abnormal peristalsis with pan-esophageal pressurization following at least 20% of wet swallows, and type III exhibits premature spastic contractions with at least 20% of wet swallows [1]. The EPT patterns are shown in figure below. These subtypes account for the variability seen on barium swallow studies demonstrating the different pattern of achalasia as seen in Fig. 6.1 (Fig. 6.5).

It has been shown that patients with achalasia have different responses to therapy depending on their subtype. Type II is the strongest predictor of treatment response and type III is a negative predictor of response [1]. In the study by Pandolfino et al., type 1 patients underwent a mean number of 1.6 therapeutic interventions (botox, pneumatic dilation, or laparoscopic Heller myotomy) during a mean follow-up

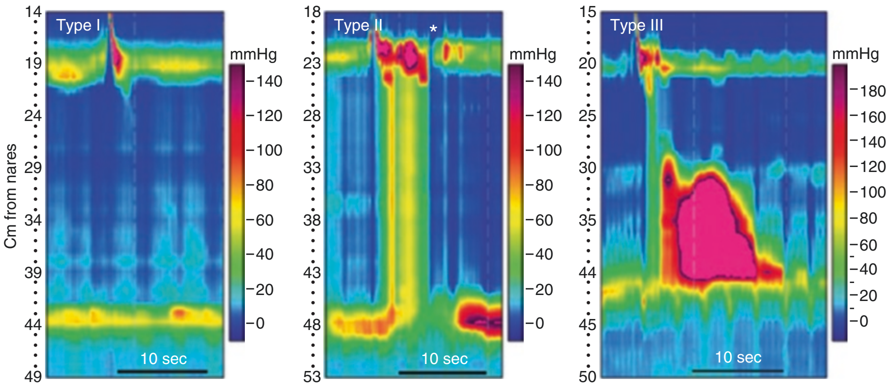

Fig. 6.5 Type I achalasia has no appreciable motor activity, type II is characterized by abnormal peristalsis with pan-esophageal pressurization following at least 20% of wet swallows, and type III exhibits premature spastic contractions with at least 20% of wet swallows [20]

period of 19 months and experienced a response rate of 56% after most recent therapy. Interestingly, these patients did significantly better with LHM than balloon dilation or botox. Type II patients underwent an average of 1.2 interventions during a mean follow-up of 20 months and had an excellent response to all three interventions with 96% success. Type III patients had the worst response to therapy despite having significantly greater number of therapeutic interventions during a mean follow-up period of 20 months. These patients had a 29% response rate. Although POEM was not available and therefore not included in this study, we can extrapolate that type I and type II achalasia patients may have better results than type III to POEM as well.

Outflow Obstruction

It is just as important to determine what is not achalasia as it is to recognize achalasia on manometry. Esophageal junction outflow obstruction is characterized by failed or incomplete opening of the EGJ, but is distinguished from achalasia by retained peristalsis in the smooth muscle esophagus [1]. Pressurization of the esophagus occurs due to the entrapment of the swallowed bolus between unyielding EGJ and peristaltic contractions. This pattern of manometry should trigger further evaluation with endoscopy to look for mechanical obstruction. When no mechanical obstruction is found, this EPT pattern might indicate a variant of achalasia, which often responds to achalasia treatment [1].

Esophageal Motor Dysfunctions

Diffuse esophageal spasm is an uncommon motor dysfunction characterized by at least 20% of wet swallows producing a short Distal Latency (DL) <4.5 s with

Table 6.2 The Chicago classification of esophageal motility [16]

Diagnosis	Diagnostic criteria
Achalasia	
Type I achalasia	Classic achalasia: mean IRP > upper limit of normal, 100% failed peristalsis
Type II achalasia	Achalasia with esophageal compression: mean IRP > upper limit of normal, no normal peristalsis, pan-esophageal pressurization with ≥20% of swallows
Type III achalasia	Mean IRP > upper limit of normal, no normal peristalsis, preserved fragments of distal peristalsis or premature (spastic) contractions with ≥20% of swallows
EGJ output obstruction	Mean IRP > upper limit of normal, some instances of intact peristalsis or weak peristalsis with small breaks such that the criteria for achalasia are not met
Motility disorders	[Patterns not observed in normal individuals]
Distal esophageal spasm	Normal mean IRP, ≥20% premature contractions
Hypercontractile esophagus (Jackhammer esophagus)	At least one swallow DCI > 8000 mmHg s cm with single peaked or multipeaked contraction

normal IRP. A short DL indicates early arrival of the esophageal contraction to the distal esophagus depicting spasm [1]. This differs from type III achalasia where the DL is also low but the IRP is high.

Hypertensive LES can overlap with other motility disorders, but the hallmark is LES pressures greater than 35 mmHg and failure or relaxation below IRP of 15 mmHg. This leads to a degree of outflow obstruction which can lead to high distal esophageal pressures or even spasms [22].

Nutcracker Esophagus is characterized by prolonged, hypertensive contractions in the context of normal propagation of the swallow waveform. DCI is over 5000 and the pressure wave shows vigorous contractions, with normal DL and IRB [22].

Jackhammer esophagus is represented by high mean contraction amplitude of the smooth muscle esophagus over the length the contraction propagates. This is measured by Distal contractile integral (DCI). DCI >8000 represents symptomatic contractile strength or jackhammer esophagus. DCI <5000 is associated with asymptomatic controls [21] (Table 6.2).

POEM Technique

Indications for POEM were initially limited to achalasia type I and II [7]; however, since then modifications of the technique have been described which allow its use for extended indications, which will be discussed in the next section. Inuoe et al. describe POEM using a mucosotomy at the 2 o'clock (anterior) position and performing the myotomy through the circular muscle layer leaving the longitudinal muscle layer intact [7]. Several centers now favor the 5 o'clock (posterior) position with a full thickness myotomy which includes the longitudinal muscle [23, 24].

POEM can be broken down into eight steps: (1) Submucosal injection is performed with saline stained with indigo carmine, (2) Mucosotomy is performed along the right anterior wall of the esophagus in the 2 o'clock position (anterior myotomy), (3) Submucosal dissection is performed with hybrid knife or triangle-tip knife, (4) Submucosal tunnel is extended into the gastric cardia and a completed submucosal tunnel is seen, (5) Myotomy is initiated 2–4 cm below the site of mucosotomy, (6) LES myotomy is performed, (7) Complete full thickness myotomy is seen on withdrawal of the endoscope, and (8) Mucosotomy closed with endoscopic clips [13].

POEM is performed under general anesthesia with the patient in the supine position. The specifics will be described based on the author's technique, which is consistent with anterior, circular muscle myotomy described by Inoue [7] and is currently the most favored technique among providers [25]. Specific modifications for situations such as achalasia type III, sigmoid esophagus, and diffuse esophageal spasm will be discussed in detail later in the chapter.

Mapping EGD

Using a high-definition upper endoscope (GIF-180, Olympus, Tokyo, Japan), an initial mapping esophagogastroscopy is performed. CO_2 is used for insufflation. The GEJ is identified and the distance from the top of the gastric folds to the incisors is recorded. The anterior and posterior orientations are defined using fluid meniscus, which will be posterior in the supine position and abdominal palpation.

Dissection of the Submucosal Tunnel

Once the mapping EGD is completed and orientation is confirmed, the endoscope is introduced with a transparent distal cap (M1-I 588, Olympus) fitted at its distal tip. An anterior location inside the esophageal lumen 10 cm above the GEJ and at the 2 o'clock position is chosen for initiation of the submucosal tunnel. Injection of normal saline mixed with indigo carmine into the submucosal space at the selected location is used to lift the mucosa away from the deeper muscular layers. An endoscopic injection needle (Carr-Locke 711811, US endoscopy, USA) is used for this injection (step1). A 2-cm mucosotomy is then made on the elevated mucosal cushion with a triangle-tip knife (KD-640L, Olympus), using electrocoagulation (ERBE, Tubingen, Germany) (Step 2). Once access to the submucosal space is achieved, the endoscope is advanced into the submucosal plane and dissected caudally to create a tunnel (step 3). Cautery and repeated injections of the saline mixture can be used to help define the planes and develop the tunnel. The tunnel is extended distally until the tip of the scope reaches 2 cm beyond the distance measured at the GEJ. The anterior orientation of the tunnel at the 2 o'clock position is confirmed by withdrawing the scope out of the submucosal tunnel and advancing through the lumen to the stomach. Using the retroflexed view presence of the blue-stained mucosa extending onto the lesser curvature confirms adequate length of the myotomy (step 4).

Myotomy and Closure

Now that the length and location of the submucosal tunnel are confirmed, the scope is reinserted into the tunnel to perform the myotomy. The circular muscle fibers are identified and selectively incised using the triangle-tip knife, beginning 6–8 cm above the GEJ (step 5). The myotomy is extended distally 2 cm below the GEJ. The muscle fibers are hooked and pulled into the distal cap to avoid injury to deeper issue (step 6). Once the myotomy is completed, the scope is once again inserted through the lumen to evaluate the immediate effects of the myotomy (step 7). The esophageal mucosal incision is then closed using endoscopic clips (HX-201LR--135.A, Olympus) (step 8) [26] (Figs. 6.6 and 6.7).

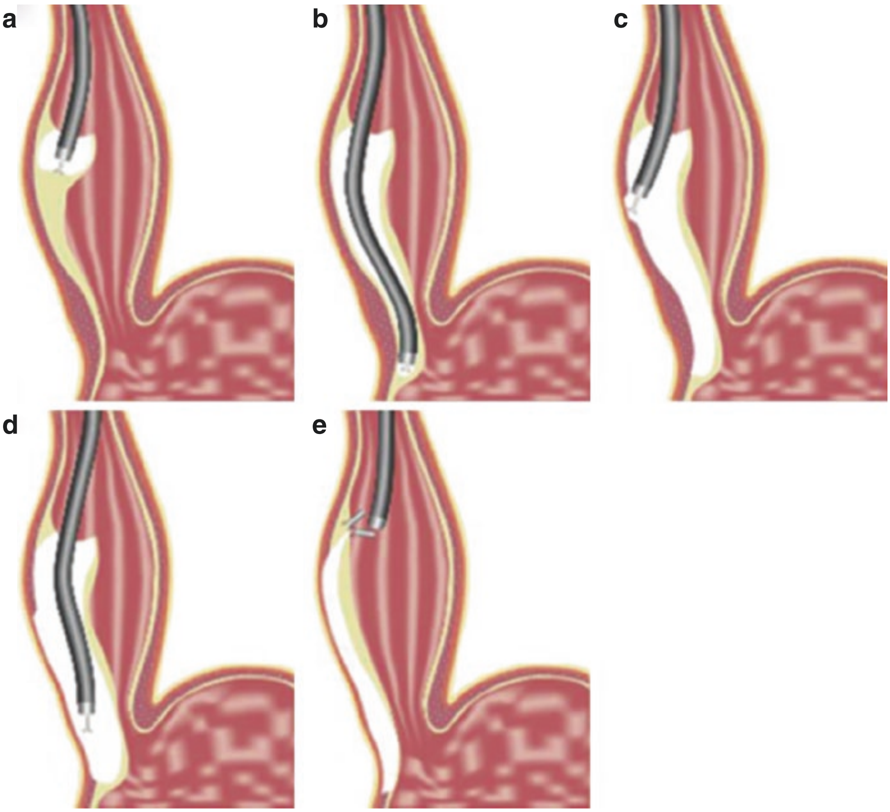

Fig. 6.6 Per oral endoscopic myotomy technique (S.N. Stavropoulos, Winthrop University Hospital, 2012). (**a**) Submucosal injection, and mucosal entry. (**b**) Creation of the submucosal tunnel. (**c**) Esophageal myotomy. (**d**) Lower esophageal sphincter and gastric cardia myotomy. (**e**) Closure of the mucosal incision

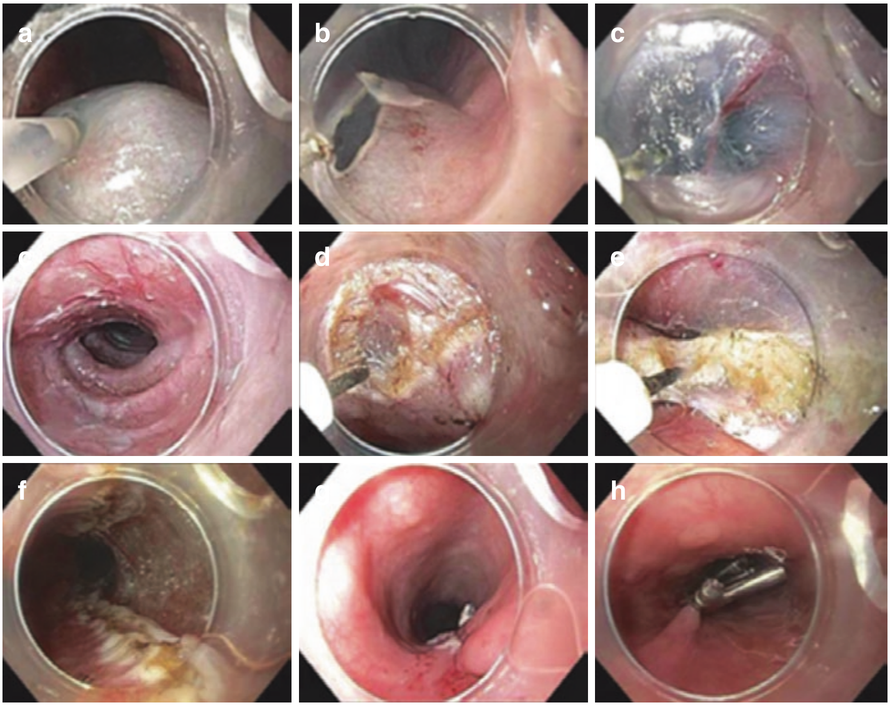

Fig. 6.7 Per oral endoscopic myotomy endoscopic steps. (**a**) Submucosal injection is performed with saline stained with indigo carmine. (**b**) Mucosotomy is performed along the right anterior wall of the esophagus in the 5 o'clock orientation. (**c**) Submucosal dissection is performed with hybrid knife. (**d**) Submucosal tunnel is extended into the gastric cardia and a completed submucosal tunnel is seen. (**e**) Myotomy is initiated 2 cm below the site of mucosotomy. (**f**) LES myotomy is performed. (**g**) Complete full thickness myotomy is seen on withdrawal of the endoscope. (**h**) Mucosotomy closed with an endoscopic suturing device. (**i**) Mucosotomy closed with endoscopic clips [13]

EndoFLIP

At the end of the procedure, the surgeon is able to immediately assess the adequacy and completeness of the myotomy by passing the endoscopic through the GEJ at the end of the procedure [27]. However, endoscopic measurements of adequate myotomy are subjective, often imprecise and may be affected by biases [28]. Some groups have looked at the use of EndoFLIP (Endoluminal Functional Lumen Imaging Probe) system to try to objectively confirm the adequacy of the myotomy [29, 30]. The EndoFLIP system (Crospon LTD. Galway, Ireland) uses impedance planimetry for real-time measurements of the EGJ diameter, through a specific balloon-tipped catheter [30]. According to these studies, EndoFLIP was found to be potentially useful during LHM, but no real benefit was proved in POEM Cases [29, 30]. It was thought to be confusing, time-consuming, troublesome, and costly.

Extended Criteria

The initial indications for POEM include the treatment of classic achalasia as described first by Inoue in 2010 [7]. However, due to the safety profile in his first five patients, he extended the criteria to include sigmoid esophagus. Since this time, there is data to support the use of POEM for the treatment of hypertensive motor disorders such as diffuse esophageal spasm and type III spastic achalasia, end-stage achalasia with sigmoid esophagus, patients after failed conventional treatments, children, and obese patients. Treating patients with these extended indications may require modification to the POEM procedure to tailor it to the specific condition.

Hypertensive Motor Disorders

Hypertensive motor disorders including diffuse esophageal spasm, hypertensive LES, Type III spastic achalasia, nutcracker esophagus, and jackhammer esophagus are rare, accounting for approximately 2% of all motility disorders [31]. These patients tend to present with both chest pain and dysphagia with chest pain as the prominent symptom rather than dysphagia [32], the prominent symptom of classic achalasia. In the international POEM survey, 11 of the 16 participating centers reported performing POEM for these extended manometric indications, accounting for 28% of the POEMs performed [25].

Diffuse esophageal spasm is differentiated from type III spastic achalasia on manometry by IRP greater or less than 15 mmHg. Both disorders have premature distal contractions (DL <4.5 s) [1]. Patients with both type III achalasia and DES have a longer LES [32]. As far back as 1960, it has been recognized that the best results after myotomy were achieved if the surgical myotomy was extended to the upper limit of the motility disorder [33–35]. For this reason, there was experimentation with thoracic approaches to achieve adequate length of myotomy [4, 18]. Due to the ease of creating a longer myotomy, POEM is thought to have an advantage over LHM in treating these diseases [36, 37]. Treatment of DES and type III achalasia with POEM should therefore include a longer myotomy (12–20 cm long) as the diseased segment is usually longer than that in classic achalasia [38]. Type III achalasia and DES are reported to respond worse to POEM, even when a longer myotomy is done, compared to patients with classic type I/II achalasia [9]. However, several sources report successful treatment of both conditions with 93% of patients having clinical improvement based on Eckardt scores [37, 39, 40], which is better than 70–85% success in this population with LHM [40].

The initial treatments for patients with nutcracker esophagus are with medications that target esophageal muscle relaxation such as calcium channel blockers (diltiazem) or nitrates in combination with acid suppression. Tricyclic antidepressants, specifically amitriptyline or imipramine, are also used. Botox injections and balloon dilations can also have some success, but need to be repeated [41]. Surgery has classically been reserved for patients who fail medical management. Interestingly, patients with hypertensive LES and nutcracker esophagus have the same or better reported outcomes than patients with classic achalasia when treated with POEM [25, 42].

Patients with Jackhammer esophagus have the least optimal results, with 70% of patients improving with POEM [31]. These patients also require a long myotomy, and although the worst responders, the majority of patients still have symptomatic relief with POEM [43].

In conclusion, POEM should be considered when treating patients with hypertensive motor disorders. The length of the myotomy should be tailored based on manometry, endoscopy, and upper GI studies to encompass the entire diseased portion of the esophagus [35]. POEM may have an advantage over LHM as greater length of myotomy is achievable in POEM.

End-Stage Achalasia

End-stage achalasia includes patients with severe sigmoid esophagus and mega-esophagus (diameter > 8 cm). Most published series exclude these patients as it is considered a relative contraindication. Inoue originally excluded sigmoid esophagus, but then included it as long as it was not considered severe [7]. Traditionally, esophagectomy has been recommended as primary treatment for sigmoid-type achalasia as it was believed that myotomy will not improve emptying [44, 45]. However, esophagectomy for sigmoid esophagus is associated with significant morbidity and mortality [46]. There are several studies that have demonstrated success with treatment of sigmoid esophagus with LHM and the morbidity and mortality profile is much less severe [4]. Therefore, LHM is gaining support as the primary surgical option. Adhesions after surgical intervention with LHM, however, can make subsequent esophagectomy more difficult. POEM does not "burn any bridges" as it results in minimal adhesions. Therefore, it could be considered as an initial treatment in these patients instead of LHM, with esophagectomy reserved for those with inadequate clinical response [2].

Hu et al. [47] reported on a series of 32 consecutive patients with end-stage achalasia treated with POEM. The patients were subdivided based on descriptions by Inoue et al. [7] into sigmoid type I (S1) and sigmoid type II (S2) achalasia. They are subdivided based on tortuosity seen on CT scan. In S1, the esophagus is significantly dilated and tortuous, but only a single lumen is seen on CT scan. In S2, the esophagus is very dilated and severely tortuous with U-turns in a proximal direction resulting in a double lumen identified on CT scan (Fig. 6.8).

The degree of dilation was also determined and classified into three grades according to maximum diameter of the esophageal lumen on barium swallow or CT scan: Grade 1 (<3.5 cm), grade II (3.5–6 cm), and grade III (>6 cm) [47]. In this case series, 29 patients had S1 and 3 patients had S2 type achalasia. Submucosal

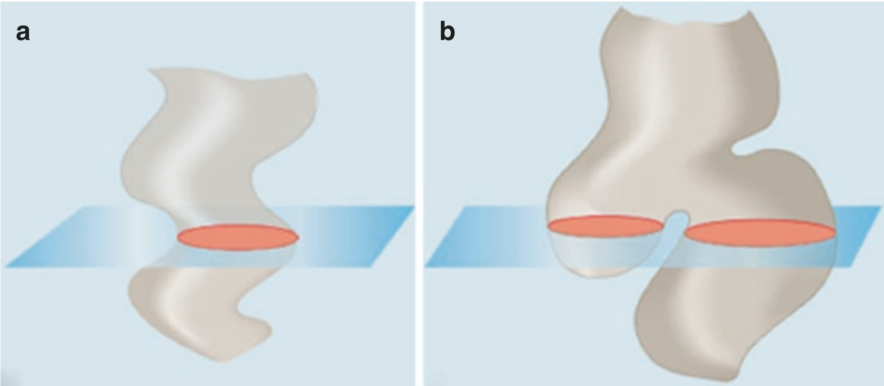

Fig. 6.8 Subclassification of sigmoid-form achalasia. (**a**) Sigmoid type I (S1): the esophagus is significantly dilated and tortuous, but only a single lumen is seen on any computed tomography (CT) slice. (**b**) Sigmoid type II (S2). The esophagus is very dilated and tortuous and some CT slices show a double lumen

tunneling was described as difficult and time-consuming in these patients as it was hard to maintain the direction of the submucosal tunnel. A posterior myotomy is recommended for this reason as the spine can be used as a steady landmark and allows for a lesser degree of tortuosity. A standard length myotomy (average 10 cm) was made and there was a preference for full myotomy dividing both circular and longitudinal muscle fibers as it was felt to give superior results.

Lv et al. [48] reported a series of 23 patients, 19 with S1 type achalasia and 4 with S2 type achalasia. All 23 patients were treated with a 7–10 cm full thickness posterior myotomy. An additional modification was made by starting the myotomy 0–1 cm below the mucosotomy instead of 2–3 cm below in order to shorten the distance needed to travel in the challenging submucosal plane. Treatment success defined as postoperative Eckardt score of three or less was achieved in 95% of patients. A change in the morphology of the esophagus was reported in a majority of patients which included curvature straightening and diameter reduction. The major complication was subcutaneous emphysema or capnomediastinum which was self-resolving in all but one case which required deflation via subcutaneous puncture.

In summary, end-stage achalasia is challenging to treat with POEM and may include longer OR times, but when done successfully, has shown safety and efficacy. A posterior myotomy is recommended as this may lead to the straightest submucosal tunnel. A full thickness myotomy may allow for better results; however, there is no reported study to show that a circular muscle myotomy is an inferior approach. A shorter distance between mucosotomy and start of myotomy may allow for a shorter submucosal tunnel. There is more experience with S1 type achalasia than S2 type achalasia, which may present even more challenging anatomy to navigate. POEM in sigmoid-type achalasia should be attempted with caution and only by experienced providers (Fig. 6.9).

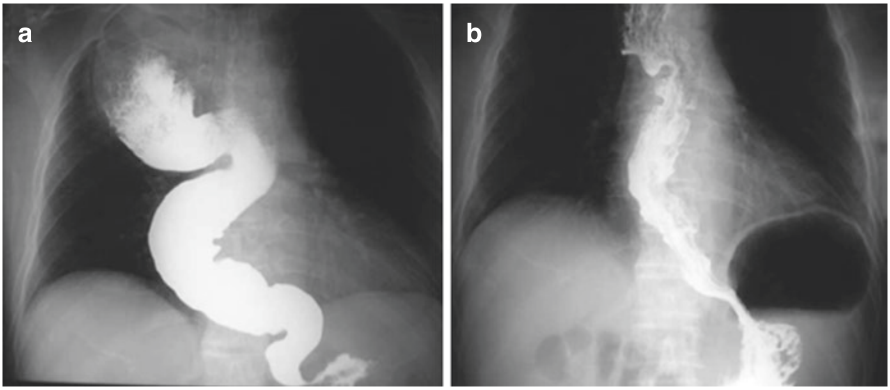

Fig. 6.9 Pretreatment and posttreatment barium esophagogram. (**a**) Before POEM, esophagogram indicated type S2 achalasia with a typical beak sign and U-turn. (**b**) The shape of the esophagus improved after POEM and the passage of the contrast agent was remarkably improved. *POEM* peroral endoscopic myotomy [48]

Previous Endoscopic and Surgical Interventions

Traditional treatment for esophageal motility disorders ranges from endoscopic botox injection or balloon dilation to laparoscopic or open surgical myotomies. The success rate of pneumatic dilation and surgical myotomy for treatment of achalasia is comparable at 90%; however, 10–20% of patients will go on to have recurrent symptoms due to treatment failure or disease progression [3]. The treatment option for failure after endoscopic treatment is currently surgical myotomy [49]; however, treatment after failed surgical myotomy is controversial and includes pneumatic balloon dilation [50], re-do myotomy [51], and esophagectomy [52]. Experience shows that performing a re-do Heller myotomy in the setting of previous endoscopic therapy or surgical myotomy proves to be technically challenging and associated with higher complication rates and conversion to open surgery [53–55]. Submucosal fibrosis is a common consequence of balloon dilation and botox injection and can make subsequent dissection difficult. As a result, mucosal perforation is not uncommon during Heller myotomy after endoscopic procedures. In addition, intraoperative and postoperative complications have been reported to be twofold or higher after previous Heller myotomy [56, 57]. As POEM becomes more common, it is important to understand how it prevails in situations of recurrent symptoms after previous interventions. We will discuss several studies that looked specifically at safety and outcomes of POEM after previous surgical or endoscopic interventions.

The first study conducted by Orenstein et al. [58] is an evaluation of a database collected prospectively of POEM procedures performed by two surgeons at a single institution between 2011 and 2013. Forty patients received a POEM procedure, of which 16 patients (40%) had prior interventions. Six had prior Botox injections, four had balloon dilations, three had both Botox and dilations, and three received prior laparoscopic Heller myotomy (two with Dor fundoplication). Anterior POEM at the 12 or 2 o'clock position was performed for all patients in the prior intervention group. This study showed no significant difference between the current therapy and the previous therapy group with respect to operative time, perioperative complications, or treatment success.

Sharata et al. [42] looked specifically at patients with prior endoscopic treatment. Twelve patients with previous endoscopic intervention were compared to 28 patients with no previous intervention between 2010 and 2012. Again, this study showed no difference in operative time, perioperative complications, or symptomatic relief. Modifications from the standard anterior POEM was not mentioned in either of these studies. However, it has been suggested that, for patients with prior Heller myotomy, the submucosal tunnel should be made at the 5 o'clock position (posterior myotomy), thus avoiding area of maximal scarring during POEM [24, 57, 59].

In summary, POEM is safe and leads to comparable outcomes as traditional interventions for patients with recurrent symptoms after failed endoscopic and surgical treatments and therefore should be added to the armamentarium for treating these patients. Considering modification to a posterior myotomy is recommended.

POEM in the Pediatric Population

Currently, treatments for pediatric achalasia can be endoscopic or surgical. Endoscopic treatments are unlikely to provide long-lasting resolution of symptoms, with most patients relapsing warranting repeated procedures and inevitably necessitating surgical myotomy [60]. It has been suggested that young age is an independent negative predictive factor for successful clinical outcome after balloon dilation [61]. LHM is therefore the treatment of choice in the pediatric population.

Chen et al. [62] report on a series of POEM done in 27 pediatric patients. The technique used was almost identical to that used in adults; however, due to the shorter physiologic length of the esophagus, sometimes a shorter myotomy length is made (5–7 cm) ensuring at least 2 cm onto the cardia. The group preferred the posterior full thickness myotomy; however, anterior, circular muscle myotomy has also been successful [63, 64]. Nineteen percent of these patients had mucosal perforations requiring clipping during the procedure, which did not result in any adverse outcomes. GERD was a significant concern with 19% having symptomatic GERD, which does not differ significantly from that seen with patients treated with LHM [65].

In conclusion, myotomy is safe and effective in children as young as 3 years old [64]. Due to shorter esophageal physiology, a shorter myotomy (5–7 cm) may be required. GERD is a critical concern in these patients and must be monitored closely.

POEM in the Obese Population

Achalasia in the morbidly obese population is rare (incidence 1%) [66] and there is not much reported experience in treating these patients since most studies to date exclude patients with BMI >40. Successful treatment of achalasia in a patient with a history of roux-en-y gastric bypass using the standard anterior, circular muscle myotomy has been described [67]. It will take more experience with POEM in this population to fully understand its efficacy.

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POEM Contraindications and Pitfalls

7

Rani Modayil and Stavros N. Stavropoulos

Introduction

Peroral endoscopic myotomy (POEM), as the first Natural Orifice Transluminal Endoscopic Surgery (NOTES) procedure to gain widespread clinical success, represents a novel type of minimally invasive surgery outside the safe confines of the gastrointestinal lumen, and outside the comfort zone of most endoscopists, particularly gastroenterologists, who are unfamiliar with the hazards of surgery in their day-to-day practice. As such, it carries a much higher risk of severe or life-threatening complications than traditional therapeutic endoscopy. Furthermore, it requires a high level of skill as it attempts to replicate the results of a time-honored laparoscopic operation, the Heller myotomy, with much more basic tools than are available to the laparoscopic surgeon. It follows that in order to maximize efficacy and safety in this technically complex and risky undertaking, the operator needs to be acutely aware of potential pitfalls along with preventive and corrective strategies to address such pitfalls. These strategies consist of "tips and tricks" painstakingly acquired by pioneers and early adopters at high-volume centers, often via an arduous trial-and-error process. Unfortunately, this type of experiential practical

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information is hard to come by in the peer-reviewed literature which focuses heavily on evidence-based aggregate data to the point of near exclusion of empirical data. We hope that this chapter will help address this knowledge gap particularly for POEM operators early in their learning curve. We review the scant information regarding POEM pitfalls and contraindications gleaned from the literature and augment it with pitfalls, practical tips, and advice from our own extensive experience derived from the largest Western single-operator series at well over 300 POEMs spanning a period of 7 years.

POEM Contraindications and Pitfalls in Patient Selection

POEM Contraindication Due to Comorbidities

An international survey of 16 pioneering POEM centers in 2012 (including all high-volume centers at that time) used 17 brief clinical scenarios illustrating comorbid diseases of varying severity to poll respondents on whether POEM was contraindicated in each of these clinical scenarios. A majority of respondents considered POEM to be relatively or absolutely contraindicated in the following scenarios [1]:

1. Extensive esophageal wall fibrosis due to prior irradiation of the esophagus/mediastinum or extensive endoluminal mucosal resection or ablative therapy (e.g. endoscopic mucosal resection, radiofrequency ablation, photodynamic therapy).
2. Severe pulmonary disease (e.g. extensive bullous disease or prior lung resection, home oxygen dependence, ASA class III, FEV1 or FVC $< 70\%$, $pCO_2 \geq 45$, or $pO_2 < 75$).
3. High risk of major intraoperative bleeding due to uncorrectable coagulopathy (e.g. baseline platelet count <30,000 due to disorders such as ITP, myelodysplasia) or cirrhosis with portal hypertension (even in the absence of gastric or esophageal varices).

Another potential contraindication to POEM is severe cachexia due to malnutrition. In these patients, poor immune function and tissue healing as well as thin and structurally unsound mucosal and submucosal layers may complicate POEM. In such patients, we defer POEM until optimal nutritional status can be achieved via feeding tube alimentation.

Patients in Whom POEM May Not Represent Appropriate Therapy

1. *Patients with poorly defined and/or treatment-naïve nonachalasia esophageal motility disorders.* In the IPOEMS survey of 16 pioneering centers, surprisingly, nearly one quarter of the 841 POEMs reported was performed for nonachalasia disorders [jackhammer/nutcracker esophagus, hypertensive lower esophageal sphincter (LES), and distal esophageal spasm (DES)]. Most cen-

ters applied POEM almost exclusively to typical achalasia patients, whereas a small number of centers such as The Oregon Clinic and Shanghai reported over 25% of POEMs performed to treat nonachalasia conditions [1]. Several studies have demonstrated reasonable efficacy of POEM for spastic nonachalasia conditions but, nevertheless, inferior efficacy compared to that seen in POEM for classic achalasia [2–4]. POEM when applied injudiciously to such patients may not provide relief and may even exacerbate the patient's symptoms [5]. Therefore, in nonachalasia spastic disorders, it is prudent to reserve myotomy for patients refractory to pharmacological therapy options such as proton pump inhibitors, calcium channel blockers, phosphodiesterase inhibitors, pain modulators, or botulinum toxin injections [6]. A treatment plan for these poorly understood disorders should be developed within an expert multidisciplinary team including motility specialists and surgeons. In patients refractory to pharmacological therapy that are being considered for POEM, detailed discussion with the patient regarding outcomes and expectations is important prior to proceeding with POEM.

2. *Previously myotomized achalasia patients in whom LES-related outflow obstruction may not be the cause of symptom relapse or persistence.*

   Symptom persistence after Heller myotomy is most often due to inadequate myotomy usually due to inadequate extension through the gastroesophageal junction (GEJ) and cardia, especially if the myotomy was performed by a low-volume operator. In these patients, POEM is an extremely effective therapy [7–10]. Probably, the best predictor of POEM success in this setting is a high pre-POEM LES pressure, which has also been reported as one of the best predictors of laparoscopic Heller success [11, 12]. During POEM, the sphincter high-pressure zone can be identified very easily and precisely and effectively ablated.

   Less commonly, a failed Heller myotomy may be due to a tight fundoplication. It is difficult to distinguish a tight fundoplication from residual sphincter. Amyl nitrite enhanced barium esophagram has been used anecdotally in this setting. It has been theorized that improved transit after administration of amyl nitrite (a LES relaxant) would be consistent with inadequate myotomy, whereas the absence of such an effect would be consistent with a tight fundoplication. However, this technique has not been adequately studied and, in practice, clinical judgment needs to be applied. When significant uncertainty remains, POEM can in some cases be performed empirically prior to attempting a take-down of the fundoplication since it may be less invasive than this type of surgical revision.

   One needs to be cautious in patients who display a cycle of initial excellent durable response to therapy including Heller myotomy or aggressive pneumatic dilation only to be followed by late relapse of symptoms years later. Unlike patients with persistence of symptoms signifying a failed Heller discussed above, in many of the patients with late relapse of symptoms, the relapse is not due to LES-related outflow obstruction and will not respond to POEM. Detailed evaluation including timed barium esophagram, pH studies, and endoscopy is very important to exclude conditions for which POEM would not be appropriate therapy. Such conditions include GERD, peptic stricture, or end-stage failed esophagus:

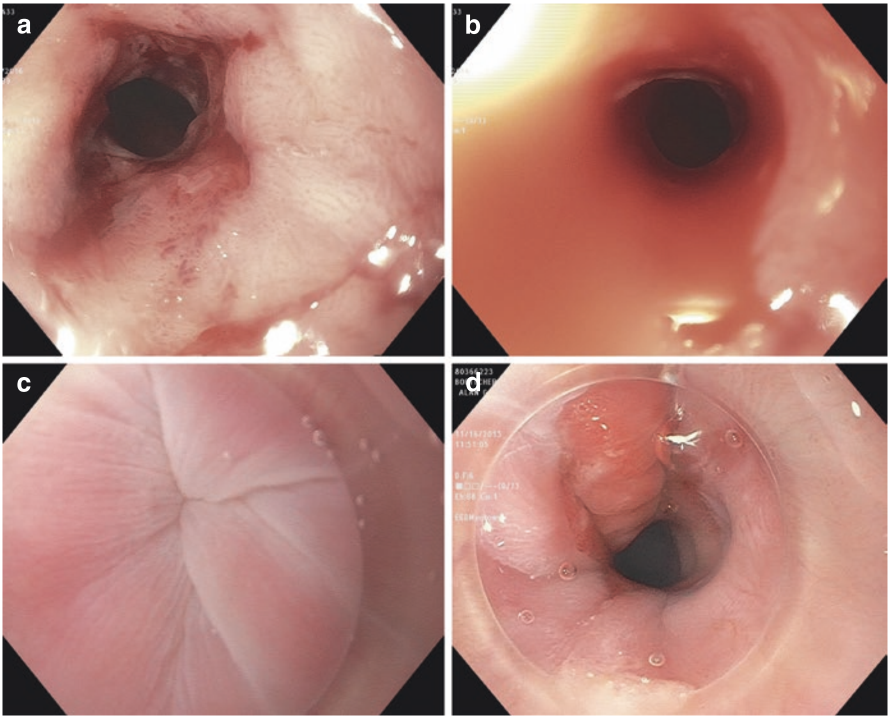


Fig. 7.1 (**a**, **b**) Demonstration of luminal narrowing secondary to peptic strictures after Heller myotomy. (**c**, **d**) Demonstration of luminal narrowing secondary to achalasic sphincter

(a) GERD in postmyotomy achalasia patients may manifest with symptoms such as globus sensation, dysphagia, regurgitation, and chest pain that may be indistinguishable from classic achalasia symptoms. On EGD, one often encounters erosive esophagitis and a patulous LES. If endoscopic findings are equivocal, pH studies performed off-medication can help confirm presence of GERD. Appropriate treatment would include an antacid regimen or partial fundoplication rather than POEM which would further exacerbate GERD symptoms.
(b) Peptic strictures due to long-standing GERD resulting from effective initial therapy for achalasia may cause dysphagia and may mimic "residual sphincter" on barium esophagram. However, on endoscopy, peptic strictures can be easily identified as unyielding firm tight stenoses quite different from the short elastic high-pressure zone of a nonrelaxing LES associated with achalasia that yields to scope insertion (Fig. 7.1).
(c) A failed, end-stage esophagus can be diagnosed by the following findings on barium esophagram, endoscopy and high resolution manometry: On

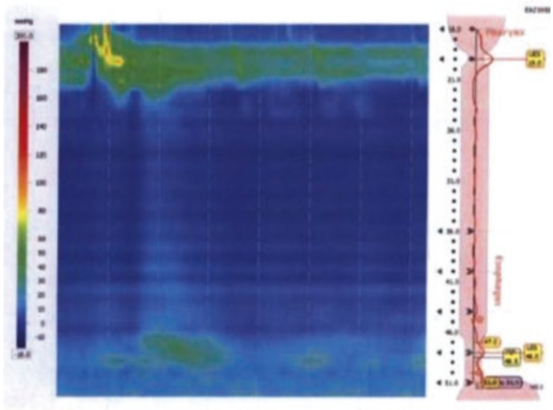


Fig. 7.2 Patient status after prior remote Heller with good initial response now referred for possible POEM for recurrent dysphagia and poor emptying on barium. HRM shows minimal residual LES pressure (mean LES pressure of 9.6, residual pressure of −1.2!) and common cavity between the stomach and esophagus. This patient would not benefit from POEM and should be considered for possible esophagectomy

endoscopy, findings include the presence of significant dilation of the esophageal body and patulous GEJ. On barium esophagram there will be marked esophageal dilation, with the absence of the "bird-beak" sign. On high-resolution manometry/impedance, findings include lack of any contractile activity, very low LES pressure, very low esophageal body pressure with equalization of esophageal and gastric pressures and no bolus transit on impedance (Fig. 7.2).

3. *Achalasia in the setting of prior bariatric surgery.* Patients that have undergone bariatric surgery such as gastric bypass or sleeve gastrectomy may suffer from idiopathic achalasia or achalasia secondary to the bariatric surgery itself [13]. POEM has been anecdotally reported to be efficacious in patients that have had prior bariatric surgery. However, based on our preliminary unpublished experience, some caution is indicated. The excellent efficacy of POEM in disrupting the LES (which underlies its dramatic and durable relief of dysphagia and, on the downside, clinically relevant GERD in approximately 30–40% of patients) may be a cause of concern in patients with prior bariatric surgery. POEM may significantly increase the severity of GERD in sleeve patients and may facilitate regurgitation from the surgically restricted small-capacity gastric pouch in bypass patients and the high-pressure narrow stomach in sleeve gastrectomy patients. In these patients, severe GERD or regurgitation can diminish any post-POEM quality-of-life improvement from dysphagia relief. Effective management of such symptoms can be difficult since surgical revision or antireflux procedures are limited in these patients.

Procedural Pitfalls

Preprocedure Preparation

POEM is unique in that it is a mediastinal surgical procedure that can be performed in endoscopy units where procedure protocols may be somewhat less stringent than in formal operating rooms, as they are geared toward traditional endoscopic procedures in which reaction time delays, omissions, or other errors are much less likely to result in mission-critical disruptions compared to surgery. To minimize serious and potentially life-threatening events, it is important to replicate operating room protocols including detailed equipment checklists that ensure that all devices that may be needed, particularly ones that may be needed infrequently (such as overtubes, stents, and specialized clips or sutures) or emergently (such as Veress needles or angiocaths for decompression), are readily available. Detailed "time-out" protocols are essential, including, for example, confirmation that air insufflation has been turned off and appropriate antibiotics have been administered. It is instructive to look at air insufflation as an example of a potentially catastrophic event that may result from a minor oversight that would be of little import in most other endoscopic procedures. The high frequency of adverse events and severe adverse events resulting from use of air rather than CO_2 was amply illustrated in a study by a group that intentionally utilized air in their first 119 POEMs [14]. Endoscopy consoles at the present time still have air as the default insufflation setting with add-on appended equipment required to use carbon dioxide. To avoid air insufflation one needs to ensure prior to the procedure that the unit's default air insufflation is switched off. Including the "air switch-off" step in the standard procedure "time-out" minimizes the risk of inadvertent air insufflation which can occur even in expert centers. Inadvertent air insufflation was reported as the cause of the single occurrence of pneumothorax requiring chest drainage in a recent study by Inoue et al. following a series of 500 POEM cases [15]. This is not a "learning curve" related event and is most likely to occur when the procedure becomes more routine, and vigilance by the operator and support team decreases. We recommend including an "air-off/CO_2 on" check to the preprocedure "time-out", as we have done at our institution, and positioning an angiocath and betadine wipes at a standard location within immediate reach of the operator to minimize any delay in emergent venting of capnothorax or capnoperitoneum.

Other routine preprocedure setup tasks should be included in the preprocedure checklist. For example, routine taping of the distal cap attachment with a water-resistant tape can avoid dislodgment of the cap in the submucosal tunnel, which can result in a quite cumbersome and time-consuming extraction of the dislodged cap [16, 17].

It is also important to have a highly trained dedicated team. Since achalasia is a rare disorder and POEM is performed in small numbers in most centers, errors can result without a dedicated team. The anesthesiology team needs to be prepared for circumstances that may result in severe morbidity. For example they need to anticipate the presence of massive amounts of food debris in patients with advanced or end-stage achalasia and severely dilated esophagus and preemptively apply cricoid pressure and rapid sequence intubation. At our center, on some occasions, we employ additional maneuvers such as semi-erect intubation in certain severe end-stage patients with the history of aspiration episodes during prior endoscopies. An endoscopy team that is unfamiliar with POEM may also fail to correctly interpret signs of pneumothorax or pneumoperitoneum. Delay in diagnosis of such conditions may result in cardiac arrest, whereas prompt recognition allows correction by desufflation or venting with an angiocath, thus minimizing morbidity. Anesthesiologists familiar with traditional endoscopic procedures performed under general anesthesia but unfamiliar with POEM need to recognize signs of emerging tension pneumothorax or pneumoperitoneum (e.g. difficulty in ventilating the patient and high airway pressures) versus endotracheal tube displacement by the endoscope, bronchospasm, or inadequate paralysis. The latter sort of differential diagnosis would be appropriate for a traditional endoscopic procedure performed under general anesthesia such as endoscopic retrograde cholangiopancreatography, but in the case of POEM, it could result in delay in diagnosis of tension pneumothorax or pneumoperitoneum. If having a dedicated POEM-operative team is not feasible, it is incumbent upon the surgeon or gastroenterologist to discuss with the anesthesiologist the potential POEM anesthesia pitfalls prior to the procedure.

Tunnel Initiation and Orientation

On insertion of the endoscope, one may encounter a situation where excessive loss of insufflation from the upper esophageal sphincter is encountered with the resultant inability to properly distend the esophageal lumen (or submucosal tunnel lumen later in the procedure). In such cases, insertion of a short esophageal overtube with an air-tight silastic ring around the shaft of the endoscope may be helpful (Guardus Overtube, US Endoscopy, Mentor OH).

After removal of any debris from the esophagus, we recommend irrigation with at least 500–1000 cm^3 of saline based on studies regarding NOTES indicating significant reduction in bacterial colonies after copious irrigation with similar reductions, whether or not a disinfectant was included in the irrigant [18].

During this step, a common mistake involves aggressively and repeatedly inserting the endoscope through the GEJ, which in patients with an extremely tight LES results in mucosal tears compromising the mucosal flap which serves as the essential barrier that prevents leaks in POEM.

Careful measurement of the location of the GEJ from the incisors is required to determine the proximal and distal extents of the tunnel and myotomy. A common pitfall here involves overly rigid adherence to standard recommendations such as initiating the tunnel at a certain fixed distance proximal to the LES to the GEJ. Recent data suggest that a standard surgical myotomy of at least 8 cm may be longer than necessary in the esophageal body for nonspastic achalasia patients (type 1 and 2) [19]. Employing this approach in patients with advanced disease and dilated esophagus with mild (S1) or severe (S2) sigmoidization is likely excessive since these patients have a very short obstructing segment consisting of the LES only. Extension of the myotomy proximal to the LES on the expansive esophageal body may be of no benefit and even predispose the patient to diverticulum formation in the area of weakened muscle. Furthermore, in these advanced stage patients, severe angulation and lumen-indenting folds in the dilated distal esophageal body can make POEM technically challenging unless tunneling is initiated close to the LES distal to the meandering expansive lumen. With proper technique, POEM can provide substantial symptomatic improvement even in patients with sigmoid esophagus [20, 21]. Other scenarios that may complicate POEM can also be alleviated by judicious selection of the initiation site. Orientation that would require traversing areas of ulceration, diverticula, severe angulations, or a prior Heller myotomy should be avoided. It should also be noted that initiating the tunnel in an area that may make tunnel initiation and, importantly, tunnel closure difficult should be avoided even if this requires selecting a more proximal site by creating a longer submucosal tunnel than required for the planned myotomy length. This approach allows one to avoid areas with scarring and scant submucosa from recurrent ulcerations due to food stasis, areas in which a sigmoid esophagus "dives posteriorly" (making contact with the endoscope for a posterior POEM tenuous) or "ascends anteriorly" (causing the endoscope to be perpendicular to the wall or nearly retroflexed rather than in the optimal tangential position). Selecting an initiation site that is more proximal, away from areas where chronic food stasis may have caused the mucosa and submucosa to be thickened, may also facilitate closure as reviewed below in the "Tunnel Closure" section of this chapter.

Although a specific discussion regarding anterior vs posterior orientation is offered below in the "Submucosal Tunnel" section, we should note here that there is no consensus regarding the optimal orientation among expert centers with some favoring the anterior approach popularized by Inoue and some the posterior approach favored by the group in Shanghai and our group [1] (Fig. 7.3).

Initial Submucosal Injection

In achalasia patients, injection into the submucosa may be difficult due to alterations in the thickness of the layers of the esophageal wall. For example, in patients with long-standing achalasia, the entire wall of the esophagus may be severely thickened including the mucosa which may result in inadvertent injection of the deep mucosa superficial to the muscularis mucosae. In this case, attempts to establish a submucosal tunnel will be in vain unless the operator appreciates that what he/she considers to be muscularis propria is in fact a hypertrophic muscularis mucosae and proceeds to incise it (Fig. 7.4).

In severely malnourished patients in whom the submucosal layer may be very thin and in some early nonspastic achalasia patients with thin esophageal wall layers, the operator may inadvertently inject deep to the submucosa into the muscularis propria, adventitia, or mediastinal pleura. This may be recognized by appreciating that the resultant bleb is flatter than usual and has a pale white coloration with very little blue hue seen due to lack of transmission of the color of the injectate through the thickened overlying layers (Fig. 7.5). If not recognized, this deep

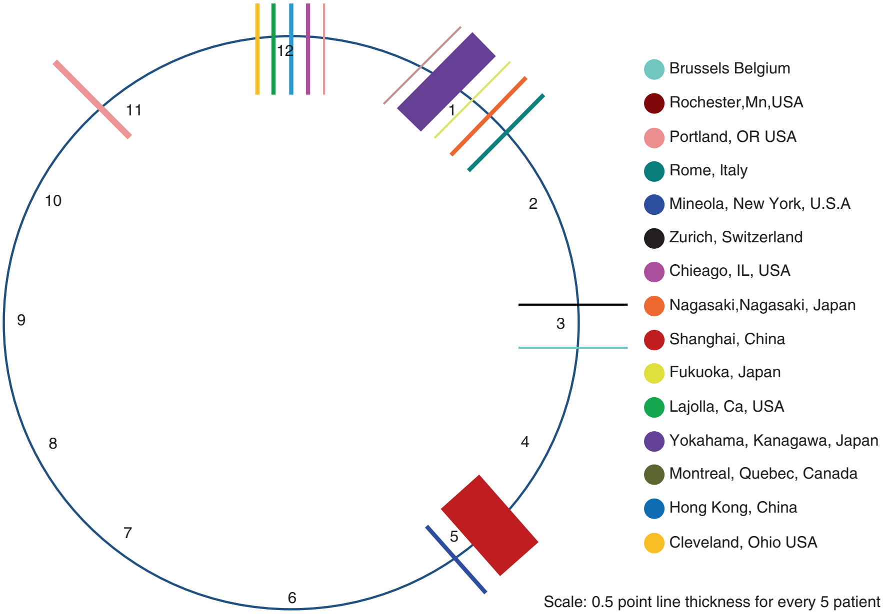
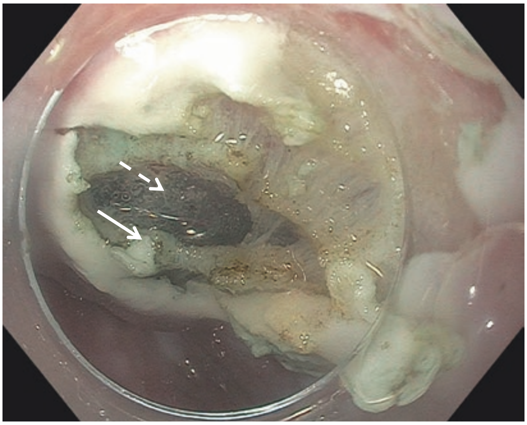


Fig. 7.3 POEM orientation among pioneering centers polled in the International POEM Survey (IPOEMS), including all centers having performed >30 POEMs at that time. Only two centers favored a posterior orientation (Mineola, Shanghai) at that time. (Figure from Stavropoulos SN, Modayil RJ, Friedel D, Savides T. The International Per Oral Endoscopic Myotomy Survey (IPOEMS): a snapshot of the global POEM experience. Surg Endosc. 2013 Sep;27(9):3322-38. doi: 10.1007/s00464-013-2913-8). Permission obtained

Fig. 7.4 Patient with long-standing achalasia with thick muscularis mucosae (*full arrow*) that can be confused for muscularis propria. Incision of this thickened muscularis mucosae reveals the submucosal space (*dashed arrow*)



bleb can result in layer confusion since the injected areolar tissue of the adventitia and pleura can mimic the submucosa. This can induce even experienced operators to incise through the muscularis propria and start tunneling in the adventitia or pleura plane deep to the muscularis propria with high attendant risks to injury to adjacent organs [22]. Once this is recognized, correction would necessitate closure

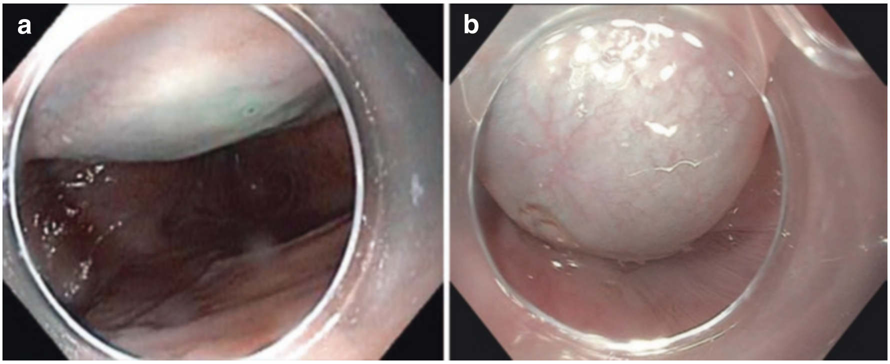


Fig. 7.5 Initial submucosal injection. (**a**) Shows a flat pale mount with very little blue hue suggesting that an inadvertent deeper injection into the muscularis propria or beyond has been performed rather than the desired submucosal injection (demonstrated in (**b**) as a markedly raised translucent bleb)

of the full thickness perforation leading to this deep mediastinal tunnel with a secure modality such as suturing [22].

Regarding the injectate used for submucosal injection, unlike endoscopic submucosal dissection, most operators avoid epinephrine due to the risk of necrosis of the devascularized mucosal flap. Such severe necrosis has been reported by one group [3].

Initial Mucosal Incision

Optimal incision is important in order to facilitate tunnel entry and facilitate secure closure at the conclusion of the procedure.

To avoid oozing from the edges of the incision from sizable mucosal and submucosal veins present in the midesophagus, we recommend selecting a site with the lowest density of such visible vessels and using a current with a significant coagulation component (e.g. dry-cut current in the ERBE VIO generator) for the initial incision.

As noted above, site selection and orientation should also take into account esophageal morphology in that area. Extensive nodularity from chronic food stasis likely represents cycles of ulcerations and healing that may make establishing a submucosal tunnel difficult. Even mild angulations of the esophagus may make tunnel entry and closure technically difficult.

Generally, it is accepted that a longitudinal incision allows easier closure with endoscopic clips than a transverse incision. Our group has used endoscopic suturing for closure in the last 250 POEMs and we prefer a transverse incision to avoid luminal narrowing. It should be noted, however, that even for closure with endoscopic clips, at least one group has advocated initially a transverse incision [23] and more recently an “inverted-T” incision [24]. Their argument, as we understand it, is that a transverse incision allows easier entry into the tunnel and also allows better escape of CO_2 from the tunnel, thus potentially decreasing insufflation-related adverse events. One would think, however, that this might also result in poor tunnel distension and decreased visibility. Furthermore, the closure issue remains since placement of clips along a transverse incision in the esophagus is more challenging.

The initial submucosal dissection at the entry site should be made close to the muscularis propria in order to avoid denuding the underside of the mucosal flap of submucosa, resulting in a structurally weakened flap at the tunnel opening that can tear during endoscope manipulations within the tunnel. Such tearing results in a much larger opening with devitalized torn edges that may be hard to approximate securely at the time of tunnel closure.

Initial Entry into the Submucosal Space and Tunnel Initiation

Operators early in their learning curve may have some difficulty in achieving initial entry into the submucosal space. As noted in the "Initial Incision" section, it is helpful to select a propitious entry site based on flat favorable morphology, lack of visible vascularity, and lack of submucosal scarring. Methods that may assist in submucosal entry include use of an oblique transparent distal cap attachment as initially used by Inoue or a tapered distal cap attachment (e.g. ST Hood; Fujifilm, Tokyo, Japan). In our first few POEMs in 2009–2010, we employed balloon dilation to establish the submucosal tunnel [25]. This technique greatly facilitates entry into the submucosal space and also carries the risk of balloon catheter perforation of the muscularis propria or mucosa during the blunt insertion prior to inflation [26].

For posterior POEM, which is our favored orientation currently, entry into the tunnel may be hampered by the much lower maximum down-angulation versus up-angulation capacity of gastroscopes (e.g. 90° vs 220° for Olympus GIF-HQ190 gastroscope). Therefore, we have developed and taught a technique that facilitates posterior entry which consists of reversing the orientation of the endoscope during entry by torqueing 180° while simultaneously using irrigation to retract the mucosal flap (demonstrated in Video 7.1).

Submucosal Tunnel Dissection

Submucosal tunnel dissection is usually the most time-consuming and challenging portion of POEM (e.g. mean duration of 44 min for submucosal access and tunnel creation vs. 25 min for the myotomy in a recent US study) [27]. Less intraprocedural bleeding and faster procedure durations have been reported with the use of the multifunctional ERBE hybrid T-type knife (ERBE, Tubingen, Germany) which allows injection and dissection by the same device compared to the triangular tip knife (TT knife, Olympus America, Center Valley PA) [28, 29]. However, neither effect appeared to have a significant impact on clinical outcomes, and, therefore, use of the hybrid knife is not a substitute for careful, precise, deliberate dissection which is the best strategy for preventing errors such as accidental mucosal injuries and excessive bleeding. Novice operators often attempt to use blunt dissection by

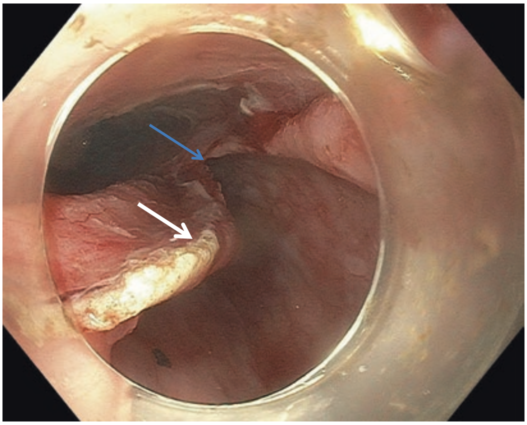


Fig. 7.6 Tearing of the tunnel opening caused by aggressive maneuvering of the endoscope during submucosal tunnel dissection. *White arrows* indicate the cautery changes that mark the original distal extent of the tunnel opening. The *blue arrow* demonstrates the distal extent of the now much larger opening after tearing occurred (note the absence of cautery along the tear confirming that this extension was caused by mechanical tissue tearing rather than electrical energy)

forceful endoscope insertion to achieve faster or easier tunnel dissection. Although this technique is often successful in the less vascular and softer porcine submucosa used in preclinical training, in humans it can have the following undesirable consequences: (1) Multiple small submucosal veins which would normally be obliterated by the electrosurgical dissection of the submucosa without any specific hemostatic maneuvers required can be avulsed via the technique of mechanical blunt dissection which then necessitates time-consuming coagulation of multifocal oozing. (2) Unrecognized buckling of the endoscope at the tunnel insertion site which may result in tearing of the opening may in turn make closure more challenging (Fig. 7.6) (3) "Muscle splitting" especially in the area of a tight LES, an important pitfall of submucosal dissection, is discussed in detail below.

Although submucosal tunnel dissection in the esophageal body is usually straightforward, occasionally certain challenging scenarios and pitfalls can occur. One such scenario is that of thin, absent, or fibrotic submucosa thwarting the endoscopist's attempts to create a submucosal tunnel. Aborted POEMs due to this phenomenon have been reported anecdotally even by expert operators. However, the best described series of such cases comes from a group in Rome, Italy [30]. This group reported a 6% early termination rate on their first 100 POEMs, with all five cases halted due to this phenomenon. We submit here an excerpt from their report as it describes this pitfall of submucosal dissection. They state that "*In 5 cases, the procedure failed because of inadequate lifting of the mucosa and the impossibility to proceed with submucosal dissection. Two patients had received radiation therapy for breast cancer. The esophageal wall appeared very thin, sclerotic, and any attempt at submucosal injection of glycerol solution ultimately failed, more likely because of severe submucosal fibrosis after radiation. The other 3 patients had no peculiar clinical history. Nevertheless, in these patients, the mucosal lifting was incomplete and submucosal dissection impossible: 2 of these patients had a* *very dilated and tortuous esophagus, which additionally complicated submucosal lifting and dissection. Any attempt at dissection resulted only in a laceration of the mucosa, which was repaired with clips.*" We focus the reader's attention on the fact that in three of the patients described, there was no clearly identifiable cause for this "absent submucosa" phenomenon which occurred in 3% of the patients in this Italian series. Based on observations from our series of over 300 POEMs [31] with no aborted POEMs, this phenomenon can usually be overcome with the maneuvers described below. It is encountered in patients with long-standing disease and severe food stasis likely resulting in pervasive inflammation and cycles of mucosal injury and healing that cause widespread submucosal sclerosis. This is most prevalent along the posterior wall of the esophagus or in patients with severe malnutrition in whom the absent submucosa is probably a sign of a severe prolonged catabolic state. We suggest the following maneuvers to overcome this challenging phenomenon: (1) Abandon the original site where tunnel initiation attempts have failed and reattempt at a new tunnel orientation (e.g. move from the posterior wall to a lateral wall) and/or new location (more distally or sometimes more proximally to the initial site, attempting to target an area with the least amount of mucosal nodularity, thickening, or other surface abnormalities). (2) Use of the I-type Hybrid knife (ERBE, Tubingen, Germany). The I-type Hybrid knife, which we have used in our last 280 POEMs, delivers a saline injection at pressures of up to 1400 PSI, which is powerful enough to dissect tissue via a tiny 0.12 μm port at the tip of this straight knife. In our experience, this can often achieve enough injection to delineate a submucosal dissection plane even in cases of very minimal fibrotic submucosa. Needless to say, even though these maneuvers may make a seemingly impossible dissection feasible, it would still remain an expert-level, slow, meticulous dissection requiring as much patience as skill.

Once the submucosal tunneling is initiated, a common pitfall involves spiraling of the tunnel dissection. Spiraling occurs due to preferential dissection on one flank of the tunnel more than the other and usually results in progressive clockwise rotation of the orientation of the tunnel. In patients with a relatively straight esophagus, it can be recognized by the operator as a progressive change in the angle between the long axis of the tunnel and the circular muscle fibers from a 90° angle to a more oblique angle [32]. Potential problems due to spiraling include the following: (1) Spiraling of the myotomy which results in a less powerful disruption of the ability of the circular muscle to achieve lumen-effacing contractions (2) Moving from an anterior POEM (2 o' clock orientation) or a posterior POEM (5 o' clock orientation) to a greater curvature-oriented POEM at a 7 o' clock position. A greater curvature POEM is much more challenging as it involves dissection across the angle of His [33]. One simple methodology first proposed by our group to avoid tunnel spiraling involves placing a marker on the shaft of the endoscope that indicates the torque rotation of the endoscope that maintains the desired orientation within the tunnel which is illustrated in our open-access narrated POEM technique video [34]. Advanced sigmoidization constitutes one of the most challenging and time-consuming POEM clinical scenarios [20, 21, 35]. The main challenge in these patients consists of completing a properly oriented submucosal tunnel. Proper orientation can be so challenging in these scenarios that experienced practitioners in India have described inadvertent retroflexion of the endoscope during tunneling, with the tunnel making a U-turn just prior to the GE junction and leading back to the esophageal body. This was recognized and corrected by the use of fluoroscopy which this group has used and now advocates in difficult sigmoid patients to help maintain orientation [36]. We have found our endoscope shaft torque marker method to be adequate in these patients, but we feel that it is important to be knowledgeable about the full armamentarium of useful adjunctive techniques such as fluoroscopy that can help avoid POEM pitfalls, particularly early in one's experience and in exceptionally challenging cases.

Submucosal tunnel dissection in the area of the GE junction can be challenging due to two potential reasons: a very tight LES or fibrosis from a variety of causes such as prior biopsies (frequently performed by referring physicians to exclude neoplasia or eosinophilic esophagitis), reflux or stasis erosions and ulcerations, prior Botox injections, or prior surgery including Heller myotomy. Fibrosis encountered as the tunnel approaches the GEJ is best approached via a detour, whereby the direction of the tunnel is deviated to the left or right of the fibrotic area depending on which side is most convenient and provides the best submucosal expansion [37]. A very tight LES can present a formidable obstacle to tunnel extension into the cardia and may also complicate the myotomy portion of the procedure. The Chinese group from Harbin has proposed a POEM technique, whereby myotomy is performed without prior separate submucosal tunnel dissection achieved by injecting the submucosa and then cutting the muscle by dissecting it off the injected submucosa as the endoscope advances in a proximal to distal direction [38, 39]. This technique may be of value in the hands of experienced operators. In the hands of less-experienced operators, it may result in "layer confusion" with resultant "splitting" of the esophageal muscle, thus leaving an unrecognized, and thus uncut, portion of the LES on the underside of the mucosal flap. This allows us to segue into a discussion of muscle "splitting," an important pitfall of submucosal tunnel dissection particularly in the area of a thick, tight LES. LES splitting is one of the two main technical causes of POEM clinical failures, with the other being inadequate myotomy extension onto the cardia to be addressed below. Muscle splitting is mainly an early learning curve pitfall which occurs as the novice operator, duly concerned about causing an inadvertent mucosal injury injects and dissects ever closer to the muscular layer, especially within the tight quarters of a high-pressure LES zone or in areas of scant fibrotic submucosa in the esophageal body. Splitting of the muscle may be initiated by excessive forward mechanical force with the endoscope in and ill-advised attempt to add blunt dissection with the endoscope to electrosurgical dissection in areas where the latter appears risky (such as segments with minimal submucosal expansion or a tight GE junction). Injection near the split muscle fibers can expand the fascia between circular muscle bundles, thus leaving some bundles attached to the mucosa camouflaged by injected fascia that mimics injected submucosa. Recognition of this pitfall of POEM can be difficult. It may be suspected in the following circumstances: (1) Once the myotomy is completed, the exposed cut edges of the LES are not significantly thicker than the cut edges of the muscle of the gastric cardia as is the norm. (2) Apparent premature entry into the peritoneal cavity, as heralded by exposure of omental fat while there is still a substantial high-pressure narrowing of the GE junction as assessed by intraluminal endoscope insertion. (3) Substantial residual narrowing and resistance to endoscope insertion at completion of the myotomy which can also be confirmed by functional luminal assessment using the EndoFLIP device (Crospon, Dublin, Ireland) [40]. Recovery from this pitfall is simple in theory but may require some experience in practice. The operator needs to "back-track" along the tunnel to the point where the muscle split originated. This can usually be determined by noting that the cut edges of the muscle appear thinner than expected and usually occurs in an area of difficult tunnel dissection. At that point, careful dissection of the underside of the mucosal flap is performed using ample submucosal injection, pure cutting current, and if necessary a specialized knife such as the hook knife (Olympus America, Center Valley, PA) to avoid injury to the mucosa. This delicate dissection exposes the true submucosal plane and isolates the split muscle bundles that remained attached to the mucosa. Figure 7.7 illustrates a case of muscle splitting in the distal esophageal body just proximal to the GEJ which was recognized and treated as discussed above. The technique for isolating and incising the missed muscle fibers in this case is

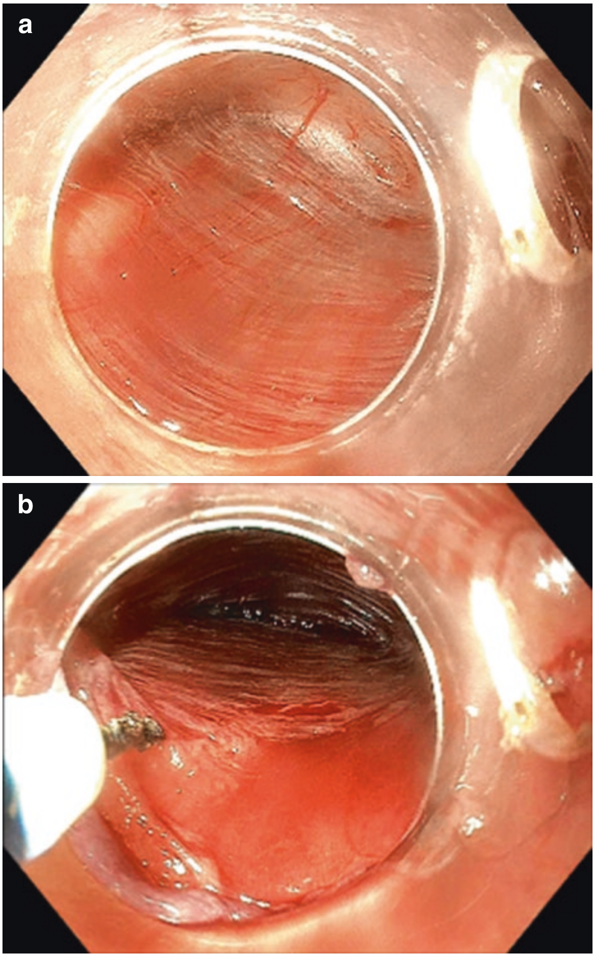


Fig. 7.7 Anterior POEM with inadvertent muscle splitting in the distal esophagus during submucosal tunnel dissection. (**a**) Demonstrates circular muscle fibers at 7 o' clock position (where normally the mucosa and submucosa forming the roof of the tunnel should be seen in an anterior POEM) in addition to the 2 o' clock position (which is the expected location of the circular muscle fibers in an anterior POEM). This can also be seen in (**b**) (i.e. circular muscle fibers at both 2 o' clock and 7 o' clock positions) as the endoscope is withdrawn in an attempt to identify the area of the dissection where the inadvertent muscle splitting commenced. (**c**) Illustrates recovery from this pitfall as the split fibers have been incised and the proper dissection plane in the submucosa has been re-established

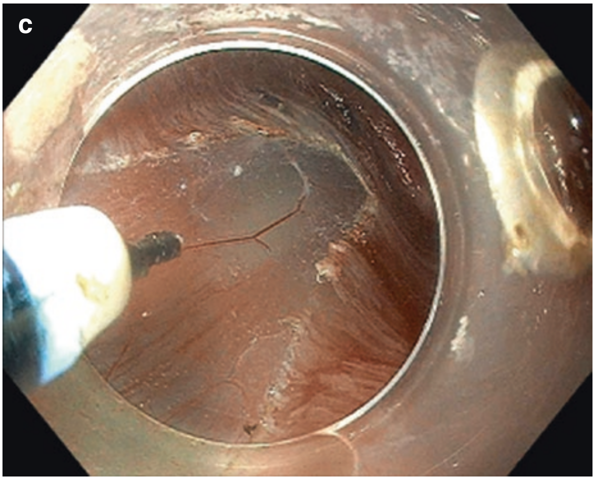


Fig. 7.7 (continued)

demonstrated in the first half of Video 7.2. After correction of this pitfall, the second half of the video illustrates resumption and completion of the anterior POEM myotomy including full-thickness muscle dissection along the high-risk location posterior to the pericardial sac (discussed below).

A number of POEM submucosal dissection pitfalls relate to bleeding. Acute bleeding can be classified as minor—usually resulting from inadvertently or inexpertly divided veins and very small caliber submillimeter arteries in the esophageal body—or major, usually resulting from accidental injury or inadequate coagulation of large arteries in the 1–2 mm range which are generally encountered in the cardia and represent branches of the left gastric artery that penetrate through the muscularis propria and arborize to supply the overlying mucosa and submucosa. The best approach to intraprocedural bleeding is prevention by identification of vessels and pre-emptive coagulation. Submucosal dissection, particularly in the area of the cardia, should be performed with short superficial swipes of the knife that ensure that the bundle of submucosal fibers being cut does not harbor undetected vessels. For this reason, it is important to avoid injection solutions that are too dark due to excessive blue dye and may prevent visualization of submucosal vessels. Treatment of bleeding is inferior to prevention for a number of reasons: (1) Even if successfully controlled, bleeding episodes can result in significant prolongation of the procedure time, since identification of the bleeding vessels and effective treatment can be quite time-consuming. (2) Copious bleeding can stain the submucosa red, which can make submucosal tunnel dissection substantially harder since the usually pink/tan underside of the mucosa and submucosal vessels do not appear distinct from one another (Fig. 7.8). (3) Multiple poorly targeted coagulation efforts resulting from the suboptimal visibility conditions of an active bleed can result in mucosal thermal injury or deep injury to the muscle and adjacent structures or at a minimum heavily coagulated, contracted, or even charred tissue. This hinders progress since the submucosa needs to be carefully dissected before a clean submucosal dissection plane can be re-established.

The endoscopist needs to distinguish arteries from veins since even small arteries generally require more coagulation treatment with graspers rather than simply using

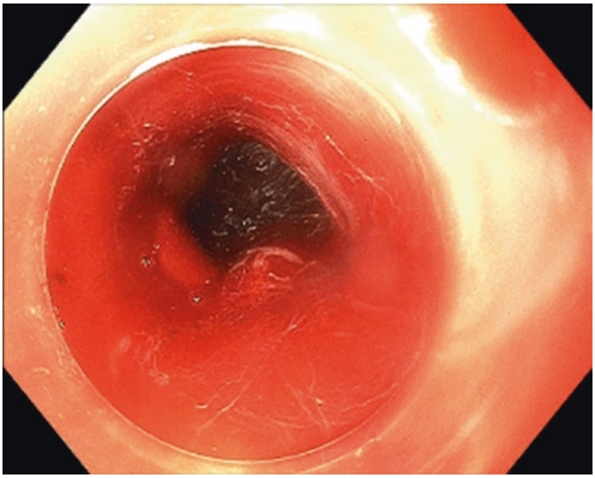


Fig. 7.8 Clot and extensive red staining of the submucosa after a large arterial bleed that required several minutes to identify and control. *Red* staining of the submucosa hinders proper identification of the submucosal dissection plane and identification of vessels within the submucosa that should be avoided or pre-emptively coagulated, thus predisposing to further intraprocedural bleeds until a clean unstained submucosal plane can be recovered distally as the tunnel is extended

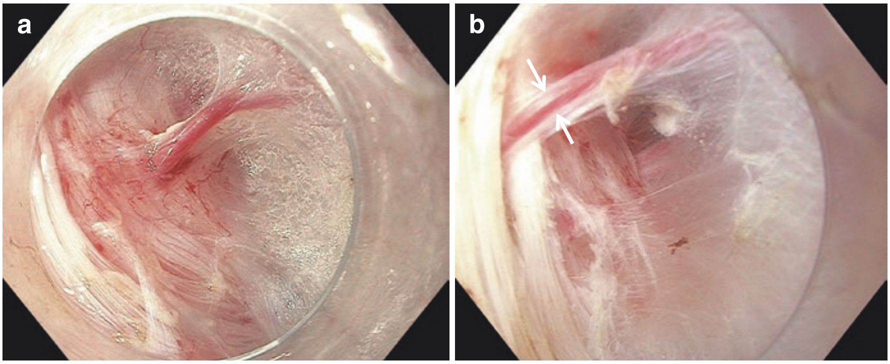


Fig. 7.9 (**a**) Illustration of a penetrating vein, larger, cylindrical bulging, soft, compressible with deeper red color. (**b**) Illustration of a penetrating artery which is smaller, flatter, firmer, often with visible pulsatile flow and *paler red color* often with *pale white borders*, annotated with *white arrows* here (an appearance caused by the thick muscular wall)

the tip of the endo-knife (which conversely is adequate for all but the largest veins when properly applied). Figure 7.9 illustrates the differences in the appearance of veins (generally larger, more cylindrical, more compressible with a deeper red color than arteries) and arteries (smaller, flatter, paler, sometimes with detectable pulsations, and with well delineated pale white borders representing their thicker muscular wall). Proper coagulation technique using the tip of the knife (Fig. 7.10) involves first heating the vessel indirectly by addressing the submucosa surrounding it and only proceeding with the division of the vessel once it has been desiccated and its lumen obviously

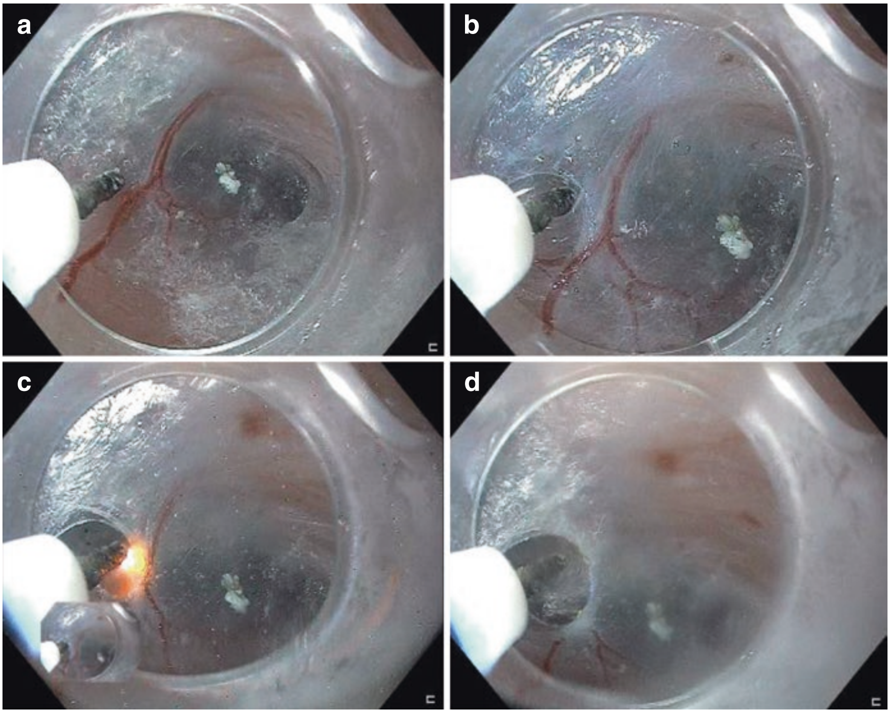


Fig. 7.10 Proper coagulation technique using the tip of the knife. (**a**) The submucosa surrounding the vessel is injected (**b**) A small incision is made with the knife in the submucosa next to the vessel (**c**) Electrosurgical energy is delivered to the vessel initially indirectly by targeting the submucosa surrounding it (**d**) Direct energy to the vessel to effect division of the vessel is only applied once the vessel has been desiccated and its lumen obliterated

obliterated. This avoids the potential for electrosurgical energy applied directly to the vessel, resulting in the division of the vessel prior to luminal sealing. A coagulation grasper should be used rather than the tip of the knife in the case of arteries (including the large arteries in the cardia), where the rapid luminal flow results in a powerful heat sink effect that can only be overcome by using a grasper to coapt the walls and disrupt blood flow prior to coagulation. A coagulation grasper should also be used for vessels under tension being stretched between their origin at the muscle layer and their insertion in the mucosa by the presence of the endoscope and insufflation within the emerging submucosal tunnel. In such vessels under tension, attempted coagulation with the tip of the knife may result in tearing of the vessel as soon as the structural integrity of its wall is weakened but prior to effective sealing of the lumen of the vessel. In fact, veins under such tension are fragile enough that injudicious use of suction via the endoscope can injure them and cause bleeding emphasizing the importance of gentle suction within the tunnel (unlike the customary use of suction in traditional luminal endoscopy [41]. Proper pre-emptive coagulation technique with the coagulation grasper (Fig. 7.11, Video 7.3) involves skeletonizing the entire circumference of a large vessel or multiple vessels within a vascular bundle. They can be grasped followed by extensive coagulation using a coagulation current algorithm that minimizes spread, and avoiding mucosal injury. The coagulation should be continued until impedance sharply

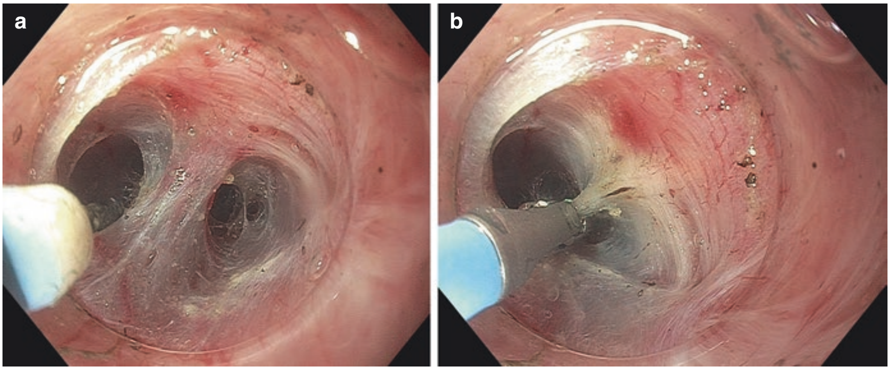


Fig. 7.11 Proper technique for coagulation of larger vessels or vascular bundles. (**a**) A vascular bundle containing at least three penetrating vessels has been "skeletonized" using careful dissection with the knife (blunt dissection using the tip of the forceps can also be used to skeletonize vessels as shown in the accompanying video). (**b**) The isolated vascular bundle is grasped and coagulated with a coagulating forceps

rises and energy delivery sharply drops indicating tissue desiccation. Only then can the vessel be safely divided to proceed with tunnel dissection.

Massive pulsatile bleeding from an accidentally divided penetrating branch of the left gastric artery can result in substantial hemorrhage. Such events require immediate intervention since the tunnel may rapidly fill with blood, eliminating visibility and thus the ability to identify and effectively treat the source of the bleeding (Fig. 7.12). A coagulation grasper should be immediately available. We use the hot biopsy forceps rather than the Olympus coag-graspers for this type of predicament since the thinner caliber and larger jaws of the hot forceps allow for better suction of blood and irrigation of fluid and less need for precision placement of the jaws compared to other devices. Tamponade of the bleeding by exerting pressure with the tip of the endoscope should be applied before proceeding with definitive coagulation. Once the grasper is applied, irrigation should be employed to clean the site and ensure that the flow of blood has been arrested. If this is not the case, suction should be applied to remove fluid mixed with blood that may obscure visualization. Suction should be combined with insufflation and avoidance of excessive irrigation while the grasper is readjusted. Another useful technique involves placing a sticker on the shaft of the coagulation grasper that marks the proper length of insertion to the tip of the endoscope, which allows much faster insertion of the grasper since the operator is less concerned about overshooting with the grasper insertion and causing further injury. We also note that there may be a higher density of large cardia vessels when POEM is performed anteriorly (2 o' clock orientation) rather than posteriorly (6 o' clock orientation) which may shift the desired route for POEM to a posterior course [41].

Mucosal flap injury is usually a minor technical error that can be corrected by clip placement [42]. However, occasionally, mucosal perforations can be very challenging to close and may subject the patient to a risk of leakage with resultant severe morbidity. Such challenging perforations are usually located in the difficult area of the GE junction and cardia, in a background of devitalized tissue due to extensive coagulation (e.g. secondary to hemostatic maneuvers), and/or tissue with little resiliency due to malnutrition, comorbidities, prior Botox injections, or extensive fibrosis

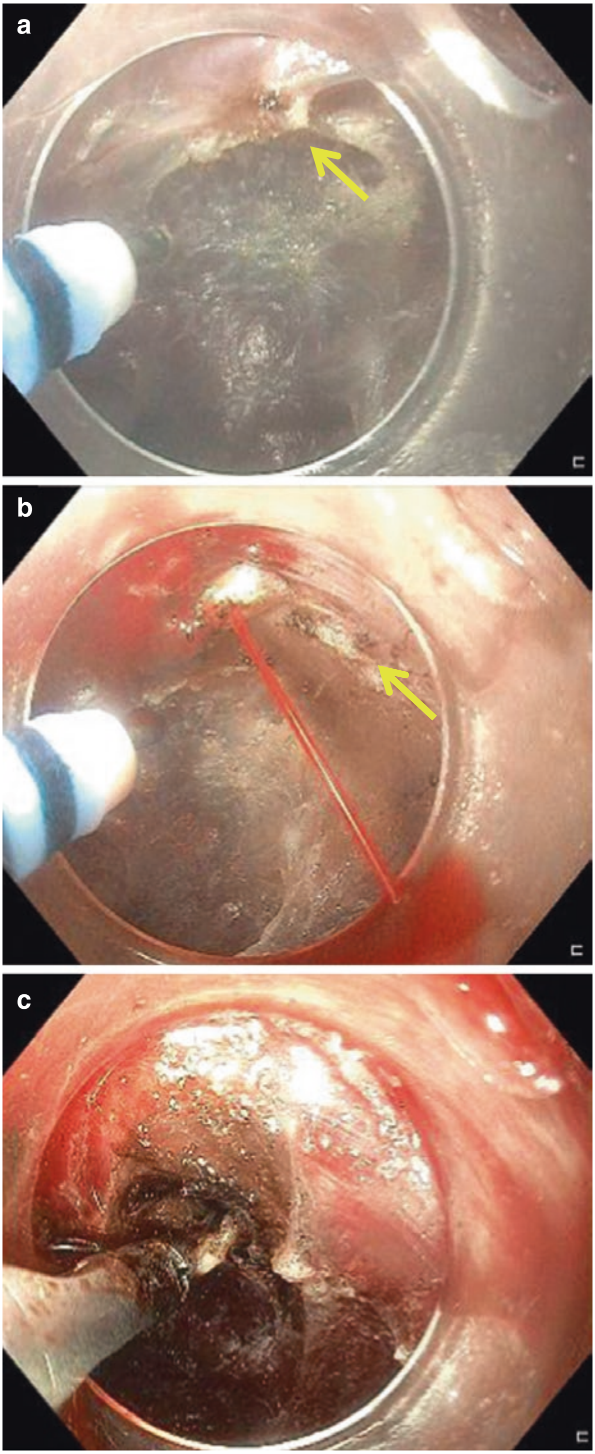


Fig. 7.12 Pulsatile bleeding from inadvertent injury to the wall of a penetrating artery expeditiously coagulated. (**a**) A penetrating artery (yellow arrow) is difficult to identify in this case due to partial coagulation of its wall giving it a similar white color to surrounding partially coagulated muscle (**b**) Pulsatile bleeding from inadverent injury to wall of this undetected penetrating artery (**c**) The hot biopsy forceps is used to expeditiousy coagulated the artery in order to avoid accumulation of blood that may eliminate visibility and hinder endoscopic coagulation efforts

due to other causes such as prior biopsies taken aggressively. This devitalized and/or delicate tissue is difficult to approximate and tears when clip placement is attempted, thus enlarging the defect. Furthermore, such defects tend to enlarge with continued insufflation (since closure is often deferred until the end of the procedure). We have reported on the use of endoscopic suturing (Overstitch, Apollo Endosurgery Austin, TX) for such challenging perforations in the GEJ and cardia (Fig. 7.13). We believe suturing to be the most robust and secure closure method for this scenario [43]. Others from China, where endoscopic suturing is not available, have reported using fibrin glue [44] or stent placement [45] to seal such defects.

Inoue et al. recently speculated that the anterior approach that has commonly been advocated may result in more accidental mucosotomies than the posterior approach due to a wider path of knife movement during the myotomy portion resulting in mucosal injury [41]. Since we have varied our approach between posterior and anterior orientation over our 7 year POEM experience, we have observed differences between the two techniques including a potentially higher rate of mucosal injuries when an anterior approach was followed. We attributed this to the closer proximity of the dissecting knife to the mucosa in the anterior approach (due to the knife exiting at 7 o' clock position in Olympus gastroscopes and the mucosa being

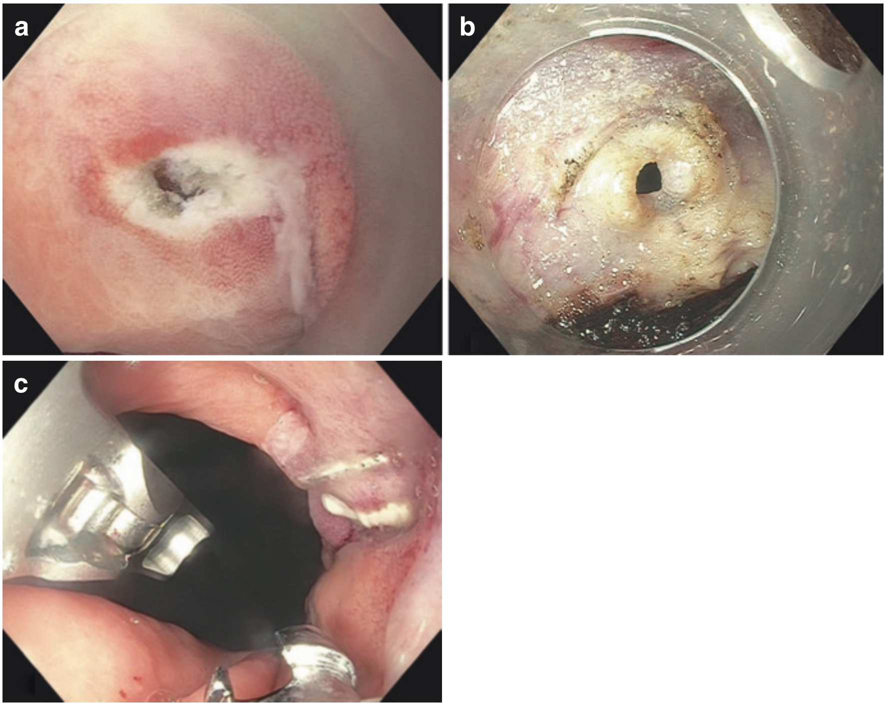


Fig. 7.13 Inadvertent mucosal perforation just distal to the Z-line at the GE junction in an anterior POEM (a POEM orientation that, as discussed in the text, may be more prone to such injuries). This location can be challenging for clip application, and attempts at clip placement can result in tearing of the mucosal flap with enlargement of the defect. (**a**) Demonstrates the defect from the luminal side, whereas (**b**) shows the defect from the submucosal tunnel side. (**c**) Shows effective closure using endoscopic suturing (the metallic t-tag and white plastic cinch at the two ends of the suture can both be seen on the right side of the image)

located at 6 o' clock position during anterior POEM compared to 12 o' clock position in posterior POEM) (Fig. 7.14). Our group is completing a single-center randomized study comparing anterior and posterior orientation and we recently presented data from a comparison of anterior and posterior POEMs in our single-operator series using data from a prospectively maintained database [46]. In this study, we analyzed all POEMs performed at our center from 10/2009 to 10/2015, 248 consecutive POEMs (120 anterior, 128 posterior), all successfully completed, with no aborted POEMs or surgical conversions. No learning curve bias was expected as we performed a similar percentage of anterior POEMs in the first 3 years of our series (48/91, 53%), as in the last 2 years (72/157 46%). There were no differences in efficacy or significant adverse events, but it should be noted that there was paucity of such events in our series with no leaks, no tunnel bleeds, and no surgical/IR interventions or aborted POEMs. There were more accidental

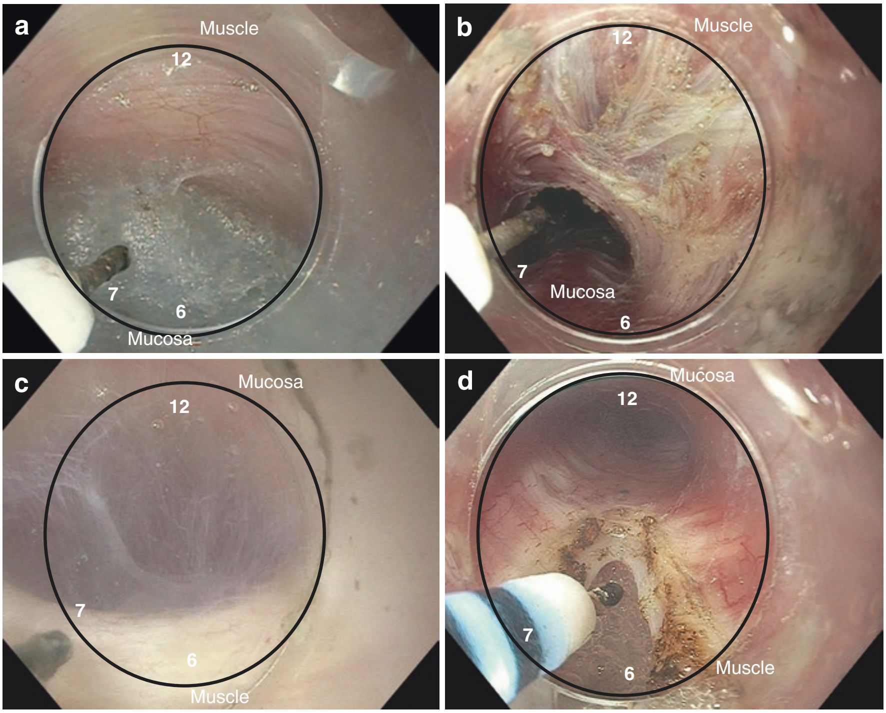


Fig. 7.14 (**a**, **b**) Illustration of knife position relative to the mucosa and muscularis in an anterior POEM during tunnel dissection (**a**) and myotomy (**b**). (**c**, **d**) Illustration of knife position relative to the mucosal and muscularis in a posterior POEM during tunnel dissection (**c**) and myotomy (**d**). The knife is much closer to the mucosa in anterior POEM (possibly resulting in higher rates of mucosal injury). In posterior POEM, the myotomy is on the same side of the tunnel as the knife and endoscope, possibly resulting in faster myotomy by forward advancement of endoscope and knife and minimal if any lateral movement of the knife. In contrast, in anterior POEM, incising the muscle at 2 o' clock position, the diametrically opposed position to that of the endoscope and knife (exiting the endoscope at 7 o' clock position) can only be done by interrupted lateral cuts hooking and cutting individual muscle bundles which result in large lateral swings of the knife from the muscle at 2 o' clock position to the knife's neutral position at 7 o' clock, very close to the mucosa which may suffer "countercoup" injuries

mucosal injuries (defined as any visible injury including even minor nontransmural blanching) (29% vs 23%) following 284 POEMs (mucosal injuries in 42/131, 32% of anterior POEMs vs 33/153, 22% posterior POEMs, $P = 0.046$). Posterior approach for POEM was significantly faster overall (97 min A, 79 min P, $P = 0.0007$) including a faster closure (Suturing $n = 177$, clips $n = 71$) (9.6 min A, 7.9 min P, $P = 0.02$). More patients had pain, requiring narcotics in posterior POEM (17% A vs 27% P, $P = 0.007$). We discuss this issue further on the myotomy section below. There was a trend for less acid exposure in anterior POEM: +BRAVO studies 21/58 (36%) A vs 29/58 (50%) P, $P = 0.13$, reflux esophagitis 22/57 (38%) A vs 33/60 (55%) P, $P = 0.076$. In summary, based on the preceding discussion, a posterior approach may result in encountering fewer high-risk vessels in the cardia and result in less mucosal injuries with additional benefit including a faster procedure.

A final important pitfall in submucosal tunnel dissection involves inadequate extension of the tunnel onto the cardia. This may represent one of the most important contributors to a failed POEM. Extension of the tunnel into the cardia is the most challenging part of the submucosal tunnel dissection as it entails dissecting through the narrow submucosal space of the high-pressure zone of the LES (which may also be quite fibrotic in previously treated or biopsied patients) and then extending the tunnel into the submucosal space of the cardia which is rich in high-risk large penetrating arteries as noted above. Therefore, operators early in their experience should emphasize adequate extension of the tunnel onto the cardia. Surgical studies have suggested extending the myotomy to the cardia by 2–3 cm is important for clinical efficacy [47]. In a recent small study, extension of the POEM myotomy 2 cm onto the cardia resulted in a small but significant augmentation of LES distensibility as measured intraoperatively with the Endoflip device, but further lengthening of the myotomy to 3 cm past the esophagogastric junction did not increase distensibility further [48]. Indicators that can be used to ensure adequate extension of the tunnel onto the cardia have been covered in other POEM publications including review papers such as the POEM NOSCAR white paper [42] and the International POEM survey [1] as well as step-by-step videos (VJGIEN video) [34]. Table 7.1 lists these indicators. Figure 7.15 illustrates the indicators that require recognition of endosopic signs and landmarks that can be subtle at times.

Table 7.1 Indicators identifying gastroesophageal junction

1	Insertion depth of the endoscope measured from the incisors
2	Marked narrowing of the submucosal space with resistance to endoscope advancement at the level of the LES followed by a prompt expansion of the submucosal space in the cardia with easier dissection (see Fig. 7.15c)
3	Large caliber vessels in the submucosa of the gastric cardia (penetrating branches of the left gastric artery emerging from the muscularis propria and arborizing to supply the mucosa) (see Fig. 7.15d)
4	Venules with segmental spindle shaped fusiform dilations (so called “spindle veins”) (see Fig. 7.15a)
5	Palisading vessels seen on the under-surface of the mucosal flap (see Fig. 7.15b)
6	Short aberrant extraneous-longitudinal muscle bundles located on the inner (luminal) side of the circular muscle layer at the GE junction (see Fig. 7.15e)
7	Blue dye staining of the gastric cardia mucosa seen on retroflexed luminal view (see Fig. 7.15f)

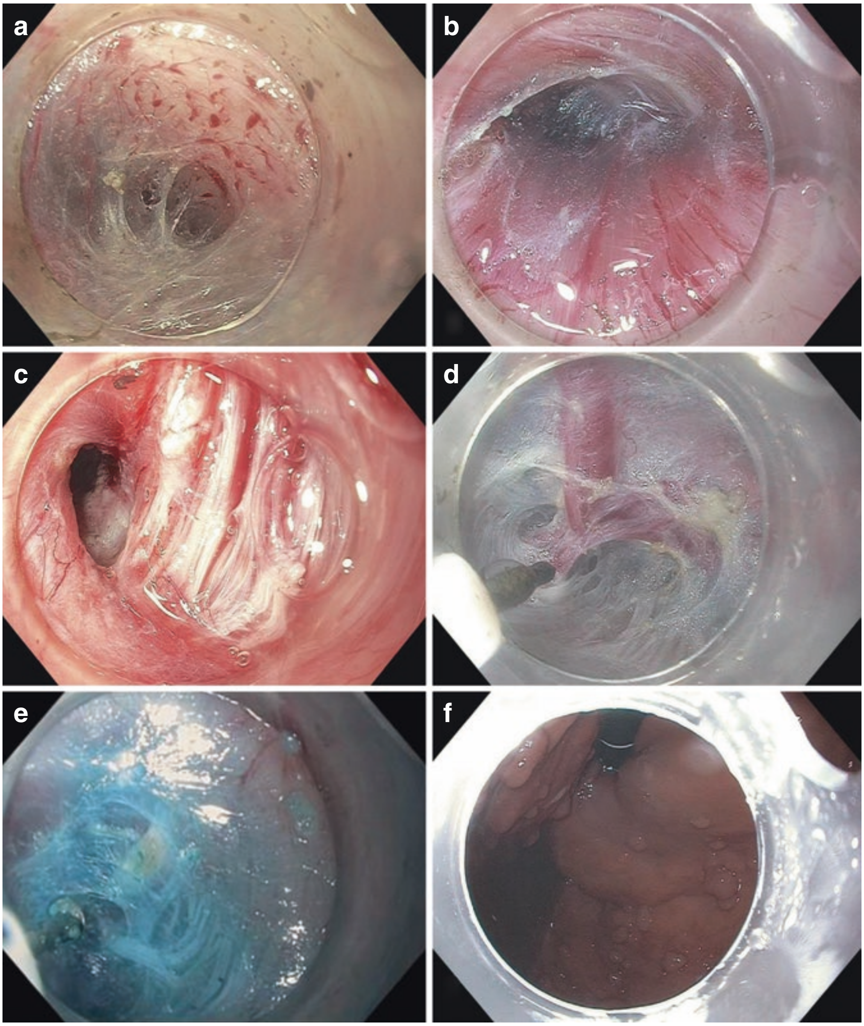


Fig. 7.15 Indicators used to confirm adequate extension of the submucosal tunnel to the cardia. (**a**) "Spindle" veins on the surface of the muscularis propria in the area of the GEJ. (**b**) Pallisading vessels in the GEJ mucosa (these are only visible if the submucosa on the underside of the mucosal flap has been extensively dissected which is generally not the case, since dissection preferably should be performed as close to the muscle as possible to avoid mucosal injury). (**c**) Prominent lower esophageal sphincter impeding scope progress and resulting in constricted submucosal space. This is best appreciated in patients with hypertensive sphincters (**d**). Once the tunnel is successfully extended over the sphincter and into the cardia, the constriction of the submucosal space at the LES is followed by expansion of the submucosal space making tunnelling easier again but more risky, given the presence of a high density of large vessels. The expansive submucosal space and large vessels signify that the tunnel has reached the cardia (**e**). Bundle(s) of aberrant inner longitudinal muscle fibers running in the submucosa, few cm in length, inserting into the circular muscle on their proximal and distal ends are encountered just proximal to the GE junction in some patients (**f**). Adequate extension of the tunnel into the cardia can be confirmed by retroflexing the endoscope in the lumen of the stomach and noting raised edematous mucosa at the tunnel terminus resulting from the submucosal injectate used during tunnel dissection. In patients with thick mucosa and submucosa, this sign may not be easy to visualize, particularly in posterior POEM where the tunnel terminus lies largely behind the shaft of the retroflexed scope

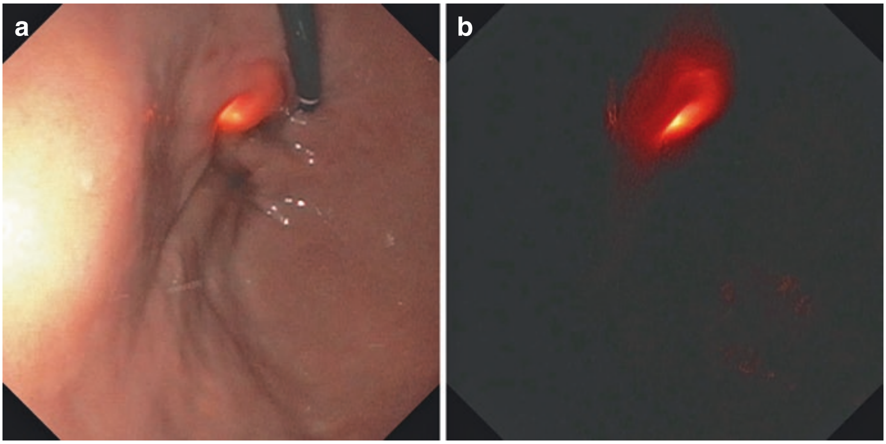


Fig. 7.16 Transillumination technique to confirm adequate extension of the submucosal tunnel to the cardia. (**a**) A second small-caliber transnasal endoscope is inserted next to the gastroscope and retroflexed in the proximal stomach to detect transilluminated light from the tip of the gastroscope located within the submucosal tunnel at the tunnel terminus which allows precise determination of the extent of the tunnel in the cardia. Here, the technique confirmed adequate extension of the tunnel in this posterior POEM (at least 2–3 cm extension in the cardia). (**b**) This image demonstrates transillumination detected with the light of the transnasal endoscope in the stomach turned off for illustration purposes

It should be noted that two adjunctive techniques have been described to ensure adequate extension into the cardia when this may remain in doubt despite use of the indicators listed. This may occur with operators early in their learning curve or in challenging patients such as those with sigmoid esophagus where anatomical landmarks can become obscured. One of these techniques involves fluoroscopy with a metallic marker used to mark the GE junction either intracorporeally (endoclip) or extracorporeally (e.g. paper clip) [49]. Another technique involves the use of two endoscopes. The gastroscope used for the POEM is inserted to the tunnel terminus, while a second small-caliber endoscope is inserted transnasally next to the gastroscope and retroflexed in the proximal stomach to detect transillumination from the gastroscope which allows precise determination of the extent of the tunnel (Fig. 7.16). This technique was originally described in a 2013 publication [50] with its utility confirmed more recently in a small randomized trial [51].

Myotomy

The myotomy is optimally initiated at least 2 cm distal to the distal extent of the tunnel opening to decrease the risk of leak, should dehiscence of the closure occur. This is important since centers using clips for closure and performing routine second-look endoscopy at 24–48 h after POEM have anecdotally reported frequent loss of clips and occasional partial dehiscence of the mucosal edges without leak. The absence of leak in these situations is attributed to independent sealing of the tunnel by mucosal flap adherence to the muscle proximal to the myotomy.

There is no consensus at present regarding full-thickness versus circular layer myotomy. Proponents of circular layer myotomy offer as the main rationale for this technique possible increased safety. Preservation of the longitudinal layer by the operator may be less likely to cause injury to adjacent organs. Proponents of full-thickness myotomy argue that this procedure is a more faithful endoscopic version of the full-thickness myotomy performed during a surgical Heller myotomy, and therefore would be expected to have the excellent long-term efficacy results of that procedure. The only current data comparing these techniques consist of a large retrospective study from the Shanghai group comparing their initial circular-layer only POEMs to later full-thickness myotomy POEMs [52]. They demonstrated equivalent outcomes except for a shorter procedure duration in the full-thickness myotomy group. However, these results may be confounded by a possible learning curve effect, given the retrospective methodology utilized. It should be noted that the positions of the two myotomy "schools" may be less entrenched than one might imagine, since operators that favor circular-only myotomy tend to inadvertently mechanically disrupt the insubstantial longitudinal layer in areas of the esophageal body during endoscope movements, and at the area of the GEJ they often perform full-thickness myotomy due to a complicated multidirectional bundle orientation as the two layers of the esophagus fuse with the three muscle layers of the stomach. Conversely, operators that favor full-thickness myotomy often start the myotomy in the esophageal body with a circular-only myotomy, since the utility of any myotomy in the esophageal body is uncertain in achalasia type I/II patients [48] and, in addition to the risk of injuring adjacent organs, full-thickness myotomy in the esophageal body may increase the likelihood of formation of diverticula through the weakened myotomized wall.

During anterior myotomy, one needs to be particularly mindful of the pericardial sac extending from approximately 30 to 35 cm from the incisors and "bulging" intraluminally (as illustrated in Fig. 7.17 and the second half of Video 7.2), which makes it particularly prone to injury or irritation during an anterior myotomy. Injury to the pericardial sac leading to tension capnopericardium has been reported [53]. We also know via personal communication of a case from a center early in their

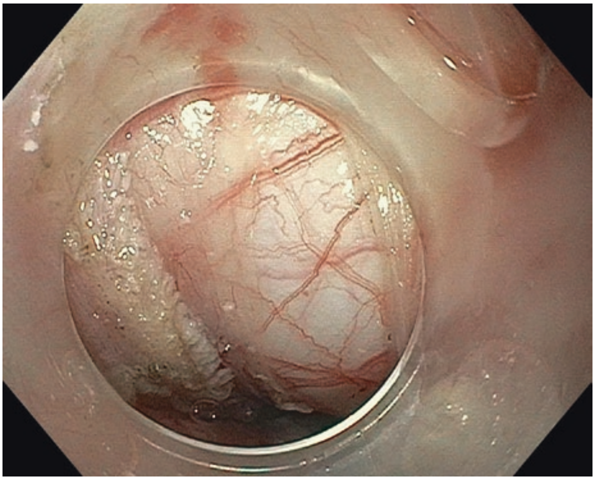


Fig. 7.17 The left atrium covered by pericardium (whitish bulging structure with dense network of superficial vessels) seen protruding through the edges of the full thickness myotomy incision in anterior POEM. Careful myotomy technique is required to avoid injury to the pericardium that can result in capnopericardium and possible tamponade and cardiac irritation that may increase the incidence of atrial arrhythmias

POEM learning curve of delayed post-POEM presentation with severe mediastinal sepsis requiring emergency thoracic surgery revealing an esophago-pericardial fistula. Despite the young age and good general health of this patient, this was a near-fatal event resulting in prolonged SICU stay and overall admission of 2–3 months. We are also aware of an adverse event from a moderate volume center consisting of tension capnopericardium due to inadvertent air insufflation treated with drain placement. Atrial fibrillation has also been reported [54] and, as is the case in traditional thoracic surgery, it is not uncommon to observe tachycardia after POEM or arrhythmias such as atrial tachycardia or atrial fibrillation (which can represent a de novo episode self-limited to the perioperative period as in the cited case report or a paroxysmal episode in the setting of known paroxysmal atrial fibrillation). Therefore, one might suggest that an anterior myotomy should be “paired” with a partial thickness myotomy in an effort to avoid any contact with the pericardium.

As noted above in the submucosal tunnel section, it has been speculated that there may be more accidental mucosal injuries during anterior POEM compared to posterior POEM [41]. We confirmed this in our recent retrospective comparison of anterior and posterior myotomy [46] summarized in the submucosal tunnel section. This is likely due to the closer proximity of the knife to the mucosa during submucosal tunnel dissection in the anterior orientation (where the mucosa is located at 6 o’ clock position very close to the location of the knife at 7 o’ clock position) (Fig. 7.14). Furthermore, during anterior myotomy, the location of the muscle to be cut at the 1–2 o’ clock position (opposite the location of the endoscope, which, due to gravity lies on the mucosal flap, and opposite to the location of the knife at 7 o’ clock position) results in interrupted muscle dissection, as individual fibers need to be hooked and cut with large excursions of the knife from 12 o’ clock to 7 o’ clock position that may cause opposing injury to the mucosal flap. In contrast, during posterior myotomy, gravity causes the knife to sit within the emerging myotomy groove and thus dissect the muscle straight-ahead in the continuous linear fashion. Furthermore, the knife and muscle are located at 6–7 o’ clock position away from the mucosa located at 1–2 o’ clock position (Fig. 7.14). For these reasons, injury to the mucosa is less likely. In posterior POEM, one needs to be mindful of potential injury to the posterior trunk of the vagus nerve which can often be seen through the transparent esophageal adventitia and pleura when a full-thickness myotomy is performed (Fig. 7.18) (the anterior vagus nerve due to its deeper and more lateral location cannot usually be identified during “anterior” POEM). Irritation to the vagus nerve which carries sensory afferent fibers may account for the higher rate of immediate perioperative pain found in our study in posterior POEM vs anterior POEM [46]. It should be emphasized however that this finding is not of major clinical significance as the pain is mild, controlled with few administrations of low doses of analgesics, and resolves within 12–24 h. However, more significant injury to the vagus may result in gastroparesis, diarrhea, and other motility disturbances. Due to the overall apparent increased safety of posterior POEM (less risk of pericardial injury or mucosal injury) as well as faster procedure times [46], and potentially improved LES disruption by cutting sling fibers rather than the mainly shorter weaker clasp fibers cut during anterior myotomy [46], posterior POEM appears to incorporate some anatomical advantages.

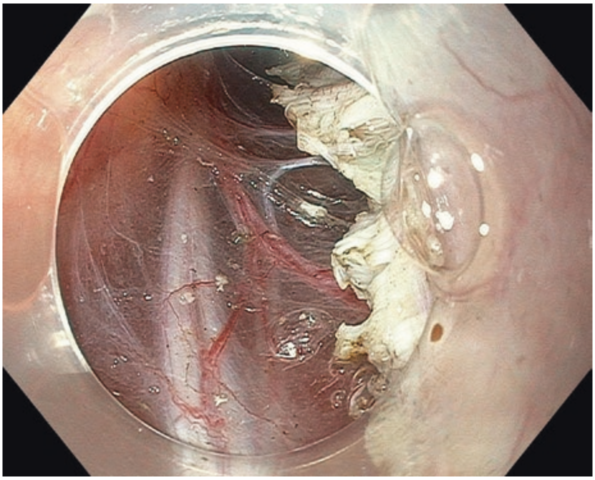


Fig. 7.18 Posterior trunk of the vagus nerve. In this posterior full-thickness POEM, the posterior trunk of the vagus nerve is seen through the transparent adventitia of the esophagus as a white shiny linear structure running parallel to the esophagus and dividing into multiple branches in the area of the cardia

Another common myotomy pitfall involves inadequate extension of the myotomy in the esophageal body in patients with spastic achalasia (Chicago type 3) or spastic disorders involving the esophageal body such as DES and jackhammer. These patients require a long esophageal body myotomy (exact length is guided by manometric data and endoscopic evidence of spasm but can range from 16 to 26 cm in our experience) in order to myotomize the long spastic segment along the distal two-thirds of the esophagus. Such a "long" myotomy is essential to relieve dysphagia and particularly pain which is often a dominant symptom in these patients. Inadequate extension of the myotomy in the esophageal body has been reported as a cause of residual symptoms in patients with spastic disorders [3] and can be diagnosed by high-resolution manometry demonstrating a residual spastic segment proximal to the myotomized segment (Fig. 7.19). This scenario has been successfully addressed with a second POEM targeting this proximal spastic segment [3]. Avoiding this pitfall hinges on having access to high-quality HRM studies that can allow differentiation of a spastic disorder requiring long myotomy such as type III achalasia from type I and II and also access to expert HRM interpretation to determine the length of esophageal body myotomy required in spastic patients. However, it should be noted that even among motility experts there can be substantial interobserver variability in HRM interpretation. For example, in a recent multicenter trial that included expert centers, there was only "moderate" agreement in the HRM diagnosis of type I, II, and III achalasia (kappa value of 0.48, 0.60, and 0.56, respectively) [55]. Therefore, it behooves the POEM operator to develop experience in HRM interpretation and to use complementary information from endoscopy, barium esophagram, and clinical history to maximize diagnostic accuracy and minimize the probability of performing a myotomy of inadequate length in patients with spastic disorders.

A final pitfall involving the "extent of myotomy" involves patients with esophageal spastic disorders such as jackhammer or nutcracker esophagus that (unlike achalasia patients) demonstrate normal LES relaxation on manometric evaluation. Initially, many POEM operators eschewed extension of the myotomy through the

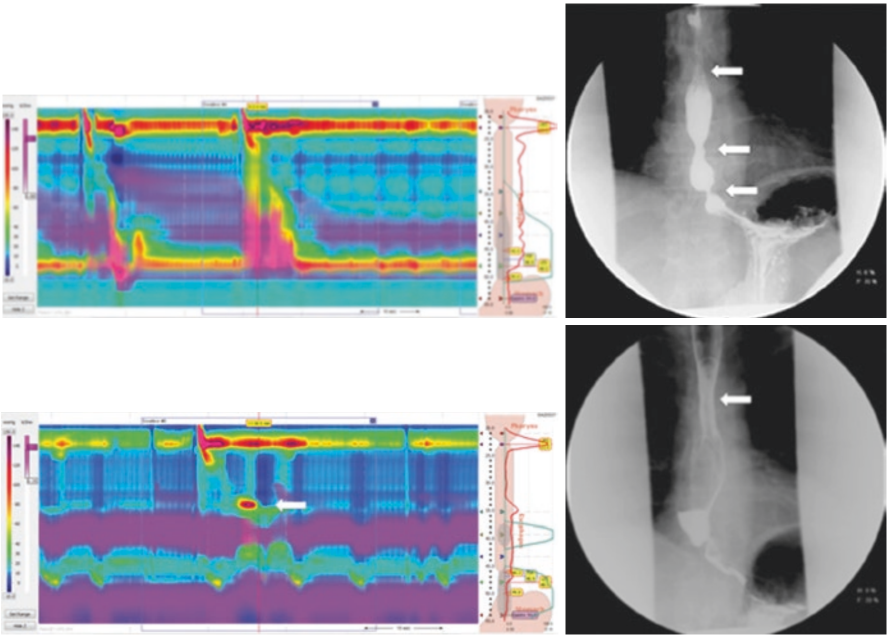


Fig. 7.19 Illustration of the pitfall of inadequate proximal extension of the myotomy in spastic patients. This patient with Chicago classificaiton type III (spastic) achalasia underwent POEM with a 15 cm “long” myotomy which proved not long enough as he had a residual 3 cm proximal spastic segment on post-POEM HRM and barium esophagram causing persistent discomfort. The patient declined a second POEM to extend the myotomy proximally and opted for pharmacological management with antispasmodics

LES and cardia in these patients. The rationale was that, since the LES relaxes normally in these disorders, performing LES myotomy may have no therapeutic benefit and may in fact subject the patient to acid reflux, which, apart from resulting in GERD and possible sequelae such as Barrett’s esophagus and strictures, may also exacerbate the underlying spastic disorder. It gradually became apparent, however, that performing esophageal myotomy without concomitant LES myotomy in these patients may result in suboptimal outcomes. It appears that the substantial weakening or virtual obliteration of peristalsis by the esophageal body myotomy results in poor emptying unless the LES is also proportionately weakened by extending the myotomy through the LES. In Fig. 7.20, we present a case of LES-sparing POEM in a jackhammer patient that illustrates this point.

Unlike immediate bleeding which most frequently occurs during dissection of the submucosal tunnel and was addressed in the earlier section of this chapter, delayed bleeding has been reported to usually occur from vessels at the cut muscular edges “because of an abundance of blood vessels and collateral circulation in the muscle layers of the esophagus” [56]. In our experience, the vessels encountered during myotomy include small vessels intercalated between the muscle bundles and large vessels (mostly veins, but also few scattered arteries) running transversely in the space between the esophageal muscle and mediastinal pleura. The vessels are

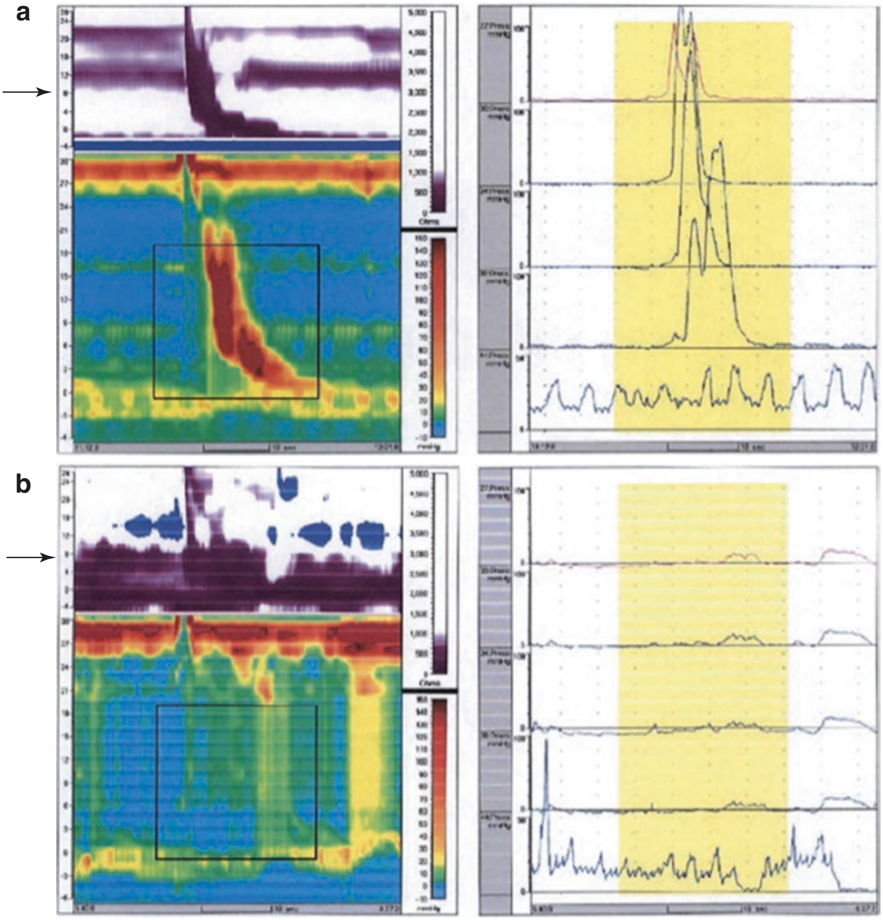


Fig. 7.20 This figure illustrates the potential pitfalls of POEM, particularly POEM without LES myotomy, to treat spastic disorders with intact peristalsis and normal LES relaxation. This patient with jackhammer esophagus underwent POEM with preservation of the LES. On the pre-POEM HRM (**a**), classic jackhammer features are present with high-amplitude peristaltic contractions extending from the LES to 21 cm proximal to the LES (see scale on left of HRM plot) which were causing severe pain, moderate dysphagia, and rare regurgitation. The patient had minimal response to pharmacological therapy and was referred for POEM. We performed POEM with long esophageal body myotomy of 21 cm and no incision of the LES since it demonstrated normal relaxation on HRM. On the post-POEM HRM (**b**), the patient has essentially abolished peristasls with only minimal pressurization waves. Note the poor emptying noted on the post-POEM impedance graph compared to the pre-POEM impedance graph (*white arrows*). Residual fluid (denoted by *purple color* on the impedance graph) remains in the esophagus after POEM, whereas there was prompt and complete clearance of fluid prior to POEM. After the POEM, even though the patient's pain symptoms improved dramatically, dysphagia and regurgitation worsened slightly. A second POEM was performed with LES myotomy which improved but did not normalize emptying with moderate improvement in dysphagia and regurgitation

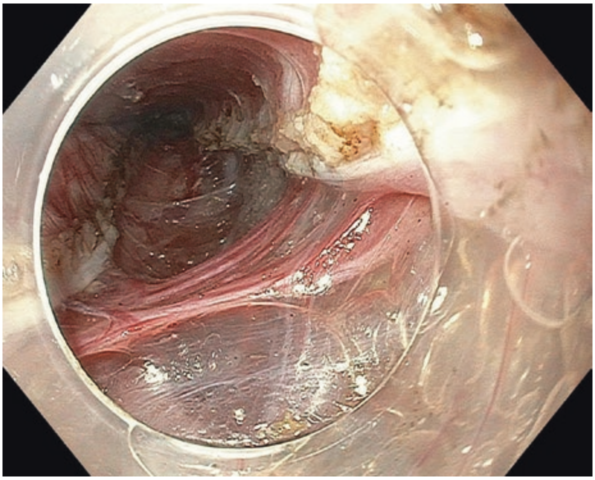


Fig. 7.21 The vascular plexus deep to the muscularis propria layer exposed during POEM with full-thickness posterior myotomy. This plexus consists of a "ladder" of transvserse arteries and veins located between the esophageal wall and mediastinal pleura

largely adherent to the esophageal wall and thus often divided during full-thickness myotomy. The density of the small intramuscular vessels can be variable, whereas the deeper vessels forming a plexus in the form of a "ladder" in the bed of a full-thickness myotomy is a reliable finding that needs to be considered during the myotomy (Fig. 7.21). Bleeding from the small intramuscular vessels can be easily controlled by short pulses of a coagulation current using the tip of the knife. If a high density of such vessels is encountered, increasing the coagulation effect in the current used for the myotomy (e.g. by using a higher "effect" setting on the commonly used Endocut Q program in the ERBE VIO generator) can effectively coagulate these vessels as the myotomy is being performed. Bleeding from the larger, transverse, submuscular vessels can be riskier to control since extensive irrigation is ill-advised in an exposed mediastinum, and coagulation will by necessity involve some current escape to the underlying mediastinal pleura and other adjacent structures such as the pericardium and pleura potentially injuring these structures. Therefore, prevention of bleeding from these deeper vessels is the optimal strategy. Identification of the vessels as the muscle bundles are being hooked prior to cutting is optimal since, if such vessels are detected, the myotomy can be performed with high coagulation (e.g. with spray coagulation on the VIO 300 D generator) or a plane for the knife can be found between the vessels and the muscle thus avoiding division of these vessels altogether. It should be noted that identification of such vessels (as well as other structures deep to the muscle to be cut) is not possible when myotomy is performed in distal to proximal fashion as has been advocated by some operators [57].

Closure of the Submucosal Tunnel

Although in the majority of cases tunnel closure is uneventful, in a small percentage of cases closure can be difficult. This situation can be very stressful for the endoscopist given the critical role of tunnel closure in preventing leakage and the potentially life-threatening adverse events such as mediastinitis, empyema, and abscess formation.

Advance planning is essential in avoiding closure pitfalls. As noted above in the "Site and Orientation Selection" section, it is important to pick a site away from potential submucosal fibrosis. It is also important to avoid creating the opening of the tunnel in an area of esophageal angulation or next to the spine in an area where the spine severely indents the esophagus. An angulation of the esophagus can be easily overcome for the purpose of making the initial incision by creating a large submucosal injection. However, at the time of closure with submucosal lifting no longer present, the operator may discover that what appeared as a minor lumen indenting fold or angulation at the time of tunnel initiation after a generous submucosal injection now presents a major obstacle to clip or suture placement. Applying clips or even sutures may be very challenging if the incision is placed along the downsloping mucosa draped over the right side of a prominent spine impression. Again, the potential adverse impact on closure may not be appreciated when the initial incision is made since a large submucosal injection can elevate the mucosa and submucosa well above the prominent spine impression. However, at the time of closure without the assistance of a lifted mucosa and submucosa, the firm concave protruding bone under a downsloping everted left edge of the tunnel entry site makes it difficult to apply clips and even sutures. Also, as briefly alluded to above in the "Submucosal Tunnel Dissection" section, forceful blunt insertion of the endoscope can result in tearing of the insertion site creating a much larger defect than the one initially created (Fig. 7.6). Finally, again as briefly mentioned above, submucosal dissection closer to the mucosa rather than muscularis propria during tunnel initiation can result in thin mucosal edges without significant underlying submucosa (which is much stronger structurally).This can also occur in cases of severe fibrosis and malnutrition with resultant paucity of submucosal tissue. Finally, thick mucosal edges resulting from chronic inflammation due to long-standing disease and severe food stasis can be difficult to approximate with the usual endoscopic clips. In this scenario, use of larger over-the-scope clips (OTSC) has been reported [58]. Endoscopic suturing using the only such device currently available in the United States (Overstitch, Apollo Endosurgery, Austin, TX) can also be effective in this situation. We have used endoscopic suturing routinely and exclusively for POEM tunnel closure for the past 4 years (including over 200 POEMs) and have published a retrospective comparison of the two techniques [59]. We collected and analyzed data on our first 62 consecutive POEMs closed with clips and the subsequent 61 consecutive POEMs closed with sutures. To avoid learning curve bias from early cases, we compared the most recent 25 consecutive closures in each group with regard to cost, procedure time, and adverse events. There were no significant differences in closure time (8.8 min for endoclips and 10.1 min with OverStitch), cost ($916 versus $818), and hospital stay (1.9 days versus 1.7 days). The Portland group also conducted a smaller retrospective case-controlled study evaluating closure with hemostatic clips versus endoscopic suturing [60]. Out of the 124 POEM cases that were assessed, endoscopic suturing was employed in only 10 (8%). Five of these cases were selected for the study and were matched to five cases where conventional clips were used. Median closure time was significantly shorter for the endoscopic clip group (16 ± 12 min) as compared to the suturing group (33 ± 11 min),

p = 0.044. The very long median closure time for endoscopic suturing is not explained and was the main reason for a cost advantage when endoscopic clips were used (the device costs were similar with the OR time difference accounting for most of the cost difference according to the authors). The authors concluded that endoscopic suturing seems best suited for cases of difficult mucosotomy closure. Special situations are occasionally encountered. When attempting to close very thin devitalized mucosal edges that tear even with attempted interrupted suture placement or very large linear defects as can be caused by extensive tearing in a narrow-lumen esophagus where suturing may occlude the lumen, neither clips nor suture closure is optimal. In these situations, third-line methods may need to be applied such as fibrin glue [44] or stent placement [45]. Such methods provide less reliable closure and should be accompanied by longer observation under NPO status, intravenous antibiotics, and radiographic leak assessments similar to the management of contained esophageal leaks.

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Learning Curve and Initial Outcomes

8

Joel M. Sternbach and Eric S. Hungness

Abbreviations

DI	Distensibility index
EGJ	Esophagogastric junction
FLIP	Functional lumen imaging probe
POEM	Per-oral endoscopic myotomy
SCJ	Squamocolumnar junction

Introduction

Per-oral endoscopic myotomy (POEM) represents the prototype for successful natural orifice surgery; an incisionless, endoscopic approach combined with the precision of a surgical myotomy. Since the initial description by Haru Inoue of the procedure in 2008 and publication of his initial results in 2010, POEM has been adopted at high-volume esophageal centers around the world [1]. The procedure is being performed by both surgical endoscopists and interventional gastroenterologists. This chapter reviews the characteristics and initial experience of early POEM operators, the existing literature regarding the learning curve for POEM, and initial outcomes in published series.

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Early Outcomes

The early global POEM experience was summarized in the International POEM Survey (IPOEMS) [2] and formed the basis for a white paper published by the American Society for Gastrointestinal Endoscopy and the Society of American Gastrointestinal and Endoscopic Surgeons. The survey included initial results from the 16 centers around the world that had performed >30 procedures as of July 2012, when the survey was conducted. IPOEMS confirmed the high success and low complication rates initially reported by Inoue, in addition to outlining the training and techniques of the 25 POEM operators (14 surgeons and 11 gastroenterologists). The majority of the respondents reported having experience with either endoscopic submucosal dissection (ESD) or natural orifice translumenal endoscopic surgery (NOTES) prior to introducing POEM at their institutions. Overall, the operative technique described by the participating centers was similar to that initially described by Inoue [1]: submucosal access through a longitudinal mucosotomy ~10 cm above the squamocolumnar junction, creation of a submucosal tunnel extending 4–5 cm onto the stomach, performance of a selective myotomy of the inner, circular muscle fibers, and finally closure of the mucosotomy with hemostatic clips. Minor variations were reported in instrumentation choice and position on the esophageal wall for the creation of the mucosotomy and entry into the submucosal space. Most centers perform POEM with the patient supine and create the submucosal tunnel and subsequent myotomy in the anterior or right-anterior aspect of the esophageal lumen (the 12–2 o'clock position), with two centers reporting the use of a right-posterior approach (the 5 o'clock position). Ten of the 16 centers included in the survey contributed initial outcomes data for treatment efficacy, in terms of symptomatic relief as assessed by the Eckardt score and objectively in terms of decrease in lower esophageal sphincter (LES) pressure and improved bolus clearance on timed barium esophagram (TBE), and the safety of the procedure. All of the centers reported symptomatic relief in at least 80% of patients, with all but two centers reporting >93% efficacy. Significant decreases were also seen in LES pressure and column height at 5 min on TBE. Adverse events were rare in the combined early experience of the survey participants with rates of postoperative leak and bleeding of 0.2% and 1%, respectively [2].

Learning Curve

Retrospective studies of the POEM learning curve at single centers have evaluated a variety of different components of the procedure [3–6]. Aspects that have been studied include: overall procedure duration, duration of procedure per centimeter of myotomy, time to complete the four main steps of submucosal access, tunnel creation, myotomy and mucosotomy closure as well as the rate of inadvertent mucosotomy creation and number of clips required to close the mucosotomy.

Kurian and colleagues reported the intraoperative learning curve observed during the first 40 cases performed by a surgeon with extensive endoscopic experience and by minimally invasive surgery fellows [3]. The senior author (Swanström) performed the first 16 cases and then transitioned to increasing participation by two fellows. Based on decreases in total procedure length, reduced variability in minutes/cm of myotomy, and reduction in the rate of inadvertent mucosotomies, the authors reported a learning curve of approximately 20 cases; their presented data, however, indicate that the last inadvertent mucosotomy during the cases performed by the senior surgeon occurred during case 14, with no additional events over the next seven cases.

Patel and associates at Winthrop University Hospital, in the largest series to date [4], reported the learning curve for a gastroenterologist with expertise in advanced endoscopy including endoscopic submucosal dissection (ESD) (Stavropoulos). In their study, the authors used cumulative sum (CUSUM) analysis and found efficiency to be achieved after 40 cases and mastery after 60 cases.

Recently, El Zein and colleagues reported on the technical aspects of the first 60 cases performed by a single interventional gastroenterologist, using a variety of methodologies to evaluate the learning curve for POEM [5]. Focusing on the learning plateau and learning rate, the authors reported a plateau of 102 min for total procedure time and 10 min/cm of myotomy, with learning rates of 13 and 11 cases, respectively. Analyzing the components of the POEM procedure individually revealed significant decreases in time to completion for each step besides myotomy creation; however, the time per cm of myotomy did decrease significantly over time, reflective of the inclusion of patients with more complex, spastic motility disorders, who received extended proximal myotomies. The learning plateau for each of the four steps of the POEM procedure was attained after performing 14–16 cases. The number of clips required to close the mucosotomy (median 5, range 4–12) also decreased significantly over time.

Teitelbaum and colleagues previously reported on the learning curve for the two minimally invasive surgeons who jointly performed the initial 36 cases at our institution [6]; a component analysis revealed a learning rate of seven cases for achieving submucosal access and performing the myotomy. Submucosal tunnel creation time, the longest component of case, started to “funnel” toward the mean at case 15. Based on these data and similar findings from the Oregon Clinic group, we believe the learning curve for POEM by minimally invasive surgeons with significant achalasia and endoscopy experience is approximately 15 cases.

The potential impact of the learning curve for a technically demanding procedure such as POEM was highlighted in the results of follow-up from the multi-center European POEM trial. In that study, approximately one in five patients had suffered a recurrence of symptoms or required further intervention [7], raising a question of POEM durability. However, half of the failures occurred during the initial ten cases performed at each of the three participating centers, suggesting a learning curve effect that may have biased the rates of long-term treatment success.

Recently, published results from our center for 115 consecutive patients *beyond* the learning curve (initial 15 patients) revealed durable symptomatic relief and physiologic improvement at an average of 2 years of follow-up. The symptomatic relief reported by 92% of patients and objective GERD in ~40% of those studied is in line with previously published reports on the outcomes following laparoscopic Heller myotomy (LHM) [8]. Limitations of these learning curve analyses include the previously mentioned heterogeneous outcome measures as well as the appropriate exclusion of "difficult" cases during the initial POEM experience at each center.

Measuring EGJ Distensibility During POEM

The functional lumen imaging probe (FLIP), a novel catheter-based test of esophageal function, consists of an 8 cm, compliant balloon that is placed across the LES and can be progressively filled with a saline solution surrounding 17 impedance rings. Utilizing impedance planimetry, the commercially available EndoFLIP (model EF-325N; Crospon Inc., Galway, Ireland) device generates a geometric representation of luminal structures and also includes a solid-state pressure transducer within the balloon. When obtaining measurements with the EndoFLIP at the level of the EGJ, dividing the minimum cross-sectional area by the intra-bag pressure allows the calculation of the EGJ distensibility index (DI). Prior work has shown the EGJ DI to be pathologically low in patients with achalasia and elevated in patients with GERD [9, 10]. During both POEM and LHM, the FLIP can be used to measure stepwise changes in EGJ distensibility following key components of each operation (induction of anesthesia, submucosal tunnel creation/hiatal dissection, myotomy completion and in LHM, construction of a partial fundoplication) [11, 12].

Overall, POEM resulted in a greater increase in distensibility than LHM with a partial fundoplication [12]. Serial measurements of EGJ DI during incremental extension of the esophagogastric myotomy were evaluated to determine the proximal and distal extent necessary to "normalize" distensibility [11]. The greatest increase in EGJ DI during both operations occurred after extension of the myotomy across the EGJ. During LHM, it was observed that proximal extension of the myotomy to 6 cm above the squamocolumnar junction was required to normalize the EGJ DI. The same effect was achieved during POEM with a more limited proximal myotomy. Also during POEM, incremental extension of the distal, gastric myotomy beyond 2 cm below the SCJ did not result in significant additional increases in EGJ DI [11].

The mechanism of distensibility increase following creation of the submucosal tunnel is unclear and may represent only a temporary effect related to CO_2 infiltration of the musculature or disruption of the submucosal tissue architecture, untethering the mucosa. Anecdotally, we have observed increased distensibility driven by both decreases in pressure and increased cross-sectional area following creation of the submucosal tunnel, prior to performing a selective myotomy of the inner, circular muscle layer. Additionally, it is the increase in distensibility resulting from the myotomy that appears to drive symptomatic relief. We have previously shown that the highest rates of "optimal" outcomes following POEM (relief of dysphagia without GERD) are obtained by achieving a final distensibility within the "sweet spot" of 4.5–8.5 mm^2/mmHg [13].

Conclusion

POEM is now an acceptable treatment for esophageal motor disorders which has an initial learning curve of about 20 cases. Beyond the learning curve, comparable results to that of Heller myotomy are expected. Measuring EGJ distensibility is a novel method to ensure an adequate myotomy during POEM and may help surgeons shorten the expected learning curve.

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9 Comparative Outcomes: POEM Versus Balloons, Botox, and Surgical Myotomy

Steven R. DeMeester

Symptoms in patients with achalasia are produced by outflow obstruction at the level of the lower esophageal sphincter (LES). As a consequence of neural destruction, the LES does not undergo normal swallow-induced relaxation. In addition, the esophageal body loses normal peristaltic function and esophageal emptying is on the basis of gravity. All therapies for achalasia are palliative in that normal LES or esophageal body function cannot be restored. The efficacy of any therapy for achalasia is directly related to its ability to reduce the outflow obstruction at the LES. In its untreated form, achalasia is at the opposite end of the spectrum from gastroesophageal reflux disease (GERD). Treatment for GERD is to augment the defective LES, while treatment for achalasia is to render the LES less competent. Consequently, overzealous augmentation of the LES for GERD can lead to an achalasia-like condition, and all treatments for achalasia risk inducing significant GERD. Likewise, the importance of obtaining an appropriate diagnosis of GERD or achalasia with objective testing including esophageal manometry prior to instituting therapy is critical to prevent inappropriate treatment and poor outcomes.

Recently, the role of manometry has taken on importance beyond confirming a diagnosis of achalasia. On high-resolution manometry (HRM), three achalasia types have been defined, and the outcome with achalasia treatment has been linked with the specific subtype. Type I or "classic" achalasia has incomplete LES opening and an aperistaltic, flaccid esophageal body. Type II has panesophageal pressurization, and Type III has no normal peristalsis, but evidence of distal esophageal spasm. Characteristic of all three types is an elevated integration relaxation pressure (IRP) above 15 mmHg [1]. The highest success rates with treatment for achalasia appear

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to be in patients with Type II achalasia [2, 3]. Laparoscopic myotomy and POEM are effective in all subtypes of achalasia, but the outcome with pneumatic dilatation has been shown to be poor in patients with Type III achalasia [2]. In these patients, alternative therapies are recommended.

Until recently, the treatment of achalasia involved trade-offs between efficacy and invasiveness. On the low efficacy and low invasiveness side are Botox injection and a single pneumatic dilatation. While these can be efficacious, they tend to less reliably produce good long-term outcomes than therapies on the more invasive end of the spectrum. Moving toward more invasive and better efficacy are multiple pneumatic dilatations and finally Heller myotomy. The introduction of laparoscopic techniques for the Heller myotomy reduced the invasiveness without compromising efficacy. Now, with the introduction of POEM, a paradigm shift has occurred where patients can have the efficacy of the laparoscopic Heller myotomy with essentially the invasiveness of a single pneumatic dilatation.

Injection of botulinum toxin is an attractive option for patients with achalasia, given the simplicity of the procedure. During endoscopy, 100 units of botulinum toxin A is injected in equal aliquots around the gastroesophageal junction, typically in four or eight locations. Efficacy with botulinum toxin is typically the lowest of the achalasia treatment alternatives and its effects are temporary [4]. Consequently, botulinum toxin is typically reserved for patients who are poor candidates for other more definitive therapies, or as a temporizing measure until a more definitive therapy can be arranged. A drawback to botulinum toxin injection is that it can induce submucosal scarring which can make a laparoscopic myotomy or POEM procedure more difficult. Further, although very safe, excessively deep injection in the area of the LES can lead to aortic injury and must be avoided.

Pneumatic dilatation is done with an achalasia balloon that is at least 150% the normal size of the esophagus, in an effort to disrupt the dysfunctional LES musculature. A single dilatation with a 30-mm balloon is unlikely to provide permanent relief of symptoms, but repeated dilatations and use of larger (35 and 40 mm) balloons for recurrent symptoms leads to improved results. In a randomized trial from Europe, an aggressive pneumatic dilatation protocol led to success rates similar to that observed with a laparoscopic Heller myotomy, but with a 4% risk of esophageal perforation [5]. Success, defined as a reduction of the Eckardt symptom score to three or less, occurred in 90% of patients after laparoscopic myotomy compared to 86% of patients after pneumatic dilatation at 2 years. The frequency of an abnormal pH test and endoscopic esophagitis was similar for the two treatments (15% and 19%, respectively, for pneumatic dilatation and 23% and 21%, respectively, for laparoscopic myotomy with partial fundoplication). Risk factors for the need for re-dilatation included preexisting daily chest pain, age younger than 40 years, and a > 10 cm column of retained barium 5 min after contrast ingestion on a timed barium esophogram 3 months after dilatation [5]. Long-term results after pneumatic dilatation either as a single dilatation or after multiple dilatations show a success rate of 78% at 5 years, 61% at 10 years, and 58% at 15 years [6]. Recently, the outcome with pneumatic dilatation has been shown to be poor in patients with type III achalasia [2]. Consequently, patients with type III achalasia are considered to have a relative contraindication to pneumatic dilatation and alternative therapies are preferred.

The Heller myotomy dates back to over 100 years and is named after the German surgeon Ernest Heller. This procedure, with three important modifications, has become the gold standard therapy in the US and most centers worldwide for the treatment of achalasia. The three modifications consist of the introduction of a minimally invasive laparoscopic approach, the addition of a partial fundoplication, and extension of the myotomy 2–3 cm down onto the stomach. The initial foray into minimally invasive surgery for achalasia was a thoracoscopic myotomy described by Pellegrini and colleagues in 1992 [7]. However, the laparoscopic approach has been proven superior and is now the standard of care for a minimally invasive myotomy for achalasia [8]. Similarly, following publication of a randomized trial showing that the addition of a partial fundoplication to a Heller myotomy reduces gastroesophageal reflux compared to myotomy alone without imposing increased outflow obstruction, a partial fundoplication should be added to a Heller myotomy [9]. Lastly, an analysis of outcome after myotomy showed that an extended gastric myotomy was associated with improved results. Consequently, extension of the myotomy 2–3 cm down onto the stomach is now accepted as the appropriate technique during laparoscopic myotomy [10].

A laparoscopic Heller myotomy with these modifications has been shown to produce excellent, durable results at centers around the world [11–13]. In a series of 400 laparoscopic myotomies from Italy, 82% of patients were free of symptoms 10 years after the operation [14]. Further, a laparoscopic Heller myotomy and Dor has been shown to have a lower rate of re-intervention compared to pneumatic dilatation and to be effective for all subtypes of achalasia [15].

Complications can occur with a laparoscopic myotomy, but mortality should be extremely rare. In an analysis of the American College of Surgeons National Surgical Quality Improvement Program database, Niebisch et al. showed that the overall 30-day mortality after a laparoscopic fundoplication was 0.19% and was only 0.05% for patients under the age of 70 years [16]. Further, the most common complications following fundoplication were pulmonary (1.3%) and urinary tract infections (1.1%). These low mortality and complication rates for fundoplication should hold for myotomy and partial fundoplication as well [17]. There are three potential complications with a laparoscopic myotomy and fundoplication that deserve focused attention. The first is mucosal perforation during the myotomy. The literature and personal experience would suggest that perforation occurs more frequently in patients previously treated for achalasia, particularly with botulinum toxin injection [18]. Most perforations occur during the myotomy on the stomach since the mucosa below the gastroesophageal junction is very thin. Immediate recognition is of paramount importance and repair with fine absorbable sutures and covering the site with the partial fundoplication leads to successful healing in nearly all cases.

The second complication to focus on is a leak from the myotomy site. The possibility of a leak should be considered in any patient who has fever, chest pain, or clinical signs consistent with sepsis postoperatively. The work-up should include a water-soluble contrast swallow and/or upper endoscopy. Contrast radiographic studies are known to miss small leaks, and in the clinical setting of sepsis, they should not be relied upon to rule out a leak definitively. A CT scan can be useful and may show evidence of an abscess or air/fluid level near the hiatus or small air bubbles in the mediastinum. Endoscopy is a sensitive test and should be used to evaluate the esophagus if a leak is suspected or confirmed. Most small leaks can be managed with intravenous antibiotics and no oral intake, and in some cases, can be treated endoscopically with clips or endoscopic suturing. Larger leaks may require CT-guided drainage or, rarely, reoperation.

The third focused complication is recurrent or persistent dysphagia. Causes include an inadequate myotomy, typically related to insufficient extension onto the stomach, scaring and closure of the myotomy, excessive fundoplication, typically from a Nissen fundoplication, or a GERD-related complication such as erosive esophagitis or a peptic stricture. Determining the etiology usually requires upper endoscopy and a repeat manometry. In some patients, a timed barium swallow or a pH test can also be useful. Treatment is based on the etiology.

Recently, a new procedure for achalasia has been introduced, the per-oral endoscopic myotomy, or POEM. It may be the best of both worlds, allowing a precise myotomy with the recovery benefits of no external incisions and no physical restrictions. The POEM procedure was first used to treat achalasia in a human by Inoue in 2008, and his initial experience was reported in 2010 [19]. Since Inoue's first procedure, there has now been thousands of POEM procedures performed worldwide. The POEM procedure begins with an incision in the mucosa followed by creation of a submucosal tunnel that is carried 2–3 cm below the gastroesophageal junction. A myotomy of the circular fibers of the muscularis propria down through the LES is then performed. The procedure is completed by closing the mucosal defect either with clips or sutures. There are numerous publications on the early results of POEM for achalasia. From these, a number of conclusions can be drawn.

First, POEM is very safe, even during the learning curve [20, 21]. Some complications including subcutaneous emphysema, pneumothorax, and pneumoperitoneum are much more common with the use of air rather than carbon dioxide for insufflation. The use of carbon dioxide and general anesthesia is recommended [22]. Bleeding from large submucosal vessels can be problematic, but typically is readily controlled with the use of coagulating forceps and, with experience, is easier to avoid than to treat during creation of the submucosal tunnel. Delayed bleeding occurs rarely, although in some cases has required re-exploration of the tunnel [23]. Another occasional source of morbidity is the mucosal closure. Typically, a barium swallow is done later that day or the day after the procedure to verify the integrity of the closure. A leak into the submucosal tunnel should prompt re-exploration. In a recent series of 500 patients published by Inoue, there were 16 adverse events (3.2%). Most of these were minor and none resulted in abandonment of the POEM procedure. There were no deaths [24]. Overall, for a novel procedure, there has been remarkably little morbidity, although most reports are from centers with significant experience in the management of patients with esophageal disorders.

Second, POEM results in significant improvement in dysphagia and regurgitation symptoms. In a series by Swanstom et al., the median Eckardt score in 20 patients at 1 month after POEM was 1, down from 6 pre-POEM, and over half of the patients had complete resolution of dysphagia [25]. At 18 months, the median Eckardt score was 0; most patients had no dysphagia symptoms, and all were satisfied with the results of the procedure. On objective evaluation, the median emptying at 5 min by timed barium swallow had improved from 48 to 100% at 6 months post-POEM. Similarly, in an international, multi-institution series of 70 patients, the median Eckardt score dropped from 7 to 1 at 3 months after POEM, and treatment success was achieved in 97% of patients [26]. The mean LES pressure decreased from 28 to 9 mmHg. At 12 months after POEM, sustained treatment success was present in 82% of patients, and the mean Eckardt score was 1.7 in the 51 patients available for follow-up. In the recent series of 500 patients published by Inoue, 3-year or longer follow-up was available in 61 patients. Overall success rate was excellent at 88.5% and was similar to the results at 1–2 years [24]. In addition, similar to laparoscopic myotomy, POEM is effective in all HRM types of achalasia, and in fact, may have an advantage in type III achalasia since a long myotomy can readily be achieved with POEM [27].

Third, POEM by virtue of its myotomy without a partial fundoplication appears to be more likely to lead to reflux than other achalasia therapies. In the series by Swanstom et al., 33% of patients reported heartburn at 6 months after POEM. On upper endoscopy, erosive esophagitis was seen in 28% of patients and, when combined with pH monitoring objective evidence of GERD, was present in 50% of patients [25]. In the international series, 37% of patients had reflux symptoms and erosive esophagitis was present in 42% of patients at 12 months post-POEM [26]. Initially, it appeared that the frequency of reflux after POEM was less in the Asian population compared to that from Western countries. However, in the series of 500 patients by Inoue from Japan, upper endoscopy showed reflux esophagitis in 65% of patients in the short term, and 59% at 1–2 years after POEM [24].

Fourth, compared to a laparoscopic Heller myotomy with partial fundoplication, POEM has been shown to lead to a similar good outcome in two series comparing these procedures. The first, by Hungness et al., showed that operative times were shorter with POEM, but complications and the median length of hospital stay were similar for the two procedures [28]. The second, by Bhayani et al., showed that postoperative Eckardt scores were lower after POEM and 100% of patients had relief of dysphagia after POEM compared to 97% after laparoscopic Heller myotomy and partial fundoplication [29]. Symptoms of heartburn, reflux, and chest pain were similar for the two procedures. On objective testing, the absolute and relative decreases in LES resting pressures were similar, but the resting pressure was higher after POEM. On 24-h pH monitoring, the frequency of increased esophageal acid exposure was similar at about 35% after each procedure. A meta-analysis of non-randomized studies showed that, compared to laparoscopic myotomy, there is no significant difference in operation time, length of hospital stay, or complication rates with POEM [30]. However, Eckardt scores were significantly lower after POEM compared to laparoscopic Heller myotomy.

While most POEM procedures are done for achalasia, the indications have expanded to diffuse esophageal spasm, hypertensive LES, and as a technique to remove smooth muscle tumors in the muscularis propria of the esophagus and gastroesophageal junction. The concepts have also been applied to performing an endoscopic myotomy of the pylorus for delayed gastric emptying and of the cricopharyngeous for Zenker's diverticulum or cricopharyngeal dysfunction. It is likely that endoscopic procedures employing submucosal tunneling techniques will increasingly play a role in modern therapy for a variety of gastrointestinal disorders.

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POEM for Chagas Disease-Induced Achalasia

10

Elan R. Witkowski and Ozanan R. Meireles

Introduction

Chagas disease is a relatively uncommon but fascinating cause of esophageal dysmotility. While the GI manifestations of Chagas have been studied for many years, there is relatively little data available to guide the use of Peroral Endoscopic Myotomy (POEM) in this disease. In this chapter, the pathophysiology and treatment of Chagas are reviewed.

Chagas Disease: Pathology, Epidemiology, and Manifestations

Chagas disease is the systemic manifestation of *Trypanosoma cruzi* infection and is also referred to as American Trypanosomiasis. First described by the Brazilian Dr. Carlos Chagas in 1909, the disease was increasingly recognized as an important pathogen in Central and South America in the 1960s. It remains endemic in many countries from Mexico to Argentina and is estimated to cause more than 10,000 deaths per year worldwide [1]. Because of the potentially long interval between infection and presentation with symptoms, patients infected in endemic regions can emigrate and later present for care in communities around the world (Fig. 10.1).

Transmission of the parasitic protozoa occurs mostly via hematophagous insects of the Triatominae subfamily, also known as “kissing bugs.” While vector-borne transmission typically occurs in endemic areas, other forms of blood-borne transmission have occurred through transfusion, organ transplantation, etc. Several other methods of infection have been identified; including vertical transmission from mother to child, rare cases of consumption of uncooked food contaminated with feces from infected bugs, and accidental laboratory exposure.

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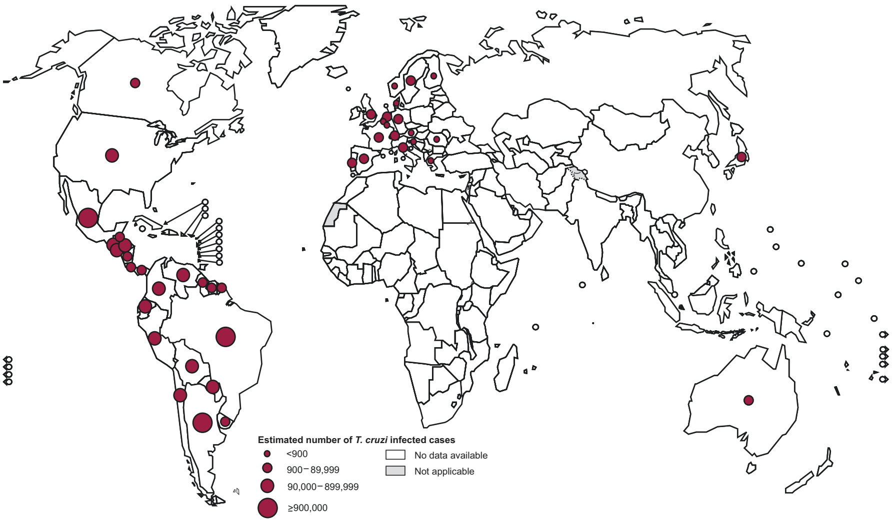

Fig. 10.1 Global distribution of cases of Chagas disease, based on official estimates, 2006–2010. Image ©World Health Organization, 2010

Once infected, the disease in humans can unfold in several patterns. An acute illness sometimes occurs in the weeks or months after infection—producing fevers, myalgias, headache, or nonspecific GI symptoms. Physical signs can include lymphadenopathy, rash, hepatosplenomegaly, or local induration at the site of the bite. It is common for acute Chagas to go unnoticed, with minimal symptoms and rapid improvement over a several weeks.

After infection, Chagas can progress to a chronic form of the disease. This occurs in approximately one third of patients, and treatment of the acute illness does not necessarily prevent chronic disease. The manifestations of Chagas can take decades to appear and are often irreversible once discovered.

Chronic Chagas disease primarily affects the heart, GI system, and rarely the central nervous system. Cardiomyopathy and conduction abnormalities are frequently seen (~20–30%). GI manifestations are also common and thought to be related to destruction of both excitatory and inhibitory pathways in the enteric plexus and damage to the interstitial cells of Cajal.

Gastrointestinal manifestations of Chagas can include any of the following: sialorrhea, achalasia with or without massive esophageal dilation, delayed gastric emptying and impaired receptive relaxation of the stomach, prolonged small bowel transit times, colonic dysmotility with massive dilation leading to megacolon, or biliary dilation and cholelithiasis.

Esophageal Manifestations: Chagasic Achalasia

Dysphagia, chest pain, or weight loss may be the initial presenting symptoms of chronic achalasia. A high level of suspicion is required to differentiate the disease from other forms of esophageal dysmotility. Further investigation is required to differentiate chagasic from idiopathic achalasia. As previously described, chronic *Trypanosoma cruzi* infection can lead to profound esophageal disease that is quite similar to idiopathic achalasia.

Symptoms of Chagas-related esophageal disease may include dysphagia, active and passive regurgitation, chest pain, odynophagia, cough, aspiration, sialorrhea, and weight loss. Megaesophagus is frequently seen in later stages of the disease.

Manometric differences between idiopathic achalasia and Chagas related have been debated [2–4]. Some have reported resting pressures in the lower esophageal sphincter (LES) that are lower than normal [1, 5], due to the destruction of both excitatory and inhibitory neuronal pathways. In contrast, patients with idiopathic achalasia often have increased basal LES pressures [6, 7]. A spectrum of other manometric findings is seen, including the typical progression of discoordination, failure of appropriate LES relaxation, and aperistalsis [8, 9].

Diagnostic Workup

Patients may present with any combination of organ systems affected, and a careful history is critical when considering an intervention for achalasia secondary to Chagas disease. Investigations should be focused on describing esophageal motility and function, testing for Chagas disease, and evaluating for extra-esophageal disease.

A large number of serologic tests have been used to detect Chagas disease in its chronic form by identifying formed antibodies to the parasite. Patients at risk for Chagas (from areas with endemic disease, etc.) should be tested with at least two different serologic assays to secure the diagnosis [10]. Additional testing to rule out other intestinal parasites may be useful including the detection of trypomastigotes in blood via microscopy following initial infection. Labs to assess for protein-calorie and micronutrient deficiencies may be indicated.

Cardiac evaluation should be performed before any surgical intervention in those with confirmed Chagas disease, including ECG and chest radiographs. Dysrhythmias can present during surgery, especially during esophagectomy [10–12]. Patients with chronic aspiration may also require pulmonary testing.

Workup of esophageal disease in patient with Chagas proceeds similarly to those with idiopathic achalasia. Routine tests should include barium esophagram and esophageal manometry [11]. Radiographic appearance of the esophagus can range from normal to a massively dilated, tortuous esophagus. Manometry is a key component of the workup, and several patterns may be identified as described earlier in this chapter. However, there is a typical finding of incomplete or absent LES relaxation in advanced Chagas disease as well as aperistalsis in its final stages with megaesophagus [8]. Endoscopy should always be performed, as it is helpful in evaluating the quality of mucosa, assessing presence of candidiasis, clearance of foreign bodies or food, ruling out alternative diagnoses, and as a therapeutic intervention.

Stage at Presentation

The timeline of progression of chronic Chagas to symptomatic and then aperistaltic megaesophagus is variable, but can often take decades. Further, patients may come from resource-limited environments with poor access to care. When discovered early, treatment is quite similar to that of idiopathic achalasia. However, there are many series of patients described in the literature (mostly from endemic regions) who present with end-stage disease and a nonfunctional esophagus. The published experiences of these centers are critically important in understanding the spectrum of disease management in Chagas achalasia, but should not necessarily be extrapolated to populations where the disease is likely to be discovered much earlier (Fig. 10.2).

Treatment

Occasionally, patients will present with acute esophageal obstruction or complications requiring immediate endoscopic intervention. However in the vast majority of patients, treatment begins after appropriate workup including serologic testing, treatment of systemic infection, evaluation for extra-esophageal disease, nutritional evaluation, and examination of the esophagus with the testing described above.

As is the case for idiopathic achalasia, therapy for Chagas-related disease is palliative rather than curative. Dysmotility is usually progressive, and thus the goal of therapy is to produce a useful conduit (for oral nutrition, to reduce symptoms, and prevent complications such as aspiration) rather than to restore truly normal function.

The general approach to a patient with Chagas is similar to that in idiopathic achalasia. Patients with unacceptable perioperative risk may be considered for botulinum toxin injection of the LES or systemic therapy with nitrates or calcium channel blockers [6]. For the vast majority of patients, more definitive therapy is preferable.

The debate over the role of pneumatic dilation as a first-line therapy is beyond the scope of this chapter [6, 15]. The authors of this chapter prefer myotomy for most patients with acceptable perioperative risk. A small early study comparing pneumatic dilation to bouginage in Brazilian patients with Chagas megaesophagus demonstrated sustained normalization of LES pressures 1 year after pneumatic dilation, but no change in pressure and a return of symptoms after bougie dilation [16]. There have been multiple series examining the effectiveness of dilation in Chagas patients, including patients with megaesophagus [17]. Overall results are good, but equivalent or inferior to minimally invasive esophageal myotomy.

The adoption of minimally invasive techniques has significantly increased the popularity of surgical therapy [18, 19]. Laparoscopic Heller myotomy has become the standard first-line therapy for patients without megaesophagus. A large body of literature has demonstrated excellent symptomatic improvement, low rates of complications, and long-term durability of this operation in patients with idiopathic and chagasic achalasia and a non-dilated esophagus.

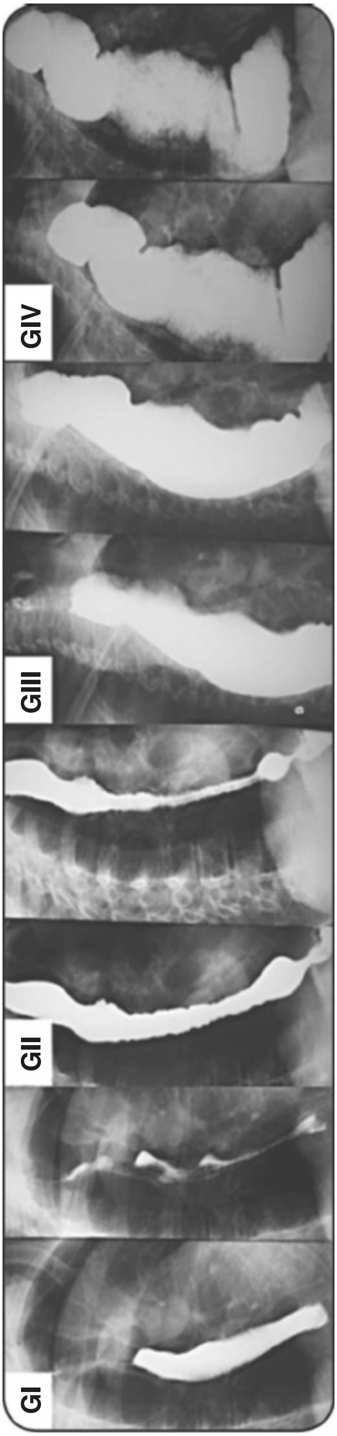

Fig. 10.2 Classic grouping (I–IV) of progressive esophageal findings with Chagas, as described by Rezende et al. [13]. Image from de Souza et al. [14]

POEM is now a well-established and increasingly common procedure. Like the Heller myotomy, POEM results in complete division of the circular muscle fibers of the LES. There have been unpublished presentations on POEM for the treatment of achalasia caused by Chagas. However, there are currently no published series or trials evaluating the use of POEM in patients with Chagas disease. It may be a good approach for patients without significant esophageal dilation, but further study is needed.

To perform POEM, it is necessary to navigate through the submucosal space. Thus, the creation of the submucosal tunnel might be more challenging when compared to idiopathic achalasia since fibrosis and chronic inflammation may be present. During the acute phase of Chagas, tissue damage occurs as a result of both parasitemia and direct tissue parasitism. An immunologic response follows, which is important in controlling acute infection, but may result in further tissue inflammation. This has been confirmed by histologic studies of many organ systems [20–23]. Esophageal parasitism and inflammation can involve both smooth muscle and the Meissner and Auerbach nerve plexuses. This can lead to neuronal death, fibrosis, and lymphocytic infiltration. At the same time, the muscularis mucosa may hypertrophy. All of these could potentially contribute to differences in the POEM submucosal dissection plane.

For patients with significant esophageal dilation and megaesophagus, decision-making is more complicated. A determination must be made as to whether the esophagus will function well as a conduit. If not, up-front esophagectomy can be considered. Patients with Chagas often present with late-stage disease, and esophagectomy became popular in the 1970s and 1980s in Brazil. Despite advances in minimally invasive esophagectomy in the 1990s and 2000s, many surgeons have embraced Heller myotomy as a first-line therapy for massively dilated esophagus [24–26].

The results for Heller myotomy in this setting are generally good, with low perioperative risk [24]. However, published case series are small and have short follow-up. These results could potentially translate to the use of POEM, but further study is needed. In particular, the risk and difficulty of creating a submucosal tunnel in a massively dilated esophagus is a critical issue that requires further investigation before the procedure is widely adopted.

Other innovative operations such as esophageal mucosectomy with endomuscular pull-through, sleeve esophagectomy and myotomy, and partial resection with Roux-en-y diversion have also been developed for patients with massive esophageal dilation [3]. There is no clear consensus on the management of this problem, and these patients should be evaluated by an experienced foregut surgeon when possible.

Patients with failed dilation or myotomy can be difficult to manage. In those with megaesophagus, esophagectomy is indicated and commonly performed. For patients with more favorable anatomy and reassuring manometry, repeat myotomy could be considered. This is another potential area of interest for the application of POEM. However, this has not yet been described in the literature and should only be performed within a clinical trial at this time.

Conclusions

Esophageal manifestations of Chagas disease are a significant cause of morbidity, particularly in areas with endemic disease. Although reversal of the disease is impossible, there is a long history of endoscopic and surgical interventions that can provide excellent palliation. Some patients with megaesophagus may require esophagectomy, but there is clearly a role for esophageal myotomy in both late-stage and especially in early-stage disease. While described, no cases of POEM have yet been published in the literature, and the role of POEM in the management of Chagas achalasia has not yet been determined. Patients with Chagas disease should undergo multidisciplinary evaluation, and consultation with an experienced foregut surgeon is advisable.

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Endoscopic Myotomy for Non-achalasia Esophageal Disorders

11

Christy M. Dunst

Non-achalasia disorders of the esophagus represent a wide variety of motor issues encountered in clinical practice. In this chapter, we will focus on those disorders that can best be described along a spectrum of abnormal contractility that may be amenable to myotomy to alleviate obstructive and/or painful symptoms. Before moving into a discussion of specific manometric abnormalities, it is important to understand the concept of why an endoscopic myotomy might be considered in the first place. The idea is that the area of abnormal contractility, by virtue of esophageal spasm or extreme contraction vigor, causes outflow obstruction and/or pain somewhere along the esophagus. It is simplest to understand the mechanism when the pathology is isolated to the lower esophageal sphincter. Formal "esophageal outflow obstruction" refers to a phenomenon unique to the lower esophageal sphincter and results from a failure in relaxation with the onset of a swallow leading to symptoms that can mimic formal achalasia or even heartburn. In this condition, relief of the obstruction by physically lysing the sphincter and rendering it non-functional makes inherent sense, especially given our understanding of achalasia and favorable results of myotomy. However, failure to propagate a normal peristaltic wave in the body of the esophagus as a result of spasm or hypercontractility can also lead to symptoms of pain and dysphagia from compartmentalization. This can occur throughout the esophageal body or in segments and represents similar pathophysiology as "esophageal outflow obstruction," but in a more proximal location. The compartmentalization in the spastic segment can also lead to feelings of regurgitation from retrograde flow depending on the size, consistency, and timing of the bolus. Theoretically, if there is excessive contractile strength in the segment, with or without official spasm and compartmentalization, the contraction could be perceived as painful. Or the pain could actually be from a trapped bolus itself and the resultant stretch on the esophageal wall.

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If the hypercontractility is isolated to the distal esophagus and lower esophageal sphincter, the symptoms of pain can be replicated, although the sensation of regurgitation may be less perceptible perhaps due to less overflow phenomena given the greater capacity of the esophagus to accommodate the bolus.

Despite the intellectualization of how compartmentalization and hypercontractility may cause symptoms, the treatment for such esophageal disorders is not uniform or agreed upon. We try muscle relaxants, tricyclic antidepressants, botulinum toxin injections, and dilation with varying degrees of success. When all else fails, finally, some interventionalists will consider myotomy. Given the unpredictable response rates of patients' symptoms with myotomy, most surgeons are not willing to put a person through a major operation to "see what happens." This is especially true when contemplating a long thoracic myotomy. However, with the advent of endoscopic myotomy, the idea of accessing the muscular wall without traversing the chest is appealing. As the experience grows, we, as an endoscopic surgical community, are enjoying quicker operating times with less and less morbidity afforded with endoscopic esophageal myotomy. Today, the risk–benefit ratio is shifting regarding endoscopic myotomy so that the thought of "trying" an esophageal myotomy when more conservative measures have failed is far more reasonable.

The classification of "non-achalasia" esophageal disorders itself represents a host of various manometric features that may not fit into a single category quite as neatly as achalasia does. Because of this, there are few good papers published specifically on the effectiveness of esophageal myotomy for these disorders and fewer still for endoscopic myotomy [1]. Furthermore, the manometric criterion for so-called spastic esophageal disorders is evolving rapidly such that published data may be quickly obsolete depending on the manometric technology used for the study acquisition and on how the manometric findings are interpreted and categorized. Lastly, the reported sample size for any specific manometric category treated by any means is low, making generalizations from the literature extremely difficult for an individual patient sitting in one's office. In 2014, we published our experience with endoscopic myotomy in 25 non-achalasia subtypes as part of a 100 POEM series [2]. Of the 25 patients, 12 were originally categorized as hyper-contractile, defined as DCI > 5000 (mmHg)(s)(cm) when able, five had diffuse esophageal spasm and eight had isolated lower esophageal sphincter dysfunction. Taken as a whole, the non-achalasia cohort had reasonable improvements in symptoms, although significantly less impressive than the achalasia group. Specifically, dysphagia and chest pain were relieved in 97 and 100% of the achalasia group compared with 70 and 75% of the non-achalasia group, respectively. Since then, we have continued to collect patient data and re-review the original manometry studies in an attempt to unify the diagnoses in line with the updated Chicago Classification V3 [3]. As our cohort grows, preliminary data suggests that the non-achalasia subtypes are doing better than expected after endoscopic myotomy with overall success rates approximately 85% (unpublished data).

Although the concept is simple: if the abnormal area of the esophagus is causing obstructive symptoms, manifest primarily as dysphagia and perhaps chest pain and regurgitation, then preventing the contraction should be helpful to alleviate such symptoms, putting the concept to action is far more complex. It is not the surgery itself that is challenging, in most cases, but the patient selection.

As with all esophageal surgery, a comprehensive diagnostic evaluation is imperative prior to endoscopic myotomy. In brief, this includes cardiac evaluation to assess for cardiac sources of chest pain, upper endoscopy with biopsy to assess for malignancy, pseudoachalasia, hernia, etc., radiographic studies to evaluate for anatomic abnormalities, and quantitate emptying, manometry, and selective pH testing to rule out pathologic gastroesophageal reflux. Isolated endoscopic myotomy should not be performed in patients with abnormal acid exposure or hiatal hernias due to the inherent "refluxogenic" nature of the procedure. Accompanying chapters in this text cover the details on preoperative evaluation prior to endoscopic myotomy.

After the alternative diagnoses have been eliminated, it is reasonable to consider an operation for a non-achalasia esophageal motility disorder. First and foremost, there needs to be a symptom profile that reasonably lends itself to the concept that a myotomy would be helpful to relieve such symptoms and that relief would have a positive impact on the patient's quality of life. The primary symptoms that fit these criteria are dysphagia, chest pain, and regurgitation in the setting of hypercontractility or esophageal spasm. Even if the person has the most impressive manometry one has ever seen: No symptoms? No surgery! This is particularly relevant when considering variations in manometric technology, techniques, and normative values across diagnostic laboratories. One must review the raw data/pressure topography when planning an endoscopic myotomy for non-achalasia disorders.

Many people create diagnoses such as "achalasia variant" or "evolving achalasia" to describe the subtypes of manometric features that do not fit neatly into a named disorder category, but have elements of obstruction/compartmentalization either in the esophageal body or gastroesophageal junction. These terms are imprecise and are not encouraged. With the latest version of the Chicago Classification of Esophageal Motility Disorders V3 [3], it should be very rare that a recognized interpretation cannot be identified that fits all findings seen on pressure topography (Table 11.1). However, until the adoption of the Chicago Classification becomes universal in all testing laboratories, it is important to clarify some areas of change between the conventional and new high-resolution terminology that frequently lead to the confusion. These key points are particularly relevant to determine if a patient

Table 11.1 Manometric features of esophageal disorders possibly amenable to endoscopic myotomy

	IRP	% Normal peristalsis	% Premature contractions (spasm) with normal DCI	DCI (mmHg)(s)(cm)
Type I/II achalasia	High	0%	0%	<100
Type III (spastic achalasia)	High	0%	20%	>450
DES	Norm	30–80%	>20%	>450
Hyper-contractile (jackhammer)	Norm or high	30–80%	<80%	>8000 (in at least 20%)
EGJ outflow obstruction	High	>20%	n/a	>450

Adapted from The Chicago Classification of esophageal motility disorders, v3.0 [3]. *IRP* integrated relaxation pressure, *DCI* distal contraction integral

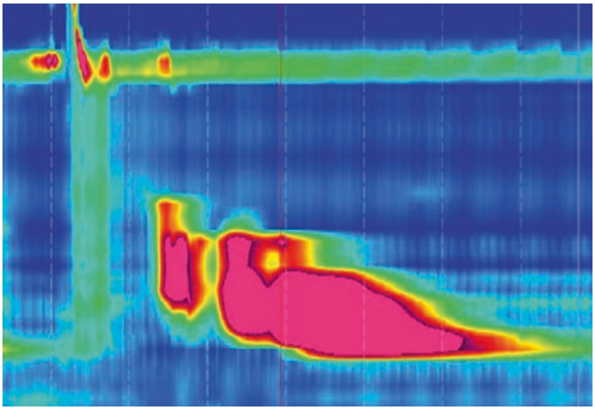

Fig. 11.1 HRM demonstrating typical hyper-contractile esophagus or Jackhammer pattern with a DCI of >1000 mmHg s cm without esophageal outflow obstruction

is suitable for endoscopic myotomy as manometric interpretation can be complex after achalasia has been ruled out. According to the most recent reiteration of the Chicago Classification, the term "hypercontractility" refers to increased contraction vigor confined to the esophageal body, extending into the lower esophageal sphincter, or confined to the sphincter alone. Such "jackhammer" patterns are conventionally known as nutcracker esophagus with or without a hypertensive sphincter (although the new criteria for "jackhammer" is more specific than "nutcracker," further discussion is beyond the scope of this chapter) (Fig. 11.1). Similarly, the new terminology "esophagogastric junction outflow obstruction" refers specifically to isolated elevations in integrated relaxation pressure, which would conventionally fall into the category of "non-relaxing lower esophageal sphincter." However, hypercontractile esophagus isolated to the sphincter in association with an elevated integrated relaxation pressure can occur (conventionally known as hypertensive non-relaxing sphincter).

The finding of esophageal spasm is considered separately from hypercontractility, although it can have similarities with outflow obstruction. Esophageal spasm is defined as premature contractions of normal contraction vigor in more than 20% of test swallows. A premature contraction is defined by the rapidity by which the wave front moves from the initiation of a swallow to the distal esophagus. More precisely, it is the time interval between the relaxation of the upper esophageal sphincter to the inflection point of the contractile front of the propagated swallow within 3 cm of the lower esophageal sphincter (contractile deceleration point) known as distal latency. A normal distal latency is >4.5 s. Anything less than that is considered premature, rapid, or spastic. Importantly, the contractile deceleration point needs to be measured along the pressure wave created from the esophageal contraction not to be confused with the potentially elevated intrabolus pressure that precedes the waveform. Many automated computer-generated interpretations make this mistake and over-call esophageal spasm when it really represents isolated gastroesophageal outflow obstruction. Patients with esophageal spasm are generally differentiated from spastic achalasia by the presence of an elevated integrated relaxation pressure. However, on occasion, some gray areas will be encountered when patients exhibit characteristics across categories. For example, achalasia should still be considered in patients with normal integrated relaxation pressures but 100% failed peristalsis, particularly if there is evidence of esophageal body pressurization. The point is, there is not a specific category for which myotomy could be applicable. The precise name applied to the disorder is less important than understanding the underlying pathophysiology that may be causing the symptoms one is trying to alleviate (Fig. 11.2).

Once one has determined that the esophageal manometric findings of hypercontractility and/or esophageal spasm are present and may correlate with a convincing symptom profile and there are no contraindications to endoscopic myotomy, the next step is surgical planning. The pressure topography from the high-resolution manometry needs to be carefully reviewed, this time as a physical map of the esophagus—again reading a report is not adequate. Look for the location and extent of the high-pressure zone. Compare the manometric findings with the films from the contrast esophagram. Where exactly is the problem? Where is the target relative to the gastroesophageal junction? Is it confined to the junction or does it extend proximal into the esophagus? This will help you build a surgical diagram and provide information directing how long a potential myotomy would need to be. Pay close attention to correlating the patient's symptoms with the objective tests. Importantly, the myotomy needs to extend across the gastroesophageal junction regardless of specific manometric findings confined to the sphincter. In our experience, leaving the junction intact in patients who have a targeted esophageal body myotomy alone leads to relative outflow obstruction and esophageal dilation along the myotomy even if the sphincter area was manometrically normal to begin with. However, determining proximal extent of the myotomy in non-achalasia disorders is determined by a combination of manometric findings, contrast studies, intraoperative visualization of the extent of the high-pressure zone, and symptoms. For example, a long myotomy may be the best choice if there is primarily sub-sternal chest pain and correlating spasm into the middle or proximal esophageal body. Similarly, if the patient describes sub-sternal dysphagia and regurgitation, the body may also need to be addressed. However, if a patient describes primarily lower dysphagia correlating with lower esophageal sphincter findings, a standard length myotomy focusing on the junction may be adequate. When in doubt, we suggest extending the myotomy proximally to release all areas of potential concern. From a technical standpoint, there are a few unique considerations associated with a long myotomy. First, make sure that the entry point is proximal enough to allow for sufficient overlap between the mucosotomy and the myotomy. Consider a few extra centimeters of overlap to account for the longer operative time and higher chance of tearing the mucosotomy with instrumentation. Importantly, be mindful that patients with esophageal body disease often have significantly hypertrophic muscularis propria, which requires much more energy delivery to achieve myotomy. We recommend actively managing the energy in the tunnel to decrease the risk of injury to

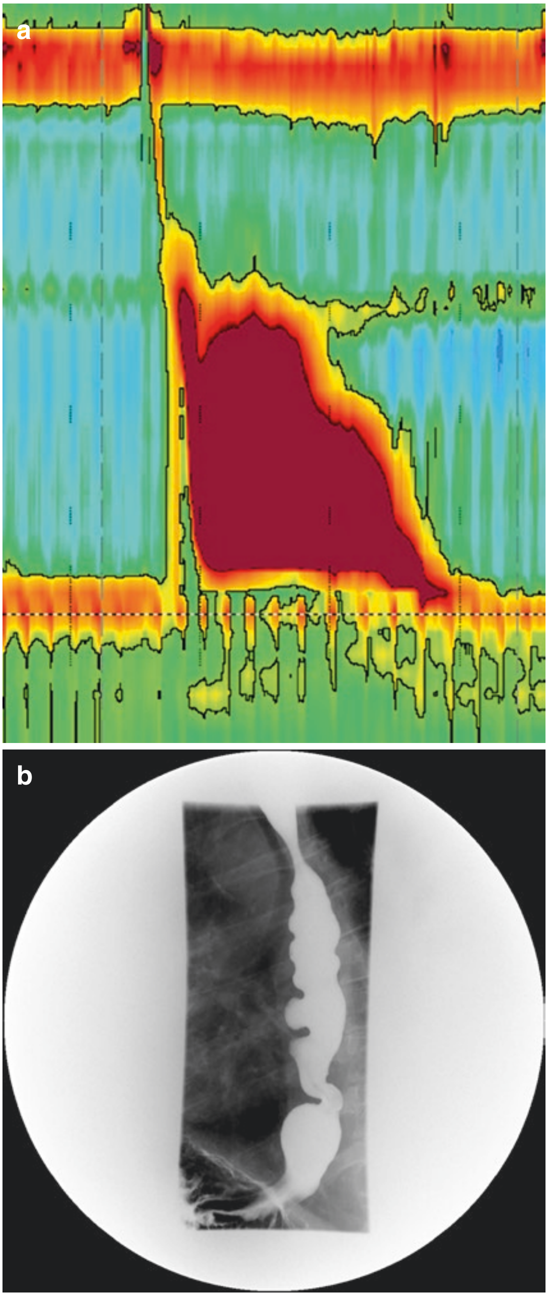

Fig. 11.2 (**a**) This swallow demonstrates a premature contraction (spasm) with elevated contraction vigor (Jackhammer) without esophageal outflow obstruction. There were 30% of swallows in this study demonstrating normal distal latency. (**b**) The esophagram from this same patient demonstrates a typical spastic pattern. Note in both studies the abnormal segment extends to just below the aortic arch (proximal indentation on esophagram and vascular artifact on manometric topography). This patient had a long endoscopic myotomy, which eliminated the dysphagia and improved but did not eliminate the chest pain

surrounding structures due to inadvertent conduction. Specifically, use the lowest energy settings possible to achieve a hemostatic myotomy, usually endocut modes, and switch to higher voltage or coagulation setting only when needed.

In summary, endoscopic myotomy for non-achalasia esophageal motility disorders is more complex both in terms of preoperative evaluation and surgical technique. The most frequent manometric classifications lending themselves to myotomy are hyper-contractile esophagus, esophageal spasm, and esophagogastric junction outflow obstruction. Despite a relative paucity of data, it seems that myotomy certainly can be performed with good results in carefully selected patients in whom the symptoms of dysphagia and chest pain correlate to manometric hypercontractility and spasm.

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Follow-Up and Surveillance

12

Eleanor Fung and Kyle A. Perry

Abbreviations

GE junction	Gastroesophageal junction
GERD	Gastroesophageal reflux disease
GERD-HRQL	Gastroesophageal reflux disease health-related quality of life
GERDSS	GERD symptom scale
LES	Lower esophageal sphincter
POEM	Per-oral endoscopic myotomy

Introduction

As there is no cure for achalasia, the goals for the management of achalasia are focused on improving esophageal emptying through a reduction in the relative obstruction at the gastroesophageal (GE) junction, to relieve patient's symptoms and prevent further dilation of the esophagus [1]. Laparoscopic Heller myotomy, botulinum toxin injection, and endoscopic pneumatic dilatation have long been considered the options for the treatment of achalasia in attempts to decrease the lower esophageal sphincter (LES) pressure. However, the effects of botulinum toxin injection and endoscopic pneumatic dilatation are usually temporary and repeated treatment is often required. As a result, laparoscopic Heller myotomy has been shown to provide the more definitive and durable treatment of achalasia with improved relief

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of dysphagia as well as less postoperative gastroesophageal reflux due to the addition of a partial fundoplication procedure [2].

However, POEM is an emerging and now well-documented endoscopic technique for the treatment of achalasia in which the circular muscle fibers are divided within a submucosal tunnel created from a mucosotomy made within the esophageal lumen [3]. It confers the safety and advantages of endoscopy, being less invasive than surgery with the added benefit of a surgical myotomy and being a salvage second-line treatment after other methods have failed. It has been shown to have good symptomatic relief of dysphagia, but given the lack of a concurrent antireflux procedure, postoperative reflux and its complications remain a concern in the postoperative period. This chapter aims to discuss the long-term subjective and objective outcomes of POEM and the role of surveillance following POEM.

Follow-Up

The goal of surveillance is to determine if there has been any symptomatic and/or functional improvement in esophageal function and to determine if any further interventions are required, especially given that there is no specific cure for achalasia. Surveillance is particularly important given that approximately 10–15% of patients with achalasia who have undergone treatment will continue to have progression of esophageal diameter leading to mega-esophagus, with up to 5% of patients eventually requiring esophagectomy [4]. Following POEM, patients are generally seen in clinic follow-up in both short-term and long-term intervals as data has shown that surveillance strategies, with either endoscopic or radiologic modalities, may be beneficial after a disease duration of more than 10–15 years with an interval of every 3 years [5].

The Eckardt symptom score has been typically used to assess for achalasia symptom severity by measuring the extent of dysphagia, regurgitation, chest pain, and weight loss. By obtaining the Eckardt score both prior and post-POEM (Fig. 12.1), patients can be monitored for symptomatic improvement and treatment

Score	Dysphagia	Regurgitation	Retrosternal pain	Weight loss (Kg)
0	None	None	None	None
1	Occasional	Occasional	Occasional	<5
2	Daily	Daily	Daily	5-10
3	Each meal	Each meal	Each meal	>10

Fig. 12.1 Eckardt score

efficacy following POEM. A meta-analysis by Talukdar et al. did demonstrate a statistically significant reduction in the improvement of Eckardt's score following POEM and was found to have a comparable efficacy compared to Heller myotomy [6]. Furthermore, this effect on subjective improvement in achalasia symptoms was demonstrated in patients seen in follow-up for up to 3 years following POEM [7, 8].

However, patients' symptoms following POEM may not necessarily be a reliable indicator of functional improvement after treatment as symptom resolution can occur without a significant improvement in esophageal emptying, which can place the patient at risk for developing long-term complications of achalasia such as mega-esophagus [4]. As such, patients should also undergo objective testing following POEM to demonstrate clinical response, such as high-resolution manometry and timed barium esophagram. Multiple studies have demonstrated that upright timed barium esophagram can predict treatment success and requirement for future intervention. Vaezi et al. demonstrated that there was an approximate 73% concordance between the degree of symptom improvement and degree of esophageal emptying by barium esophagram in patients with achalasia treated with pneumatic dilation. Furthermore, there was an association and predictive value seen in patients with poor esophageal emptying on barium esophagram in the context of complete symptom resolution and symptom relapse at 1 year. Patients in this treatment group were found to benefit from more intensive follow-up regardless of symptoms due to the risk of relapse and, as such, it was found to be reasonable to repeat barium esophagram annually to assess for esophageal emptying [9].

Esophageal manometry has also been cited as an indicator for treatment outcome, given that the diagnosis of achalasia is dependent on the manometric description of LES function. Numerous studies have supported that an LES pressure of 10 mmHg can be correlated with and can predict clinical response as well as remission in patients treated with pneumatic dilatation [10]. Despite this, manometry is not routinely used in this manner because it is more invasive and less widely available than barium esophagram. Although both timed barium esophagram and manometry can be used to assess short-term treatment success and predict long-term outcomes after pneumatic dilation, further studies are needed to infer its utility and predictability for treatment effects post-POEM.

There has also been particular interest in the extent of gastroesophageal reflux (GERD) following POEM, given that there is no combined anti-reflux procedure in contrast to Heller myotomy. The rate of postoperative reflux has been found to vary widely in numerous published studies, ranging from 0 to 53% [11–13]. Given this variability, there has been debate whether all patients following POEM should be treated with acid suppression. Standardized symptom scales, such as the gastroesophageal reflux disease health-related quality of life (GERD-HRQL) (Fig. 12.2) and GERD symptom scale (GERDSS) (Fig. 12.3), have been used to attempt to

Scale:
0 = No Symptoms
1 = Symptoms noticeable, but not bothersome
2 = Symptoms noticeable and bothersome, but not every day
3 = Symptoms bothersome every day
4 = Symptoms affect daily activities
5 = Symptoms are incapacitating, unable to do daily activities

1. How bad is your heartburn?	0	1	2	3	4	5
2. Heartburn when lying down?	0	1	2	3	4	5
3. Heartburn when standing up?	0	1	2	3	4	5
4. Heartburn after meals?	0	1	2	3	4	5
5. Does heartburn change your diet?	0	1	2	3	4	5
6. Does heartburn wake you from sleep?	0	1	2	3	4	5
7. Do you have difficulty swallowing?	0	1	2	3	4	5
8. Do you have pain with swallowing?	0	1	2	3	4	5
9. Do you have bloating or gassy feelings?	0	1	2	3	4	5
10. If you take medications, does this affect your daily life?	0	1	2	3	4	5

11. How satisfied are you with your present condition? Satisfied Neutral Dissatisfied

12. Are you currently taking any medications for heartburn or GERD? Yes No

Fig. 12.2 GERD-HQRL. *Scale*: 0 = No symptoms. 1 = Symptoms noticeable, but not bothersome. 2 = Symptoms noticeable and bothersome, but not every day. 3 = Symptoms bothersome every day. 4 = Symptoms affect daily activities. 5 = Symptoms are incapacitating, unable to do daily activities

quantify gastroesophageal reflux disease health-related quality of life. Objectively, 24 h or 48 h pH monitoring, typically performed 6 months following POEM, has been utilized to determine evidence of pathologic acid reflux defined as a DeMeester score greater than 14.72 in a 24 h period. Jones et al. demonstrated that there was no correlation between subjective symptoms of GERD and objective pH testing for pathologic acid reflux following POEM, with 58% of patients with documented abnormal distal esophageal acid exposure not experiencing clinical symptoms of reflux, which is consistent with results in achalasia patients treated with Heller myotomy [14, 15]. Given the lack of correlation, we recommended that all patients following POEM undergo routine postoperative pH monitoring and esophagogastroduodenoscopy to identify and treat patients at risk of long-term complications of uncontrolled acid reflux, such as esophagitis, stricture, and recurrent dysphagia, and

Symptom		Grade
Dysphagia	1	Occasional with course foods (meat sandwich, hard roll) lasting for a few seconds
	2	Requiring clearing with liquids
	3	Severe - semi - liquide diet or history of meat impaction
	4	For liquids
Chest pain	1	Minimal or occasional episodes
	2	Moderate, reason for visit
	3	Severe, interfering with daily activities
Regurgitation	1	Mild, after straining and/or after large meals
	2	Moderate - predictable with position change, straining or lying dowm
	3	Severe - constant regurgitation, presence of aspiration
Heartburn	1	Minimal, identifiable symptoms, occasional episodes, no prior mwdical visit
	2	Moderate - primary reason for visit
	3	Severe - constant marked disability in activities of daily life

Fig. 12.3 GERD symptom scale; http://www.hon.ch/OESO/books/Vol_5_Eso_Junction/Articles/Images/img130-1.jpg

to avoid unnecessary long-term proton pump inhibitor therapy in patients with normal esophageal acid exposure.

Patients with achalasia are also at a substantially increased risk of developing esophageal squamous cell carcinoma and adenocarcinoma theoretically due to poor esophageal emptying and increased acid exposure leading to dysplasia and, eventually, carcinoma. However, at this time, there is insufficient data to support the routine endoscopic surveillance for esophageal cancer, given the low incidence and poor outcomes once the diagnosis is made [16].

Currently, the data is limited by the length of follow-up as POEM is still an emerging technique for the treatment of achalasia. As a result, more long-term studies are required to demonstrate the effectiveness of POEM, which will help to determine defined surveillance strategies to prevent disease progression and identify treatment failure, using both subjective symptom scale surveys and objective testing.

Conclusion

POEM has been shown to be an effective treatment for achalasia, but further studies are required to determine its long-term efficacy. As there is no targeted treatment to restore normal esophageal smooth muscle function, patients with achalasia should undergo long-term routine assessment of symptom relief and objective testing of esophageal emptying. Furthermore, given the increased risk of pathologic gastroesophageal reflux with the lack of an anti-reflux procedure, there is evidence to support the benefit of routine pH monitoring and esophagogastroduodenoscopy to identify those patients with pathologic acid reflux who require long-term proton pump inhibitor therapy.

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Management of Gastric Reflux Following Per-Oral Endoscopic Myotomy

13

Silvana Perretta

Introduction

The current most effective treatments for achalasia aim at relieving the obstruction at the lower esophageal sphincter by destruction. The fact that the normal physiological functions of the lower esophageal sphincter and the esophagus are not restored sometimes shifts the problem from "no flow" to "backflow." In some patients, the reflux symptoms can be as debilitating as the achalasia itself, and in those without symptoms, there would still be a concern of transformation into Barrett's esophagus or beyond if left untreated.

Heller myotomy was considered the gold standard treatment for years. It achieves good efficacy without the need of repeated procedures, and laparoscopic approach soon took over the thoracoscopic approach after it was introduced for its superiority in many outcome parameters [1]. For decades, surgeons struggled to balance between the treatment of dysphagia and the consequence of gastroesophageal reflux disease (GERD). Coexisting fundoplication was found to decrease the chance of reflux [2], although not completely. After further studies, we now come closest to the equilibrium between dysphagia and reflux with the concurrent use of laparoscopic Heller myotomy and partial fundoplication.

Per-oral endoscopic myotomy (POEM) utilizes an endoscopic submucosal approach to cut the circular fibers of the lower esophageal sphincter, while leaving the longitudinal fibers and peritoneal attachments intact. Given the minimal disruption of surrounding components of the anti-reflux mechanism within the esophagogastric complex, POEM is commonly performed without a concomitant anti-reflux procedure.

Gastroesophageal reflux is one of the more common challenges physicians encounter in the long-term follow-up of POEM procedures. While we are seeing a

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comparable therapeutic efficacy between POEM and the traditional Heller myotomy with partial fundoplication, it is important to understand how POEM manifests in terms of gastric regurgitation without fundoplication. This chapter outlines the current updates on what is known about gastroesophageal reflux after per-oral endoscopic myotomy.

Reflux After POEM: How Common Is It?

The report of initial experience by Inoue et al. [3] described a very low rate of reflux symptoms after POEM (1 out of 17 patients) with great treatment efficacy. This has drawn much attention to investigate the actual incidence of reflux for comparison with the other treatment modalities, although a conclusive prevalence is not well-defined yet.

Multi-year follow-up with patients undergoing POEM is now being reported since clinical application of this technique began in Japan in 2008. Initial reports of longer-term follow-up by Inoue et al. [4] (105 patients in a single-center with follow-up periods of 36 months), Werner et al. [5] (a multi-center report of 80 cases with at least 2 years of follow-up), and Chen et al. [6] (45 patients in a single-center with follow-up periods of 24 months) have included that.

Reported incidence of GERD after POEM differs, depending on whether one defines it by symptom, endoscopic finding, or objective pH study. In many different reported series, symptom assessments were noted, along with reporting of esophagitis upon surveillance endoscopy. Formal pH study was performed in several centers, revealing the occurrence of reflux in the asymptomatic patients as well.

Reflux Symptoms

Presence of reflux symptoms can be defined by the presence of an isolated symptom, or more standardized using structured questionnaires. A common questionnaire used among the literature when reporting post-POEM reflux is GerdQ score [7], which is a screening test with scoring based on the presence and frequency of symptoms within the period of 7 days. It sets a cut-off score to predict whether the subject has any gastroesophageal reflux. Those with frequent and only heartburn and regurgitation without symptoms of nausea or epigastric pain would score the highest. Incidence of GERD symptoms ranges from 0 to 42% (Table 13.1), with most reports from 14 to 22%, including that of a 500-patient series [4]. In general, the rates of complete symptom assessment were quite good, with a majority of the reports having had assessed symptoms in more than 85% of their patients. Of those who used GerdQ score equal to or greater than seven as their criteria for positive reflux symptoms, the incidence lies at around 15% [8, 9]. The frequency of reflux symptoms was stratified in some reports, and 1.5–8.2% of them reported reflux symptoms on a daily basis [5, 10, 11]. For the longer-term reports, Inoue reported that 21.3% of the interviewed patients had reflux symptoms at 36 months after

Table 13.1 Reported incidence of reflux symptoms

Author	Year of publication	Location	Number of cases reported	Time point after POEM in months	Percentage of patients with symptoms assessed	Percentage of those assessed with GERD symptom	Definition of having GERD symptom
Familiari	2016	Rome, Italy	149	Mean of 7.6 ± 3.6	69%	18.4%	/
Shiwaku	2016	Fukuoka, Japan	100	3	100%	9.0%	FSSG
Chen	2015	Shanghai, China	26	Mean of 24.6	100%	14.8%	/
Inoue	2015	Yokohama, Japan	500	2 ($n = 500$)	85%	16.8%	/
			370	12–24 ($n = 370$)	78%	19.4%	
			105	36 ($n = 105$)	58%	21.3%	
Ramchandani	2015	Hyderabad, India	102	12	100%	21.6%	/
Werner	2015	International multicenter	85	3–6	93%	24.1%	Presence of heartburn
				12–18	89%	31.6%	
				>24 (mean 29)	86%	37.0%	
Ling	2014	Nanjing, China	87	3	100%	10.3%	/
Stavropoulos	2014	Mineola, New York, US		Mean of 13.3		32% (daily 3%, few times per week 13%, few times per months 16%)	/
Teitelbaum	2014	Chicago, Illinois, US	41	12	95%	14.6%	GERDQ score > 7
Li	2013	Shanghai, China	234	12	94%	16.7%	GERDQ score > =7

(continued)

Table 13.1 (continued)

Author	Year of publication	Location	Number of cases reported	Time point after POEM in months	Percentage of patients with symptoms assessed	Percentage of those assessed with GERD symptom	Definition of having GERD symptom
von Renteln	2013	European MCT	70	3	100%	32.8% (daily 1.5%, occasionally 31.3%)	/
			61	6		30% (daily 6.6% daily, occasionally 23.4%)	
			51	12		37.2% (daily 7.8%, occasionally 29.4%)	
Chiu	2013	Hong Kong, China	16	3	100%	6.3%	/
Minami	2013	Nagasaki, Japan	28	Median of 16	100%	21.4%	/
Verlaan	2013	Amsterdam, Netherlands	10	3	100%	30.0%	/
Swanstrom	2012	Portland, Oregon, US	18	6	100%	44% (daily 11.1%, occasionally 16.7%, rarely 16.7%)	/
von Renteln	2012	Hamburg, Frankfurt	16	3	100%	0.0%	/

POEM [4], while 37.0% of those in the centers reported by Werner at 24 months or beyond (8.2% with daily symptoms) [5].

Endoscopic Evidence of Reflux

Esophagitis found upon endoscopy is an objective indication of the likely presence of reflux, but endoscopy is not routinely performed in all centers that have reported their series. Stratification of severity in esophagitis is mostly reported using the Los Angeles classification of esophagitis [12].

Rate of esophagitis seen upon endoscopy had a larger variation compared with rate of symptoms, ranging from 6.3 to 64.7% (Table 13.2). The proportion of studied patients who received an endoscopy also varies quite significantly from 10 to 100%. Series with a lower endoscopy surveillance rate often report a higher incidence of esophagitis, likely due to selection bias. Studies with less than 60% of the studied patients having had endoscopy all reported an incidence of over 50% [4, 8, 13]. The incidence in the remaining reports still varies significantly, but most reports lie within 20–42%.

As in primary GERD, discordance between the rates of reflux symptoms and endoscopic evidence of reflux disease exists. Presence of symptoms has low sensitivity in predicting the presence of mucosal damage. As many as 88.9% of patients with esophagitis of Los Angeles Classification grade A or above can be asymptomatic, as reported by Shiwaku et al. [14] Some groups also reported a rate of 10% to almost 70% of asymptomatic patients having esophagitis (Table 13.2). Since long-standing esophagitis left untreated may lead to severe consequences, many authors advocate regular endoscopic surveillance to facilitate timely intervention.

Objective Studies on Reflux

Gastroesophageal reflux disease can also be objectively diagnosed using pH studies. Overall, the rate of an abnormal pH study generally ranges from 20.2% [15] to 57.7% [16], excluding one series in which pH testing was only provided for a single patient who had reflux symptoms registering 13.4% total time with esophageal acid exposure [17]. Assessing reflux with pH testing provides reliable objective data; however, diagnosing GERD with such a singular test may also lack standardization with the presence of different measurement methods and parameters.

In the literature, both 24-h probe-based monitoring and more prolonged monitoring using wireless capsules are used in different centers, some even within the same center (Table 13.3). Prolonged pH studies with wireless capsules are shown to be more sensitive in detecting pathological esophageal acid exposure and positive symptom association [18, 19]. Different normative values of percentage of total time of abnormal esophageal acid exposure for the wireless capsule system, ranging from 4.4 to 5.3%, have been reported [19, 20], which are slightly higher than the most referenced 4.2% for probe-based monitoring [21].

Table 13.2 Reported incidence of esophagitis

Author	Year of publication	Location	Number of cases reported	Time point after POEM in months	Percentage of studied patients that received endoscopy	Percentage of endoscopy done having esophagitis	LA Grade A	LA Grade B	LA Grade C	LA Grade D	Percentage of patients with esophagitis having symptoms
Familiari	2016	Rome, Italy	149	Mean of 7.6 ± 3.6 months	69%	20.4%	8.7%	5.8%	4.9%	1.0%	42.8%
Chen	2015	Shanghai, China	26	Mean of 24.6	100%	11.5%	0.0%	11.5%		0.0%	66.7%
Inoue	2015	Yokohama, Japan	500	2 ($n = 500$)	83%	64.7%	33.8%	25.8%	4.8%	0.2%	–
			370	12–24 ($n = 370$)	52%	59.2%	35.6%	13.1%	7.9%	2.6%	
			105	36 ($n = 105$)	15%	56.3%	43.8%	6.3%	6.3%	0.0%	
Ramchandani	2015	Hyderabad, India	102	12	82%	16.6%	12.0%	4.8%	0.0%	0.0%	–
Sharata	2015	Portland, Oregon, US	100	Mean of 21.5	73%	27.4%	20.5%	4.1%	2.7%	0.0%	–
Shiwaku	2015	Fukuoka, Japan	70	3	100%	64.0%	48.6%	5.7%	10.0%	0.0%	11.1%
Werner	2015	International MCT	85	3–6	80%	36.8%	20.6%	16.2%	0.0%	0.0%	–
				12–18	85%	37.5%	20.8%	12.5%	2.8%	0.0%	
Ling	2014	Nanjing, China	87	3	10%	55.6%	33.3%	22.2%	0.0%	0.0%	Only symptomatic patients had endoscopy

Stavropoulos	2014	Mineola, New York, US		Mean of 13.3	53%	32.1%	–	–	–	–	–
Teitelbaum	2014	Chicago, Illinois, US	41	12	54%	59.0%	50.0%	0.0%	0.0%	9.0%	30.8%
Li	2013	Shanghai, China	234	12	100%	8.5%	–	–	–	–	90.0%
Minami	2013	Nagasaki, Japan	28	Median of 16	100%	39.3%	25.0%	3.6%	3.6%	0.0%	–
Verlaan	2013	Amsterdam, Netherlands	10	3	100%	60.0%	30.0%	30.0%	0.0%	0.0%	50.0%
von Renteln	2013	European MCT	70	3	–	42.0%	29.2%	12.3%	0.0%	0.0%	–
von Renteln	2012	Hamburg, Frankfurt	16	3	100%	6.3%	6.3%	0.0%	0.0%	0.0%	–

Table 13.3 Reported incidence of esophageal pH studies

Author	Year of publication	Location	Number of cases reported	Time point after POEM in months	Percentage of patients with pH study done	Percentage of pH studies done with positive result	pH monitoring method	Definition of positive pH study
Familiari	2016	Rome, Italy	149	6–12	69%	50.5%	24 h pH probe at 5 cm from OGJ	>5% of total time with pH < 4
Jones	2015	Columbus, Ohio, USA	42	6	62%	57.7%	48 h Bravo capsule	DeMeester score > 14.72
Sharata	2015	Portland, Oregon, US	100	6	68%	38.2%	24 h pH probe	DeMeester score > 14.7
Stavropoulos	2014	Mineola, New York, US	100	–	52%	32.7%	48 h Bravo capsule	–
Teitelbaum	2014	Chicago, Illinois, US	41	12	32%	30.8%	24 h pH impedence/96 h Bravo capsule at 6 cm from SC junction	>4.5% of the 24-h period of highest acid exposure with pH < 4
Chiu	2013	Hong Kong, China	16	3	94%	20.0%	24 h pH probe at 4 cm above OGJ	>4.5% of total time with pH < 4
Verlaan	2013	Amsterdam, Netherlands	10	3	10% (one symptomatic case)	100.0%	24 h pH impedence	–

Table 13.4 Reported DeMeester scores

Author	Year of publication	Location	Time point after POEM in months	Number of patients with pH study done	Number of patients with DeMeester score > 14.7	Number of patients with DeMeester score > 30
Familiari	2016	Rome, Italy	6–12	102	52	N/A (mean 39.7 ± 43.2)
Jones	2015	Columbus, Ohio, USA	6	26	15	7 (26.9%)
Sharata	2015	Portland, Oregon, US	6	68	26	21 (30.9%)
Shiwaku	2015	Fukuoka, Japan	3	67	N/A	10 (14.9%)
Teitelbaum	2014	Chicago, Illinois, US	12	13	4	0

Some centers also performed pH impendence studies, but did not address the issue of non-acid reflux in their results. Whether symptomatic patients with normal time of esophageal exposure to acid are having non-acid refluxes remains unknown.

Parameters adopted to define a positive test also varied between centers, namely using a cut-off of DeMeester score of greater than 14.7 or percentage of total time with esophageal pH less than 4 of greater than 4.5 or 5 (Table 13.3). The parameter chosen does not always correlate with the device chosen to perform the test. The reported incidence defined by either DeMeester score (57.7% [16] and 38.2% [22]) or percentage of total time of esophageal acid exposure (50.5% [23], 30.8% [8], and 20.0% [15]) between the different centers did not seem to differ, but there was no report of both figures from one center. Reports that showed the distribution of DeMeester scores [16, 22, 24] suggested that around 15–30% of patients would have DeMeester score of over 30 (Table 13.4).

The benefit of a routine pH study as a management guide is not yet evident, although it is still suggested to be done as part of the protocol for patients receiving POEM. Firstly, a low pH detected within the esophagus may not be solely due to gastroesophageal reflux. Due to persistent aperistalsis of the esophagus, food stasis and hence fermentation may still occur after treatment. Crookes et al. [25] have shown in vitro that bland food with saliva would ferment and result in a gradual drop of pH down to not below 3, and that the acid resulted would not be injurious to the esophageal mucosa in the absence of pepsin. Various studies also showed a similar pattern clinically in achalasia patients after treatment [26]. The drop in pH is slow over the span of hours, usually occurs at night, and does not drop below 3. A careful recognition of this pattern against the true gastroesophageal reflux pattern (an abrupt drop of pH down to 1 or 2 with recovery) would avoid overdiagnosing reflux.

On the other hand, an abnormal pH study may not be clinically significant: the Oregon Clinic has demonstrated that almost half of the patients with an abnormal pH study result are asymptomatic [22], and in the series by Teitelbaum et al., only

23.1% of them would have esophagitis (and only 37.5% of those with esophagitis would register a positive pH study) [8]. In fact, clinically relevant reflux disease (with the presence of concurrent reflux symptoms or esophagitis) may be present in as low as 29.1% of those with an abnormal pH study [23]. Yet of course, these are short-term results and it is too soon to conclude on the effect of the silent acid regurgitation. For this reason, we still see the value of a routine pH study in our current patients who received POEM.

POEM Compared to Other Treatment Modalities

Heller Myotomy

A common discussion surrounds POEM without fundoplication and if it results in more reflux than the standard Heller myotomy with partial fundoplication. Current data available for the two approaches reveal comparable figures. Reported direct comparisons between Heller myotomy (HM) with Dor or Toupet fundoplication and POEM are retrospective at the moment, and we also see no difference between the two relating to reflux. Bhayani et al. (The Oregon Clinic) looked into 101 patients treated with either Heller myotomy with Dor or Toupet fundoplication (37 with Dor, 27 with Toupet), or POEM (37 patients). At 6 months, symptoms of heartburn, reflux, and chest pain were similar between the two groups. Part of these patients received a 24-h pH study, and the percent of patients with a DeMeester score greater than 14.7 was similar (32.3% after HM and 39.1% after POEM, $p = 0.4$) [27]. A Hong Kong series of 33 cases with POEM and 23 Heller myotomy with Dor fundoplication performed also showed no difference in terms of GERD symptoms (26% in HM group versus 15.2% in POEM group) and need of proton-pump inhibitor treatment (13% versus 9%) [28]. Prospective randomized trials would provide a better comparison, and there are a few currently in progress.

Diminished reflux was demonstrated using limited hiatal dissection in surgical myotomy in a recent study [29], where the phrenoesophageal ligament was not completely dissected during the operation. This may support the postulation of why POEM seems to result in modest reflux, despite its lack of concomitant anti-reflux procedure. The phrenoesophageal ligament contributes to the anti-reflux mechanism by maintaining the angle of His and is disrupted during Heller myotomy. In POEM, the myotomy is carried out without impacting the ligament, and the anatomical architecture remains largely intact.

Pneumodilatation

No direct comparison of pneumodilatation and POEM has been published at the moment. There are at least two randomized controlled trials ongoing, for some of which the recruitment phase is completed and we anticipate those results in the near future.

There are some recent prospective studies evaluating pneumodilatation and surgical myotomy, which may shed some light on how pneumodilatation compares to POEM. Randomized controlled trials showed either no significant difference in terms of percentage of time of pH lower than 4 (15% had acid exposure more than 4.5% of total time) and esophagitis at 1 year (19%) [30], or that pneumodilatation has a much higher reflux rate posttreatment as measured by percentage of time of pH less than 4 (31%) [26]. A meta-analysis of the two studies showed no significant difference [31]. Based on the finite controlled nature of the POEM technique compared to Pneumodilatation, we can anticipate that POEM will result in similar or less incidence of pathologic reflux.

Treatment for Reflux

In many publications on the subject, medical management of reflux following POEM is not documented in detail, but in general the use of proton-pump inhibitors (PPI) appears to be a common approach. Many authors reported that the use of PPI gives satisfactory control to any reflux symptom that occurred after POEM. Some authors have described the rate of PPI use, which ranged from 4 to 37% [4–6, 10, 13, 15, 32, 33], and some reported further on the frequency of use. Overall, 5.1–24.6% of patients were reported to take daily PPI [5, 10]. It is now generally accepted that around 15% of patients will require some use of medical treatment for gastric reflux after POEM.

Operative management of reflux following POEM is not widely present in the medical literature. There are few accounts of animal trials and a case report of treating refractory reflux endoscopically [34–36], but among the over 4000 cases published so far, there is no series in which a case of reflux after POEM was treated with a surgical fundoplication.

Indeed, endoscopic solutions to the problem of post-POEM reflux are emerging. Transoral incisionless fundoplication [37], radiofrequency therapy [38] and, more recently, the anti-reflux mucosectomy [39] are some of the current endoscopic approaches to treat index gastroesophageal reflux. Transoral incisionless fundoplication (TIF) with EsophyX™ was shown in 2010 to be feasible after POEM in animal models in a stepwise approach, where the TIF was performed 4 weeks after POEM [36]. The technique of TIF involves insertion of an endoscopic device that anchors the wall of the gastric fundus to the abdominal part of the esophagus to create a 2–3 cm wrap of 270° [40]. Clinical application of the technique on one patient suffering from refractory reflux after POEM was then described with a good clinical outcome [35].

Before endoscopic treatment for reflux disease becomes more established, surgical fundoplication is the standard therapy to consider for reflux after POEM. Fortunately, POEM appears to result in minimal submucosal and intraperitoneal adhesions, facilitating revisional procedures if necessary. In a report of two cases of laparoscopic Heller myotomy performed for recurrent symptom after POEM, only minimal adhesion was encountered upon establishing the submucosal plane, and no mediastinal inflammation was encountered [41].

Prevention of Reflux

The main objective of the POEM procedure is to achieve adequate dysphagia relief, while maximally preserving the anti-reflux mechanism. The site of the myotomy, its depth, and length are all being investigated; however, there is currently no consensus to what consists of the "optimal cut."

The initial location for the mucosotomy and entry into the submucosal space is currently under debate. Many practitioners report starting the mucosotomy at the 2 o'clock position (antegrade view) on the esophagus above the anterior lesser curvature of the stomach or, posteriorly, at 4 o'clock above the posterior lesser curvature [42]. Approaches can be classified as anterior and posterior, or along the lesser and greater curvature. Both anterior (10 or 2 o'clock) and posterior (4 or 8 o'clock) approaches can access the lesser or greater gastric curvature. The consequence of cutting at different sites becomes apparent as the myotomy engages the stomach, where the anatomic layers become less organized. Each approach varies in terms of ease of procedure [43], feasibility for those with previous Heller myotomy, and the ability to better identify the esophagogastric junction [44]. In terms of minimizing the incidence of reflux, it is conventionally believed that cutting along the lesser curvature would better preserve the Angle of His, which serves as a key component in the anti-reflux barrier complex. Inoue et al. looked at 21 cases of myotomy along the greater curve in their series of over 500 patients and reported 52% of esophagitis rate at 3 months; however, many were asymptomatic with a rate of symptomatic reflux rate of 9.5% [44]. The authors commented that the rate in their study may be higher than the rate of reflux reported commonly in the literature. Following subgroup analysis, it was determined that both rates of esophagitis and symptoms in the overall group of 500 patients [4] were higher than that seen in the greater curvature subgroup. As a result, there is a line of thought that myotomy along the lesser curvature, particularly at the 2 o'clock region, may be more predisposed to the development of symptomatic reflux. Currently, a multicenter study is in progress to further investigate this issue.

Thickness of myotomy and inclusion of the circular versus circular and longitudinal muscle layers have also been investigated. A randomized trial that involved 234 patients who underwent POEM either with full-thickness or circular muscle myotomy showed a trend in favor of selective circular muscle myotomy; however, this was not statistically significant [9]. The overall clinical reflux rates, defined as the rate of patients who had symptomatic reflux or endoscopic evidence of esophagitis, were 21.2% and 16.5% for the full-thickness myotomy group and circular muscle myotomy group, respectively ($p = 0.38$).

Length of myotomy has been a source of rich debate for decades. General consensus following quality comparisons involves a generous esophageal myotomy terminating a couple of centimeters below the esophagogastric junction, which includes myotomy of a portion of the gastric clasp fibers [4]. To minimize the risk of reflux, the length is ideally long enough to just obliterate the lower sphincter obstruction, while preserving some of the anti-reflux complex. In a recent study of 103 patients, no significant association is found between total, esophageal, or gastric myotomy length with reflux, whether measured in terms of symptoms, esophagitis, pH study parameters, or clinical relevancy [23]. Shiwaku et al. considered esophagitis of Los Angeles class B or above as significant reflux and found no significant correlation with the total length of myotomy as well [24].

Rather than a "one size fits all" approach, it is now being proposed that a different length may be optimal for each patient, and that myotomies should be tailor-made. The development and clinical introduction of a compliance and distensibility measurement device has propelled the concept of "tailor-made myotomy." Measuring the distensibility, or the resistance of the sphincter against pressure, is different from measuring its tonic contraction as seen in manometry [45]. In the context of achalasia, it may be a better parameter for assessment of the lower esophageal sphincter. A functional lumen imaging tool (Endoflip; Crospon Ltd, Galway, Ireland) assesses real-time distensibility of the lower esophageal sphincter to help determine the adequacy of myotomy during an esophageal procedure, using the technology of impendance planimetry. Pandolfino et al. have demonstrated the significant difference in the distensibility index between treated and untreated patients with achalasia, and also between treated patients with good clinical outcome [46]. If an optimal distensibility of the sphincter to achieve can be determined, tailored myotomies for achalasia can be calculated in each patient to achieve best relief of dysphagia with the least amount of collateral tissue destruction.

Studying the change in distensibility following POEM is helpful in characterizing how each step of the procedure affects the efficacy for future studies. Distensibility measurements in pig models showed that the diameter and distensibility of the esophagogastric junction improves remarkably after clasp circular fibers of the Laimer bracket were cut, and further proximal extension of the myotomy through higher levels of the esophagus provided only marginal additional benefit [47]. Although studies in healthy animals cannot match those of a diseased esophagus, they do provide some perspective on how much proximal esophageal extension of the myotomy above the lower esophageal sphincter is actually necessary for optimal results.

Distensibility of the lower esophageal sphincter is derived from relative changes in the diameter and cross-sectional area before and following POEM. Which of these dimensions is predictive of an optimal outcome is currently a source of intrigue. Teitelbaum et al. suggested that the distensibility index, defined as the minimum cross-sectional area at the esophagogastric junction divided by distensive pressure, could predict the clinical outcome of a myotomy [48]. They reported that the difference in distensibility index measured after induction and after the completion of operation correlates with postoperative Eckardt score for patients with Heller myotomy. The absolute value of the final index after both Heller myotomy with partial fundoplication and POEM also can predict postoperative symptoms: a small final distensibility index results in higher chance of persistent dysphagia, while a large value predicts the likelihood of iatrogenic reflux symptoms. In the study group, the range of final distensibility index of 4.5–8.5 mm^2/mmHg best predicted optimal symptomatic results (Eckardt scores ≤1 and GerdQ scores ≤7) with a sensitivity of 68% and a specificity of 80%. Ngamruengphong et al. reported a retrospective multicenter study, which showed a difference in the post-myotomy diameter and cross-sectional area between patients with and without post-POEM reflux esophagitis at 30 mL filling. Distensibility was not significantly different between the groups [49]. Familiari et al. then reported the contrary, showing no significant difference in post-myotomy diameter measured by EndoFLIP for those with and without esophagitis, reflux in pH monitoring, or heartburn symptom. Further studies, evaluating the relative change in these parameters instead of an absolute value, may reveal a predictive reference range.

Conclusion

POEM is a promising novel technique for treatment of achalasia, giving very good initial treatment outcomes. In terms of the development of gastric reflux, we now see that POEM compares well with standard surgical myotomy coupled with partial fundoplication. Although objective studies show a prevalence of abnormal esophageal acid exposure from 30 to 40%, only a portion of patients (15%) are symptomatic and thus in need of antacid medication for symptom control. Esophagitis is found to be present in some of those who are otherwise asymptomatic, possibly due to a lack of sensory innervation to the area of concern. Surveillance endoscopy, particularly in this patient subset, is appropriate to monitor potential neoplastic changes.

Several factors contribute to the development of reflux after POEM, including the inherent components of myotomy sans reconstruction, extent of dissection and myotomy as well as the procedural learning curve. Pending long-term results as well as ongoing prospective studies will allow us to determine the long-term incidence of gastroesophageal reflux after POEM.

In conjunction with the development of POEM, endoscopic anti-reflux procedures will likely contribute substantially to the durable success of the treatment of achalasia and related obstructive conditions.

To coalesce each of the advancements thus far, the development of imaging modalities that allow us to perform intraoperative real-time assessment of changes within the esophagogastric junction is ushering in the era of tailored myotomy.

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Training, Credentialing, and Developing a Clinical Program for POEM

14

Brian E. Louie, Andreas Schneider, and Ralph W. Aye

Introduction

Over the last 100 years, the treatment of achalasia has been dependent on the availability of technology. Technology, as simple as the sponge-tipped whalebone, that was used by Dr. Thomas Willis to perform the first dilation described in 1674 to the modification of a single-sided distal esophageal myotomy that we have come to consider the standard of care, to the laparoscopic approach with partial fundoplication and most recently the endoscopic myotomy [1]. With each of these innovations, there was a period of transition as physicians sought to understand the benefit or detriment of the new technique, to acquire the skills needed to perform the new technique, and lastly to integrate the new skills or technique into practice.

Although many minor changes can be made by adhering to the surgical mantra "see one, do one, teach one," paradigm shifts such as the transition from an open to a laparoscopic cholecystectomy which required surgeons to replicate the surgical maneuvers with instruments mounted on long sticks while viewing the patient's anatomy on a monitor were undertaken with a more structured approach [2, 3]. Comparatively, the transition to peroral endoscopic myotomy (POEM) is infinitely more complex since it requires access to the potential space of the submucosa in order to operate, a different and confined view to the usual surgical anatomy, and acquisition of additional knowledge and new skills for both gastroenterologists and surgeons conducting the procedure. A similarly structured approach may be beneficial to the adoption of POEM.

As with most disruptive technologies and paradigm shifts, there is a period just after initial innovation where the focus shifts to training the early majority while

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ensuring safe adoption and integration of the technology by both physicians and the hospitals hosting these innovations. This chapter will discuss the importance of a structured training program in acquiring the needed skills and proficiency to competently perform POEM, propose a practical framework for credentialing endoscopists, and provide insights into the development of a clinical POEM program.

The Concept of Structured Training

During their career most physicians will acquire new skills and knowledge particularly in specialties where procedures are being performed. In the senior residency levels and fellowships, this is most often accomplished through the "see one, do one, teach one" philosophy. However, while still of some merit, it has lost its meaning in the current era of resident training and rapid technological innovation of which attending surgeons—their teachers—are trying to keep abreast. After residency, the opportunity to evolve one's practice is a daunting task that is rarely addressed during training. Several options exist to acquire new skills and achieve competency including attending a course, participating in a mini-fellowship or preceptorship with an experienced physician, or collaboration with an experienced colleague. Each of these options presents different challenges such as locating a suitable course, finding an experienced physician to support training, or taking time away from family and practice [4]. More importantly, the limiting factor with any of these options is that the integration of the new skill safely into practice from a single option is incomplete.

In situations where surgeons have been confronted with a paradigm shift in technique, a more structured and comprehensive training program has allowed for successful adoption and integration into practice. Just over 25 years ago, acquiring the skills to transition from open cholecystectomy to laparoscopic cholecystectomy was based on similar arguments that have been put forth for introducing POEM such as a different operative space, new equipment, a different view of the anatomy for surgeons, and new anatomy for the gastroenterologist. Unlike cholelithiasis which is very common, achalasia and related motility disorders are rarer diseases which make it more difficult for any one endoscopist to gain the necessary skills, knowledge, and experience in a reasonable time frame.

The concept of a structured training program is based on a series of steps that includes didactic teaching, hands-on training, and supervision of initial cases. It is the combination of educational events that hopefully will result in a greater rate of successful adoption and safe application to the patient. Several authors have described their approach to POEM training [5–7]. The key components in each of these papers along with our experience suggest that a structured training program should include:

- Examination of the motivation to introduce the new procedure
- Cognitive training
- Hands-on training with appropriate models
- Creation of a team including nursing, engineering, and administration

- Anticipating and addressing institution-specific equipment and technology issues
- Proctoring or preceptorship of initial cases
- Evaluation of outcomes

To demonstrate the concept, we have outlined our program below.

Structured Training for POEM at Swedish

The motivation to introduce POEM into a practice or program is the first step in a series of decisions that should guide the surgeon or endoscopist. For most physicians, they will be motivated by the desire to learn a new approach, which may improve and enhance patient care. But, for others the motivation may be from outside due to loss of patient referrals to other centers, patient preferences, or colleagues wanting to collaborate. The success of the program may be influenced by these motivations when difficulties or challenges are encountered during the initial phase of learning. Moreover, these motivations need to be placed in the context of the physician's skill sets, the type of practice, and the clinical environment.

Cognitive Training and Hands-On Courses

At the present time, several training courses exist that facilitate the need for didactic teaching and hands-on skills. These represent only the first step in training. They provide a baseline set of knowledge through the use of didactic lectures that cover the principles of endoscopic surgery including relevant anatomy, the equipment required to perform the procedure, the basic steps of the procedure, and the management of complications.

The true value of these courses is the hands-on training because endoscopic surgery represents a departure for both the surgeon and the gastroenterologist. First, there is an explant porcine model that is realistic enough to give the endoscopist a good sense of the procedure. This allows the trainee to perform at least two and sometimes four procedures if planned properly and utilized fully. Second, some of these courses also come with a live porcine model which serves as an excellent surrogate for the human esophagus. Since the swine is sensitive to pleural incursions, this model can also simulate the development of complications. Again, this allows the trainee to perform at least two and sometimes up to four POEM procedures depending on time and skill set.

One of the underappreciated aspects of these courses is the familiarization with the various tools used to perform POEM. The ability to try each of the "knives," coagulation graspers, endoscopic clips, and endoscopic suturing devices provides a good test drive. For surgeons unfamiliar with some of the endoscopic tools, this narrows the knowledge gap prior to utilization on a human patient. For gastroenterologists who may be familiar with these tools, but not the conduct and complications that may arise during surgery, this provides valuable cross-specialty training.

Lastly, each of these courses includes live case observation. The astute participant will pay close attention to the room set up and the utilization of the surgical assistant and surgical technologist or nurse. There are many key pearls of wisdom learned in this component though most observers are so focused on the conduct of the procedure that this learning opportunity is often missed. Making notes of where the endoscopist stands and where the assistant and equipment are situated is crucial to a smooth transition to your own operating room and the nuances it brings with different booms, setups, and equipment.

Team Training

The initial focus of training is on the physician side, but one must not forget that surgery is a team endeavor. Regardless of where the procedure is performed (operating room or endoscopy suite), it is important to remember that the team members on either side are likely not familiar with crossover from surgery or endoscopy. While the scrub technicians or nurses in the operating room will be well versed in patients under general anesthesia as well as the conduct of the myotomy and anatomy and the potential complications from pneumoperitoneum or pneumothorax, they will be less comfortable with an endoscope and the tools that go with it. Similarly, the endoscopy personnel will be comfortable with the scope, needle knives, and endoscopic clips, but will not have the anatomic understanding of the esophageal muscle nor the physiologic implications of carbon dioxide insufflation creating capnoperitoneum of such magnitude as to impact airway pressures followed by the need for peritoneal decompression.

Prior to our first human procedure, we met with the operating staff and explained what we were trying to accomplish and asked for interested volunteers. We also sought assurance from the operating administration that we would have the same team we trained for the initial cases to keep up skills and learning. We also assured them that we would train others as we gained comfort and experience.

Rather than simply show the team videos or pictures, we set up a live training model. We planned this training 10–14 days prior to our first cases. We were fortunate to apply for and receive grant funding to conduct a porcine training model. We brought the POEM team and set up the lab exactly the way the operating room was to be structured. The team consisted of three physicians including two surgeons and one interventional gastroenterologist, two scrub technicians, the operating room director, and the fellows and residents who train with us. Using two swine, we were able to take the full team through approximately eight procedures utilizing all four quadrants of the porcine esophagus.

Initial Cases and Proctoring

At the inception of our POEM program, we had completed 16 POEM procedures on various explant and live porcine models. Even with that experience, we organized an experienced proctor to support our initial three cases. In the first case, we had sought credentials in our organization for the proctor to be able to have direct patient contact. This was not absolutely necessary but it was worth the time to have comfort in the knowledge that the proctor could assist if necessary. We think the time we took to be prepared for introduction into clinical practice was worth the investment. Our proctors have shared with us feedback from our cases and others who simply participated in a hands-on course. Our preparedness allowed us to glean additional tips from the experienced proctor rather than the proctor having to spend his time ensuring equipment was available or educating the staff on the basics of what is happening.

Program Evaluation

As part of our POEM program, we established a research protocol and registry to prospectively collect data to evaluate our outcomes. This has been suggested by several authors, but may not be ultimately necessary in the future since the initial adoption of POEM has occurred and more physicians are being trained [7, 8].

Value of a Structured Training Program

The value of the structured training program above is difficult to measure. Qualitatively, each member of the POEM team has told us that it was invaluable to him or her. For the three endoscopists, the training gave us confidence not only in the technique but in using the equipment, while the nursing team felt they understood the equipment and the procedure. And, lastly the clinical fellows were able to experience the work required to introduce a new procedure safely and successfully.

Quantitatively, the 16 training POEMs along with the three proctored cases brought us close to the 20 cases considered to represent the learning curve [9]. We hypothesized that structured training should increase surgeon preparedness based on complexity of case mix, procedure times, and outcomes. Our initial POEM experience of 30 cases was performed for achalasia (27), hypertensive LES (2), and jackhammer esophagus (1). In this group, 12 patients had no prior interventions, 12 had either prior dilations and/or Botox, and there were 6 sigmoidal-shaped esophagi including 3 with prior myotomy or esophageal surgery. Our mean overall procedure time was 165.9 min (±69.4). There were six inadvertent mucosotomies in 30 patients. One laparoscopic re-myotomy was performed for persistent symptoms, with no change postoperatively. At 6-month follow-up, Eckardt scores improved from 6.5 to 1.1 ($p \geq 0.001$) and GERD-HRQL (Fig. 14.1) scores from 16.7 to 7.7 ($p = 0.012$).

Compared to other initial series, these results are similar (Table 14.1). However, there are some subtle differences suggesting that structure training is helpful. During the initial six cases, two attending surgeons were used similar to Teitelbaum et al., but there was enough comfort with the procedure to allow for appropriate

GERD-Health Related Quality of Life Questionnaire (GERD-HRQL)

Institution:________________ PatientID:__________________________ Date__/__/__

□ On PPIs □ Off PPIs If off, for how long?___________________days / months

Scale:
0 = No symptom
1 = Symptoms noticeable but not bothersome
2 = Symptoms noticeable and bothersome but not every day
3 = Symptoms bothersome every day
4 = Symptoms affect daily activity
5 = Symptoms are incapacitating to do daily activities

Please check the box to the right of each question which best describes your experience over the past ***2 weeks***

1.	How bad is the heartburn?	□0 □1 □2 □ 3 □4 □5
2.	Heartburn when lying down?	□0 □1 □2 □ 3 □4 □5
3.	Heartburn when standing up?	□0 □1 □2 □ 3 □4 □5
4.	Heartburn after meals?	□0 □1 □2 □ 3 □4 □5
5.	Does heartburn change your diet?	□0 □1 □2 □ 3 □4 □5
6.	Does heartburn wake you from sleep?	□0 □1 □2 □ 3 □4 □5
7.	Do you have difficulty swallowing?	□0 □1 □2 □ 3 □4 □5
8.	Do you have pain with swallowing?	□0 □1 □2 □ 3 □4 □5
9.	If you take medication, does this affect your daily life?	□0 □1 □2 □ 3 □4 □5
10.	How bad is the regurgitation?	□0 □1 □2 □ 3 □4 □5
11.	Regurgitation when lying down?	□0 □1 □2 □ 3 □4 □5
12.	Regurgitation when standing up?	□0 □1 □2 □ 3 □4 □5
13.	Regurgitation after meals?	□0 □1 □2 □ 3 □4 □5
14.	Does regurgitation change your diet?	□0 □1 □2 □ 3 □4 □5
15.	Does regurgitation wake you from sleep?	□0 □1 □2 □ 3 □4 □5

16. How satisfied are you with your present condition?
□ Satisfied □ Neutral □ Dissatisfied

________________________ ________________________
Administered by Monitored by

________________________ ________________________
Date (mm/dd/yy) Date (mm/dd/yy)

GERD-HRQL Questionnaire Page1of 2

Fig. 14.1 GERD-HRQL. *Scale*: 0 = no symptoms. 1 = dymptoms noticeable, but not bothersome. 2 = symptoms noticeable and bothersome, but not every day. 3 = symptoms bothersome every day. 4 = symptoms affect daily activities. 5 = symptoms are incapacitating, unable to do daily activities

GERD-HRQL Questionnaire–Instructions

The GERD-HRQL questionnaire was developed and validated to measure changes of typical GERD symptoms such as heartburn and regurgitation in response to surgical or medical treatment.[1]

When comparing GERD-HRQL scores post-TIF to scores pre-TIF, it is important to take medication use into consideration. It is recommended to request patients take this questionnaire twice at screening (once off PPIs and the other time on PPIs) for fair comparison at follow-ups post-TIF

Total Score: Calculated by summing the individual scores to questions 1–15.
- Greatest possible score (worst symptoms) = 75
- Lowest possible score (no symptoms) = 0

Heartburn Score: Calculated by summing the individual scores to questions 1–6.
- Worst heartburn symptoms = 30
- No heartburn symptoms = 0
- Scores of ≤ 12 with each individual question not exceeding 2 indicate heartburn elimination.[2]

RegurgitationScore: Calculated by summing the individual scores to questions 10–15.
- Worst regurgitation symptoms = 30
- No regurgitation symptoms = 0
- Scores of ≤ 12 with each individual question not exceeding 2 indicate regurgitation elimination.[2]

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Fig. 14.1 (continued)

Table 14.1 Comparison of outcomes using a structured training program

Series	*N*	Number of endoscopists	Exclusion	Prior intervention (*N*, %)	Prior myotomy (*N*, %)	Sigmoidal esophagus (*N*, %)	Inadvertent mucosotomy (*N*, %)	Mean operative time
Swedish Series (2015)	30	1 attending with fellow at case 6	None related to achalasia	11 (39.3%)	2 (7.1%)	6 (21.4%)	6 (21.4%)	141.1 min ± 43.3 (sigmoid esophagus/ redo's excluded)
Kurian et al. (2013)	40	1 attending with fellow at case 16	Previous esophageal surgery, BMI > 40	27 (55%)	0%	N/A	10 (25%)	133 min ± 41
Teitelbaum et al. (2014)	36	2 attendings	No prior interventions for the first ten cases	4 (11%)	0%	N/A	3 (8%)	112 min ± 36
Patel et al. (2015)	93	1 attending	"Contraindications to POEM"	38 (41%)	N/A	21 (23%)	24 (26%)	149.7 min ± 36.7 (estimated time first 30 cases)

fellow involvement sooner. Comparatively, Dr. Lee Swanström as an early innovator and who did not have the benefit of course training involved fellows at case 16. Similarly, comfort with the procedure allows for an early transition to more complex cases such as those that had prior esophageal surgery or sigmoidal esophagi while maintaining low complication rates. Nevertheless, these differences are minor.

Why Use a Structured Training Program?

Many physicians will wonder if all of this is absolutely necessary since the physicians who pioneered the procedure didn't rely on any sort of training. They simply "made it up" or "learned as they went." As we move away from the innovators such as Pasricha and Inoue and the early adopters such as Stavropoulos and Swanström, a lot has been learned by these physicians. A structured training program allows the experiences and knowledge of many early adopters to be passed along for the betterment of patient experience. It's ultimately about safety and achieving good outcomes from the very beginning. In addition, we have found that the time and effort invested in preparation for surgeons, team, and institution have yielded big dividends in performance satisfaction, decreased stress for the entire team, and enhanced credibility with colleagues and administrators, paving the way for a systematic approach to the introduction of new technology in the future.

Aside from the above, national organization and governing bodies are establishing best practice guidelines to guide technology adoption. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has already outlined key components required to introduce new technology into practice, and they specifically identified the POEM procedure as one where this type of structure program should be utilized [10]. These guidelines are listed in Table 14.2. Use of a structured training program allows the physician to meet each of these criteria.

Although other national societies particularly the endoscopic groups like the American Society of Gastrointestinal Endoscopy (ASGE) have yet to articulate a position, this is likely forthcoming. With awareness of the current guidelines, it will

Table 14.2 Technology adoption guidelines from SAGES

Familiarization with the device or procedure before introduction	✓
Cognitive training in new device or procedure (e.g., indications, patient selection, etc.)	✓
Hands-on practice on appropriate training models before use in patients	✓
Assessment of surgeon ability to perform safely prior to introduction	✓
Full disclosure to patient	✓
Proctoring/preceptorship of initial cases	✓
Meticulous recording and monitoring of surgeon outcomes with device or procedure	✓
Regional/national monitoring of outcomes (e.g., with the use of a database)	✓

be difficult for future physicians looking to introduce POEM to do so without acknowledging these guidelines particularly if there is a complication early on in the endoscopist's experience.

Credentialing for POEM

Credentialing physicians using new technology has become an important topic in recent years with the introduction of new technologies such as robotic surgery, endoscopic ultrasound, and navigational bronchoscopy. Robotic surgery has come under intense scrutiny after several high-profile newspapers [11, 12] highlighted the inadequacy of training physicians using new technology to perform surgery and the role the hospitals need to play in ensuring physician competence. Not only are hospitals seeking to control their liability, but national organizations are also establishing credentialing specific to technology adoption but also for general credentialing guidelines for the introduction of new technology. One such example is the credentialing guidelines from the Society of Thoracic Surgeons (STS) [13] that has defined five levels of supervision or verification for surgeons that must be achieved during credentialing for new technology or advanced procedures (Table 14.3). Adherence to a structured training program allows the learner to meet the criterion for levels 1–4.

Table 14.3 Guidelines for credentialing

Level 1	✓
Certifies that the learner attended a lecture or completed a lecture format course (no verification of skills)	
Level 2	✓
Certifies the learner completed a course and was assessed via a test or other evaluation of training and was provided feedback regarding their assessment score (a better model incorporates a minimum pass rate)	
Level 3	✓
Certifies the instructor observed the learner perform a skill and verified completion of task. Alternatively, the learner completed a course and participated in a lecture and skills lab, allowing assessment of the skills on a synthetic or tissue-based model	
Level 4	✓
Certifies the learner performed the procedure in a patient in a clinical setting with supervision (proctor or preceptor)	
Level 5	✓
Certifies the learner performed a series of clinical cases, the outcomes of which have been reviewed and verified. An example of Level 5 learning may be submitting a series of video-recorded cases with outcomes to a review committee for verification	

Growing the POEM Program

Two of the forgotten team members in program growth are the support staff in reimbursement and marketing. Involving an administrator who has responsibility for reimbursement particularly when there is no established billing code is a necessity. This person can help establish reimbursement levels for submission to insurance and help devise a strategy for insurance authorization using an unlisted code.

The second person needed to grow a program is a marketing person who can increase the awareness of the new procedure to referring physicians. In the case of POEM, we utilized local media and a happy, articulate patient to be part of an initial press interview on one local media outlet. This generated another opportunity with another local media outlet. For rare diseases such as achalasia, social media has been an important part of a designed web-marketing platform to increase the knowledge about POEM. Lastly, we reached out to our referring partners to inform them about our program and have kept them informed about the outcomes. Results of these efforts can be seen in the case numbers over the past several years in Fig. 14.2.

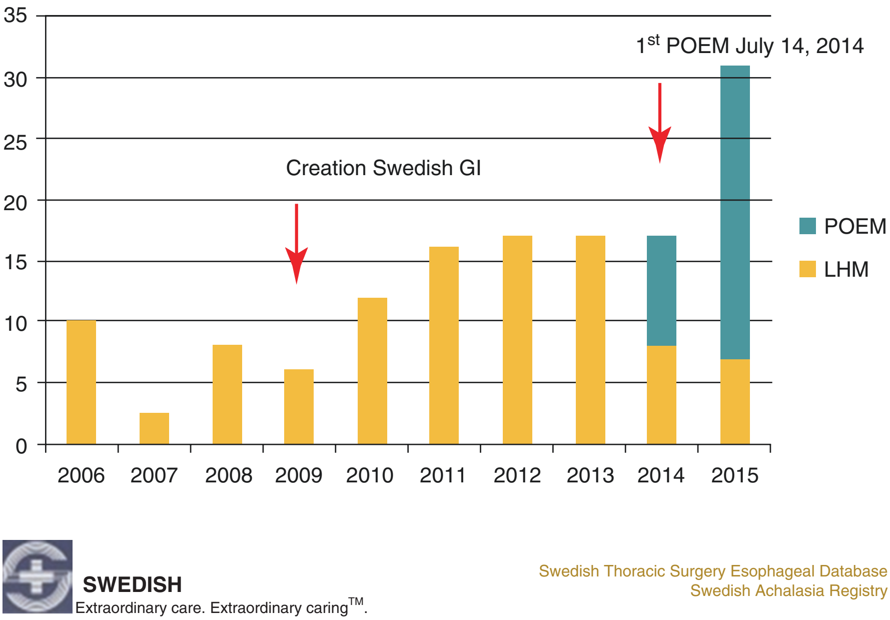

Fig. 14.2 Changes in case volume from 2009 to 2014

Conclusion

Acquisition of new skills or procedures that represent a paradigm shift in practice such as the transition to laparoscopic surgery or more recently the use of endoscopic surgery such as POEM requires a carefully delineated plan for training so that successful and safe integration into practice can be achieved. Although there are many strategies to implement a new program, a structured training program provides a framework for adoption and allows for hands-on training and practice before use on human subjects. Based on current national guidelines for technology adoption and credentialing, this structured approach appears to be best practice.

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Submucosal Surgery: Pyloromyotomy and Tumor Enucleation

15

Eran Shlomovitz and Oscar M. Crespin

If the lumen was historically the first and the peritoneal cavity the second, then the intramural space has come to represent the "third space."

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Introduction

Spurred by advances in endoscopic imaging, instrumentation, and energy devices, therapeutic endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have gained popularity and mainstream acceptance. Experience gained with these procedures in combination with the interest in natural orifice transluminal endoscopic surgery (NOTES) led to the development of the peroral endoscopic myotomy (POEM) procedure. The POEM procedure for the treatment of achalasia and other spastic esophageal disorder has quickly become the most successful and widely adopted NOTES procedure. The worldwide acceptance of POEM stimulated endoscopists to expand the techniques of operating in the submucosal space. In this chapter we aim to describe the techniques of endoscopic submucosal tumor enucleation, peroral pyloromyotomy (POP), as well as future trends in the field.

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Background

Endoscopic Mucosal Resection and Submucosal Dissection

The endoscopic resection of lesions in the gastrointestinal tract has been around for some time. In 1984, Tada et al. described the use of "strip-off biopsy" as a treatment option in early gastric carcinoma [1]. The technique included the thermal resection of a lesion utilizing a diathermy loop through the working channel of the endoscope, for the treatment of polypoid lesions. The need for resection of flat and submucosal lesions stimulated the development of submucosal dissection. The first step in this technique was the injection of a saline solution to raise flat or depressed lesions and was described by Rosenberg in 1995 [2]. By separating the mucosal lesion from the underlying muscularis propria, this submucosal injection technique has the benefit of reducing the risk of immediate full thickness perforation of the GI tract wall. Furthermore, the fluid cushion may also have the benefit of reducing the thermal injury to the muscularis propria thus minimizing the risk of delayed perforations. Although the literature is varied, mixing dilute epinephrine into the lifting solution may also provide a theoretical benefit of reducing the risk of post-resection bleeding [3–6].

Adoption of more advanced endoscopic techniques has lagged somewhat in the Western world. The introduction of CO_2 insufflation, high-definition flexible endoscopes as well as improvement in endoscopic accessories has helped greatly to promote adoption of these techniques in Western countries. Some examples include the design of the insulated tip knife by Muto et al. which helped the adoption of endoscopic resection of early gastric cancers [7].

Another landmark invention to perform interventional endoscopy was developed by Inoue who attached a clear endoscopic dissection cap to the tip of the endoscope facilitating the introduction of the endoscope in submucosal tunnel [8].

The Use of Solutions for Submucosal Injection

The most available and inexpensive solution for submucosal injection is normal saline, frequently used for EMR. However, the "cushioning effect" dissipates in terms of minutes and this is not improved by the addition of epinephrine [9]. More viscous substances as hyaluronic acid, hydroxypropyl methylcellulose, hydroxyethyl starch, glycerol, and fibrinogen or their combination may prevent dissipation. However, they may be expensive and can cause tissue damage and local inflammatory reactions at the injection sites [10–13]. The submucosal injection of autologous blood was also reported as a promising option that may last up to seven times longer than a 0.9% saline solution cushion, but it is not widely available [14]. There are ongoing industry efforts to develop dissection gels that would allow for a stable, inert, longer-lasting lifting mediums. There are however ongoing challenges with various respects of these efforts, amongst which is the difficulty in the delivery of these viscous gels through long and thin injection needles. The use of existing lifting solutions often necessitates repeat injections during the submucosal dissection process. This is both time-consuming and bothersome and interrupts the smooth flow of the procedure. Various instruments including dissection knives and snares have now been developed that allow for reinjection of the lifting solution without the need for instrument exchange.

Contrast Stains

Contrast stains have been used for a long time in chromoendoscopy to better recognize, characterize, and help outline the margins of superficial neoplastic lesions both for diagnosis and prior to endoscopic resection [15]. Indigo carmine and methylene blue are two most widely used stains utilized in this fashion. Both stains are also now frequently used in combination with saline or other lifting solutions with or without the addition of dilute epinephrine for endoscopic submucosal dissection. The addition of the dye helps to stain the submucosa and highlights the differentiation between the submucosa and the muscle layer thus helping to clarify the proper dissection plane. The strength of the colored solution is a matter of personal preference. Our choice of mixing ratio is approximately 0.5 mL of methylene blue for every 500 mL of the chosen lifting solution.

Submucosal Lesion Diagnosis

Submucosal lesions represent a challenge for diagnosis and treatment since they may be difficult to reach with biopsy forceps. The endoscopic appearance alone is often not enough to differentiate a malignant from a benign lesion. Although some endoscopic maneuvers such as changing the patient's position and "palpation" with biopsy forceps are used to differentiate an extrinsic compression from a true submucosal lesion, endoscopic ultrasound (EUS) is often needed to objectively characterize the location and potential malignant characteristics of a submucosal lesion. EUS is also useful to guide fine-needle aspiration for tissue acquisition of submucosal lesions. The ongoing challenge with this technique however is the difficulty of the procedure and the relatively low diagnostic yield when attempting to target smaller lesions (<30 mm) [16]. Aiming to obtain better samples, core needle biopsies have been used in the diagnosis of submucosal lesions. However, a meta-analysis of 21 studies comparing EUS-FNA and core needle biopsies for tissue acquisition of solid masses, including pancreatic masses, lymph nodes, and submucosal lesions of GI tract, did not demonstrate significant differences in histologic yield or diagnostic accuracy. Moreover, higher costs of core biopsy do not justify its use [17].

Tumor Enucleation

The advances in endoscopic technology and submucosal dissection techniques have led to ongoing advances in endoscopic tumor enucleation techniques.

The most straightforward enucleation technique involves four basic steps: (a) marking or delineating the lesion with electrocautery to avoid partial resection; (b) lifting the mucosa with submucosal injection; (c) circumferential submucosal incision around the lesion; and (d) resection and removal of the lesion.

Newer techniques of submucosal lesion enucleation have more recently been described in an attempt to resect lesions in more challenging locations or ones that involve the deeper layers of the GI tract wall. Such techniques which include endoscopic submucosal excavation (ESE) and submucosal tunneling endoscopic resection (STER) appear to be promising options to resect GI tumors that are located in the muscularis propria (MP). Although the names of these techniques may vary, they all tend to be based on a similar concept to the POEM techniques. These techniques involve a mucosal incision a few centimeters proximal to the target lesion followed by dissecting a submucosal tunnel all the way to the lesion. The tumor is dissected free of the surrounding tissues which may involve excavation into the muscular layer and may occasionally involve a full thickness resection. The lesion is then retrieved through the tunnel followed by mucosal closure in some fashion. These techniques aim to maintain the integrity of the overlying digestive tract mucosa but do require more advanced endoscopic skills and experience [18].

Endoscopic Treatment of GIST

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms usually located in the stomach and proximal small intestine and less frequent in any other portion of the alimentary tract [19–22].

Differential diagnoses should be made with other submucosal lesions such as lipomas, liposarcomas, leiomyomas, leiomyosarcomas, desmoid tumors, schwannomas, and peripheral nerve sheath tumors. In general, the treatment of submucosal tumors of GI tract depends on tumor size, location, or any associated complications such as obstruction or hemorrhage. Tumor size and location are of particular focus for an endoscopic approach. In terms of size, there is a general agreement that GIST greater than 2 cm should be resected. However, the indication to resect smaller tumors is debatable. The National Comprehensive Cancer Network (NCCN) guidelines suggest that patients with very small suspected gastric GISTs (<2 cm) with no high-risk EUS features (irregular border, cystic spaces, ulceration, echogenic foci, or heterogeneity) can be followed with endoscopy at 6- to 12-month intervals. The European Society for Medical Oncology (ESMO) guidelines go somewhat further in promoting resection for histologically proven small GISTs, although there is certainly a role for observation in low-risk lesions. The difficulty of course is that definitive histologic diagnosis can often be difficult to obtain in the setting of these small lesions. Endoscopic ultrasound assessment is of course a key tool if close surveillance is selected to carefully monitor for any increase in lesion size which may then require resection.

Endoscopic resection may be a particularly attractive alternative as a minimally invasive option for the resection of submucosal lesions in difficult locations such as the proximal stomach and gastroesophageal junction. Traditional resection techniques in these locations may require extensive resection with potential functional implications.

The endoscopic resection of small submucosal tumors represents perhaps a somewhat controversial but certainly progressing area of research. For example, He and colleagues studied 224 patients with submucosal tumors (SMTs), these included 92 esophageal, 14 cardiac, 61 fundus, 22 body, 25 antrum, and 10 duodenal lesions. The majority of the SMTs were leiomyoma (109, 48.7%) and gastrointestinal stromal tumors (GIST) (77, 34.4%), while other SMTs were confirmed as ectopic pancreas (21, 9.4%), adenoid tumor (8, 3.6%), lipoma (5, 2.2%), neuroendocrine tumor (3, 1.3%), and granulosa cell tumor (1, 0.4%). Endoscopic resection success rates were very high with 92.9% of lesions successfully resected en bloc ESD. Endoscopic resection was unsuccessful in 16 patients (7.1%). The procedure appears to be quite safe with a 1.8% rate of severe complications (four cases). The safety and feasibility of these endoscopic resection techniques were also demonstrated by an earlier prospective study, in which Ye and colleagues assessed the submucosal tunneling technique for the treatment of small submucosal upper GI lesions under 3 cm [18].

The safety of the endoscopic techniques has also been demonstrated for lesions in difficult locations such as the gastroesophageal junction, duodenum, and rectum. These however have often been small case series, thus highlighting the need for more studies to find the ideal role of endoscopic therapies [23–25].

Combined Endoscopic and Laparoscopic Management of Benign Lesions

The combination of endoscopy and laparoscopy for the management of submucosal lesions termed laparoscopic-endoscopic cooperative surgery (LECS) was described by Hiki in 2008 [26]. Submucosal tumors with endophytic growth are often difficult to localize laparoscopically without endoluminal guidance. This technique therefore utilizes an endoscope to delineate the lesion. A combination of endoluminal endoscopic as well as laparoscopic dissection of the lesion is then performed. The endoscopic and laparoscopic approaches eventually connect thus resecting the lesion. These techniques can utilize the advantages afforded by the laparoscopic approach with the use of coagulation devices to transect the wall of the lumen under laparoscopic control but with endoluminal/endoscopic guidance. The specimen can then be retrieved through the umbilical incision or potentially endoscopically through the natural orifice. The edges of the resection line can then be easily closed laparoscopically. The endoscope can then be finally used to control any endoluminal bleeding and to perform leak test. This technique provides the advantage of a limited resection of healthy gastric wall, compared to the conventional laparoscopic wedge resection and may further represent a useful tool in difficult tumor localization in the esophagogastric junction or pyloric ring [27].

Complications

The most frequent complications related to endoscopic tumor enucleation relate to bleeding, perforation, and strictures. Other more benign complications include pneumothorax, pneumoperitoneum, atelectasis, and pleura effusion and can often be managed conservatively [28]. Some endoscopic bleeding is a frequent occurrence. It is typically insignificant and can usually be well controlled using hemostatic graspers. Full thickness perforation either intentional or not can be managed with endoscopic clipping or where available an endoscopic suturing device. Although CO_2 should always be used for these advanced endoscopic cases, some perforation may result in clinically significant tension capnoperitoneum. Under such circumstances Veress needle decompression is usually all that is required.

Stricture formation as a sequela of endoscopic resection occurs more frequently in the esophagus and the pylorus. This is particularly of concern when more than 50% of the circumference must be resected. These complications have also been shown to be associated with the degree of experience in the particular center [29]. Less frequent complications may include gastric or colonic ischemia. These may be related to arterial complications at the time to lift solution injection [30, 31]. Strictures related to extensive resections in the distal stomach or in the rectum have been reported to be successfully treated with endoscopic balloon dilations. There is however an inherent risk of perforation with such dilations [32, 33].

POEM Experience

Endoscopic myotomy for achalasia was first reported in 1980. The technique was described by Ortega et al. as a mucosal and circular muscle myotomy that was performed around the gastroesophageal junction (GEJ) [34]. Although the initial series demonstrated promising results, the technique was somewhat ahead of its time and was not universally accepted due to concerns of high risk of perforation. In 2007, Parischia et al. reported the feasibility of performing endoscopic myotomy in four pigs by creating a submucosal esophageal tunnel. Consequently, in 2010 the first human study was published by Inoue et al. [35, 36]. Since those early reports, the procedure has been increasingly adopted by gastroenterologists and surgeons performing who have performed thousands of procedures worldwide [37].

The success of POEM for the treatment of achalasia patients has also expanded its applications to more challenging situations such as patients who previously underwent other treatments for achalasia. For example, Onimaru et al. reported outcomes 3 months after rescue POEM in ten patients with previous Heller myotomy showing significant reduction in lower esophageal sphincter (LES) resting pressures (22.1 mmHg vs 10.9 mmHg, $p < 0.01$) and Eckardt symptom scores (6.5 vs 1.1 $p < 0.001$). The author also highlighted the advantage of POEM in performing the rescue myotomy in the posterior wall of the esophagus to avoid the scarring zone of previous treatment [38]. Although qualitatively more difficult, reports of the safe use of the POEM procedure in cases of prior Botox injections highlight the safe use of the submucosal tunneling techniques in the setting of potentially scarred tissue planes.

Patients with sigmoid esophagus represent an additional endoscopic challenge. However, even in this setting, Hu et al. reported 96.8% of treatment success with POEM in 32 consecutive sigmoid-type achalasia patients. In this study, during a mean follow-up period of 30.0 months, there was only one patient with incomplete partial symptom relief that required additional balloon dilations [39].

Centers with experience in POEM have also expanded its applicability to cases of other spastic esophageal disorders such as distal esophageal spasm and hypertensive lower esophageal sphincter. POEM may have a particular benefit in the setting where ultra-long myotomies may be required such as in cases of nutcracker and jackhammer esophagus and in type 3 achalasia. The endoluminal approach of the POEM procedure can allow for longer myotomies to be performed as compared to the laparoscopic approach [37, 40, 41].

Gastroparesis and Pyloromyotomy

Gastroparesis is one of the most difficult functional gastrointestinal disorders to treat. It is characterized by delayed gastric emptying in the absence of mechanical obstruction, causing nausea, vomiting, early satiety, bloating, and abdominal pain. Any abnormality on the sympathetic or parasympathetic nervous systems, neurons, and pacemaker cells (interstitial cells of Cajal) within the stomach and intestine and the smooth muscle cells of the gut can lead to a delay in gastric emptying (gastric stasis) [42].

The annual incidence has been estimated as 2.4 per 100,000 for men and 9.8 per 100,000 for women. The need for hospitalization due to gastroparesis also appears to have increased over the past decade, highlighting the high potential morbidity associated with this disease [43, 44]. The most frequent cause of gastroparesis is idiopathic, followed by diabetes and postsurgical. Parkinson's disease, collagen/vascular disorders, and hypothyroidism have also been found to be associated [45, 46].

Although dietary modification and prokinetics are considered first line therapy in patients with mild gastroparesis, the efficacy of medical management in severe cases of gastroparesis is low, increasing the role of surgery [47]. Surgery or other therapeutic intervention is also often needed in patients with refractory symptoms, such as dehydration and other metabolic disorders related to the reduced oral intake and vomiting.

Placement of feeding jejunostomy tubes or venting gastrostomy tubes by endoscopic or fluoroscopic guidance certainly has a role in symptom palliation and improves nutritional support but is beyond the objectives of this chapter.

Laparoscopic Heineke-Mikulicz-type pyloroplasty has demonstrated to be effective for the treatment of gastroparesis by reducing the need of prokinetics (89% to 14%) and normalizing gastric emptying in 71% in a series of 28 patients. Two patients were treated with a laparoscopic-assisted endoscopic procedure using an endoscopic flexible stapler representing the initial intent for a full endoscopic pyloroplasty of that group [48].

The feasibility of peroral endoscopic pyloromyotomy (POP) was demonstrated by Kawai and colleagues in animals. Reduced pyloric pressure following the procedure was demonstrated after the procedure thus supporting the potential effectiveness of this concept whereby complete ablation of the pylorus may result in improved gastric emptying [49].

The procedure models the basic steps of POEM in which a submucosal gastric antral injection is performed followed by a 2-cm longitudinal mucosal incision (Fig. 15.1). The endoscope is then introduced into the submucosal space (Fig. 15.2)

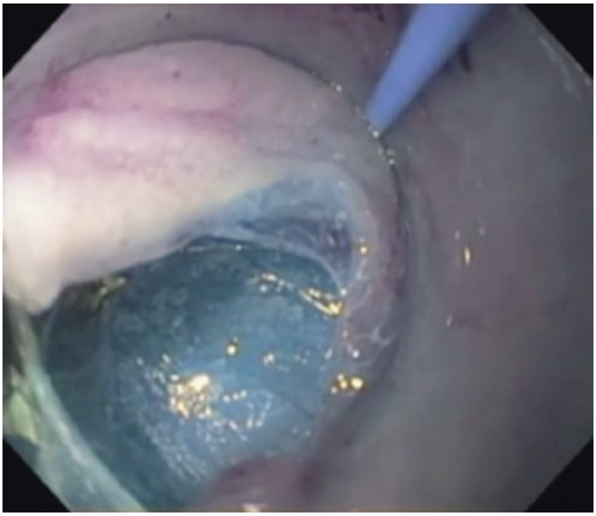

Fig. 15.1 Initial longitudinal mucosal incision is performed following submucosal injection of a lifting solution.The submucosal space stained with the dilute methylene blue solution can be seen

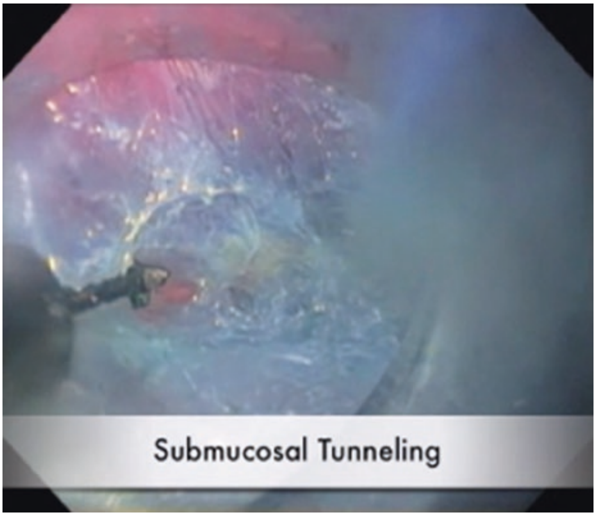

Fig. 15.2 The submucosal dissection is perfomed in the deep submucosal space to avoid injury to the overlying mucosal flap which can be appreciated at the upper portion of the image

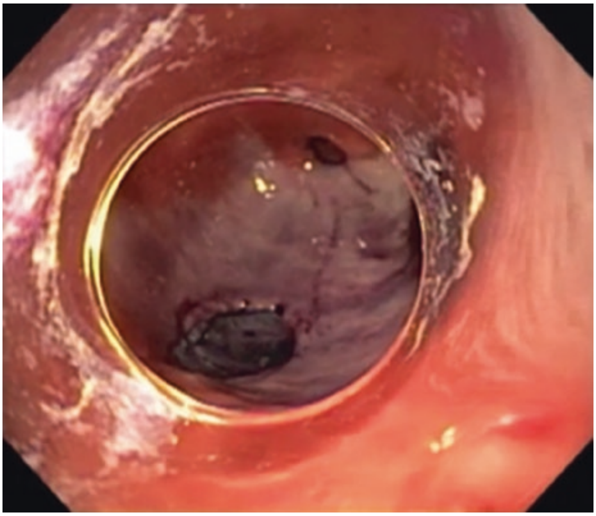

Fig. 15.3 Luminal view of the completed submucosal tunnel extending from the mucosotomy to the pylorus. Pallor of the mucosa is related to the dilute epinephrine which is mixed into the lifting solution

Fig. 15.4 Submucosal view near the end of the myotomy process. A thin residual strand of pyloric sphincter muscle is seen crossing horizontally. Care should be taken to avoid injury to the overlying duodenal mucosa which is visible draping over at the upper portion of the image

and a submucosal tunnel is performed in an antegrade direction up to the duodenal cap (Fig. 15.3). The pylorus is then divided endoscopically (Fig. 15.4) followed by closure of the mucosal entry with endoscopic clips (Fig. 15.5) or an intraluminal suturing device. A contrast swallow study is typically performed the following day to document adequate closure of the mucosotomy (Fig. 15.6).

The first human experience with POP was reported by Khashab et al. in 2013. A 27-year-old female with diabetic gastroparesis, daily symptoms of nausea,

Fig. 15.5 Closure of the musocal incision utilizing endoscopic clips is seen

Fig. 15.6 Radiologic upper GI study perfomed the day following the procedure demonstrates intact closure of the mucosotomy

vomiting, and multiple admissions for refractory symptoms and dehydration was treated with POP. No complications were reported and objective and subjective results confirmed the success of treatment [50]. A subsequent early case series was reported by Shlomovitz et al. documenting seven nondiabetic patients with refractory gastroparesis treated with the POP procedure. In this series, the most common cause of gastroparesis was idiopathic ($n = 5$). Two patients had postsurgical gastroparesis based on a history of prior foregut surgery. Six procedures were performed under laparoscopic guidance, given that patients required other concurrent laparoscopic procedures. A purely endoscopic procedure was performed in one patient who didn't require an additional laparoscopic procedures.

POP was technically successful in all seven cases, and there were no intraoperative complications. Delayed complications related to the procedure consisted of an upper GI bleed 2 weeks post-procedure necessitating a blood transfusion. This occurred in a patient that did not comply with the usual regimen of postoperative high-dose PPI use. Upper endoscopy demonstrated a 1-cm ulcer in the pyloric channel, with an exposed vessel that was clipped resulting in complete resolution of the bleeding. In this patient series, six of the seven patients reported symptom improvement or resolution at 6-month follow-up. Objective nuclear medicine gastric emptying studies (GES) were available in five of the patients. In four out of these five patients, follow-up GES documented successful normalization of their gastric emptying [51].

POP has also been shown to be effective in the treatment of gastroparesis caused by vagal injury post esophagectomy and post fundoplication [52, 53].

Technical Differences

Some technical differences do exist between the POP and the POEM techniques. Unlike in POEM we prefer to keep a fairly short submucosal tunnel with the mucosal incision that is performed only about 2–3 cm proximal to the pylorus. Also the myotomy itself is fairly restricted to the pylorus and only extends proximally by about 1 cm. During the pyloromyotomy, no specific attempt is made to selectively divide only the circular muscular layer, and it is typically divided in a full thickness fashion down to the serosal layer. Special attention must be paid when performing the distal portion of the pyloromyotomy since the duodenal mucosa will drape over it in a perpendicular direction and could be easily perforated during this portion of the dissection. Finally, there is still some disagreement as to the optimal location to perform the myotomy. We prefer to perform the pyloromyotomy on the posterior aspect of the greater curvature, adjacent to the retroperitoneum, to benefit from the natural positioning of the endoscope. An argument however can be made to perform the myotomy along the anterior aspect so that the procedure can more easily be converted to a laparoscopic pyloroplasty in case of an endoscopic full thickness perforation.

Future Perspectives

The success of POEM expanded the indications and the acceptance of the endoscopic submucosal dissection techniques. This has an especially marked effect in the Western world where these techniques were much less well known and practiced as compared to Asia. The greatest testament to this may be the increasing reports in the Western world of gastroenterologists and surgeons performing advanced endoscopic techniques such as endoscopic tumor enucleation and endoscopic pyloromyotomy.

Further studies with larger number of patients are needed to determine long-term outcomes and indications of those endoscopic therapies. Endoscopic tumor enucleation particularly must be well studied to ensure that long-term oncologic results remain equivalent to laparoscopic or open resection. With time and operator experience, even more advanced techniques such as endoscopic full thickness resection (EFTR) will also gain popularity.

Significant challenges however remain with respect to adequate physician training to perform these advanced procedures. Only few centers have evaluated the learning curve for POEM. Kurian et al. reported that mastery of operative technique in POEM can be measured by the decrease in length of procedure and incidence of inadvertent mucosotomies. He found that 20 cases are needed to reach mastery [54]. Procedure time however can be quite variable between patients and can largely depend on prior esophageal interventions [55]. Patel et al. subsequently defined efficiency after 40 POEMs and mastery after 60 POEMs elevating the threshold established by Kurian and colleagues [56]. Obtaining this required level of experience can be quite challenging especially in the setting of such a rare disorder such as achalasia. Future research must therefore also focus on improvement in the training and simulation of these procedures. With time the available endoscopic surgical platforms will continue to improve and evolve making these techniques accessible to an ever increasing group of practitioners.

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16 Future Applications of Submucosal Surgery: NOTES, Full-Thickness Resections and Beyond

Renato V. Soares, Lee L. Swanstrom, and Jacques Marescaux

Introduction

Navigation in the submucosal (SM) space is a common element in several emerging procedures in interventional endoscopy, including endoscopic submucosal dissection (ESD), POEM (peroral endoscopic myotomy), POP (peroral pyloromyotomy), and POET (peroral enucleation tumors). The use of a submucosal endoscopic mucosal flap (SEMF) technique as a valve in natural orifice translumenal surgery (NOTES) procedures has also proven to be useful. Submucosal endoscopy has an evolving role in diagnosis of neuromuscular disorders of the gastrointestinal tract (Fig. 16.1).

Past, present, and future perspectives of procedures in which submucosal endoscopy has a role will be discussed in this chapter. While some SM procedures are part of current medical practice, others are still in an animal testing phase (Table 16.1).

The Submucosal Space and NOTES

The ability to endoscopically create a submucosal (SM) working space within the wall of the gastrointestinal tract was first described by Sumiyama et al. in 2006 [1]. The original description included the use of pressurized CO_2 injected through an

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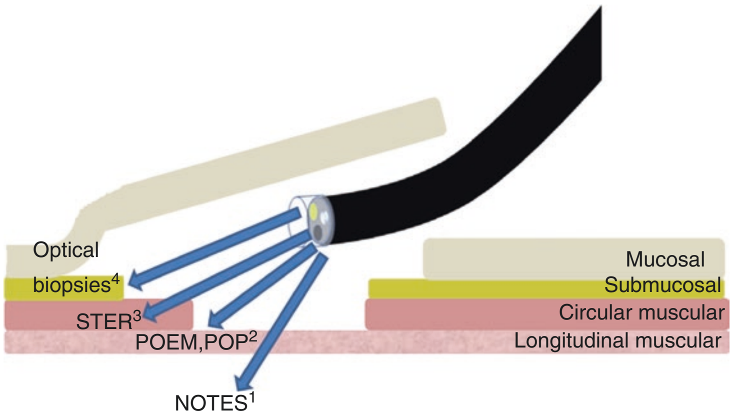

Fig. 16.1 Endoscopic interventions with submucosal navigation. (1) *NOTES* natural orifice transluminal surgery (SEMF valve approach). (2) Endoscopic myotomies—*POEM* peroral endoscopic myotomy, *POP* peroral pyloroplasty. (3) Endoscopic tumor resection—*STER* submucosal tunneling endoscopic resection. (4) Optic biopsy and tissue sampling for subepithelial lesions or neuromuscular disorders of the gastrointestinal tract

Table 16.1 Examples of procedures with submucosal navigation in different stages

<table>
<tr><th>Animal experiments</th><th>Early clinical adoption</th><th>Clinical adoption</th></tr>
<tr><td></td><td colspan="2">Per-oral endoscopic myotomy (POEM)</td></tr>
<tr><td colspan="2">Per-oral endoscopic pyloroplasty (POP)</td><td></td></tr>
<tr><td></td><td colspan="2">Submucosal tumor endoscopic resection (STER)</td></tr>
<tr><td colspan="2">Peritoneoscopy under conscious sedation</td><td></td></tr>
<tr><td colspan="2">Optical biopsies – OTC, endocytoscopy, CLE</td><td></td></tr>
<tr><td colspan="2">Trans-rectal NOTES</td><td></td></tr>
<tr><td>Transesophageal thoracic NOTES</td><td></td><td></td></tr>
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endoscopic needle placed into the submucosa with creation of a large SM gas bubble. The next step was a mucosal incision in the edge of the bubble and further development of a tunnel with a biliary extraction balloon. This technique was developed in an effort to create a self-sealing exit site for NOTES procedures. This approach was advantageous because the incision in the mucosa and in the seromuscular layer of the gut was made several centimeters apart, thus avoiding the need for single-site full-thickness closure of the GI tract in NOTES procedures. The SEMF technique was first used to perform full-thickness muscular layer resections [1]. In 2007, the same group published the technical feasibility of transesophageal mediastinoscopy [2] and trans-gastric cholecystectomy [3] in survival animal model using the SEMF technique. During mediastinoscopy, the defect in the muscular layer was not closed and the mucosa was approximated with clips. In the trans-gastric cholecystectomy, the authors used anchors or clips to close the mucosal incision. Despite complications and mortality in the animal models, the SEMF technique was felt to be potentially feasible and effective. In the same year, Pasricha et al. published the use of a submucosal tunnel as an access route for an esophageal myotomy, which started a new era in the treatment of achalasia [4].

One caveat of the SEMF technique as proposed by Sumiyama et al. was the possibility that the creation of a wide area of separation between the mucosa and the submucosa could potentially lead to ulceration and necrosis of the overlying mucosa due to devascularization [5]. To overcome this, different authors described the creation of narrow and long tunnels using ESD techniques for trans-gastric [6] and transrectal NOTES [7] procedures. Also, narrow SM tunnels helped to correctly align the endoscope with the proposed intraperitoneal target [8]. Despite theoretical advantages, a comparison between direct incision (DI) of the gastric wall and submucosal tunnel (SMT) creation for trans-gastric access in NOTES favored the DI method in one study [9]. In this animal experiment, six pigs had intraperitoneal targets implanted in predetermined positions inside the abdominal cavity. The operative time was higher in the SMT group and more intra-abdominal targets were reached in the DI group. However, when considering closure of the initial gastrotomy, most studies have favored the SMT method as it provides a more secure and lower-risk closure of the enterotomy [9–11].

Both DI method and the SMT method reached early clinical adoption. For example, Lee et al. published a study in which ten patients had submucosal tunneling (SMT) as an access route for NOTES. Five patients had a diagnostic peritoneoscopy (four with ascites and one with a lymphadenopathy of unknown cause), while the other five had a full-thickness resection due to subepithelial tumors. Remarkably, the procedures were successfully conducted under conscious sedation. No severe postoperative complications occurred [5]. Conversely, Magdeburg et al. published a series of 43 patients that had trans-gastric NOTES procedures (36 appendectomies, six bilateral salpingo-oophorectomies, and one hysterectomy) using the direct incision method to access the peritoneal cavity. In these patients, closure of the gastric incision was done using an over-the-scope nitinol clip (OTSC 12/6a-220; Ovesco Endoscopy, Tubingen, Germany). There were three adverse events in the series: two patients had bleeding originating from the clipped closure site and one patient had a local peritonitis due to insufficient closure of the gastrotomy [12].

The trans-gastric SEMF method seems to be a reasonable way of exploring the abdominal cavity under conscious sedation. No dedicated high-cost equipment is required to perform the technique, and the closure of the gastric mucosotomy is usually accomplished with regular endoscopic clips. Therefore, one can theorize that this may become an useful method for peritoneoscopy in the future, especially in cases in which general anesthesia is undesirable, such as critically ill patients [5]. Furthermore, as new NOTES platforms develop, advanced operations may be performed under conscious sedation, with minimal invasiveness and morbidity using an incision in the gastric mucosa and a submucosal tunnel as the route to the peritoneal cavity. New wide-angle endoscopes as well as navigation systems may facilitate orientation and visualization inside the abdomen [13, 14]. A number of platforms dedicated to NOTES, both robotized and mechanical, are under development [15, 16].

In addition to trans-gastric procedures, a number of experimental studies have explored the feasibility and potential utility of transesophageal access for the mediastinum and thoracic cavity. In animal studies, it has been demonstrated that procedures such as mediastinoscopy, lymphadenectomy, truncal vagotomy, pleural biopsy under direct vision, pericardial windows, myocardial and left atrium injection, epicardial ablation, and even thoracic spine procedures can be performed through the transesophageal route [17]. The SEMF technique (mucosal incision and submucosal tunneling) has been employed more frequently than the direct incision (DI) method for transesophageal thoracic NOTES [17]. To facilitate esophagotomy closure, endoscopic clips, tissue anchors, and covered stents have been used with favorable outcomes in the animals [17, 18], but stent migration with current devices is a problem.

In order to increase safety and efficacy in submucosal explorations and NOTES, it has been advocated that image guidance could be helpful. In one study, Córdova et al. [19] assessed the utility of a navigation system based on reconstructed 3D CT images and electromagnetic tracking of the tip of the scope (3D Guidance trakSTAR; Ascension Technology Corp, Burlington, Vt). In this study, 30 pigs underwent transesophageal NOTES mediastinoscopy, with half of those having the abovementioned navigation system while the other half without guidance. A mucosal incision and submucosal tunneling (SMT) technique was used to enter the mediastinum. The number of adverse events was similar in with and without guidance, and the author was able to identify the right atrium and the vena cava in more animals in the group that had the navigation system. No complications from the SMT were reported.

Indeed, transesophageal NOTES for mediastinal or thoracic exploration until now have not reached widespread clinical adoption. Nevertheless, trans-oral esophageal procedures like the peroral endoscopic myotomy (POEM) and subepithelial tumor enucleation (POET) including endoscopic full-thickness resections (EFTR) have enjoyed clinical acceptance. With this growing experience, slower yet steady progress is been made to push forward the boundaries of transesophageal NOTES. It has now been clearly demonstrated that esophageal mucosotomy and tunnel development are safe and can reach beyond the esophageal wall. Transesophageal exploration of the mediastinum and chest remains a possible future application for the SEMF technique in humans [20].

Transrectal peritoneal access using the submucosal tunnel technique has also been described in animal studies. Despite potential bacterial burden and concerns about healing in rectal wounds, possible advantages of this route are enhanced visualization and the ability to reach of the upper abdomen, due to the fact that the endoscope is in a straight position. This approach also affords less incisional pain by use of the anus for retrieval of specimens compared to a transabdominal approach. In one study [7], six pigs had transrectal SMT access for 20 min of peritoneoscopy. The author did not observe complications and noted that the healing process was more advanced at the seromuscular level compared to the mucosal level after 7 days. In this study, the mucosal incision was closed with titanium clips. Also, transrectal incision and submucosal tunnel have been the access route for a retroperitoneoscopy and feasibility of a NOTES nephrectomy in cadaver models [21].

Trans-oral NOTES access to perform operations in the thyroid gland without visible scars had used a mucosal incision and the development of a tunnel [22]. In the trans-oral thyroidectomy vestibular approach (TOETVA) described by Anuwong, the surgeon performs three incisions in the oral vestibule and inserts conventional laparoscopic ports and instruments. Then, the subplatysmal space is dissected, from the larynx to the sternal notch distally and laterally to the anterior border of the sternocleidomastoid muscle. The space is then maintained by a CO_2 insufflation pressure of 6 mmHg. The author reported 60 procedures using this method with good outcomes. Other authors reported minimally invasive thyroidectomies from the base of the tongue. It is intuitive to imagine that the vestibular incision and subplatysmal dissection can also be used to reach the cervical esophagus. As such, treatment of pharyngoesophageal (Zenker's) diverticulum and even esophageal resections could be approached without skin incision, thus leaving no scars and potentially decreasing morbidity.

Submucosal Tunneling: Beyond POEM

POEM was the first widely accepted non-NOTES application of the SEMF access technique. It has since developed into a standard treatment for achalasia. As endoscopists became more comfortable with the technology and approach, the indications in the field of esophageal dysmotility have expanded. End-stage disease, reoperative cases, spastic motility disorders, and other non-classified disorders are now routinely treated using POEM access. Several other disease states are also being treated via tunneling access. The best described is the treatment of gastroparesis by endoscopic pyloromyotomy. Idiopathic and diabetic gastroparesis has been shown to respond well to surgical pyloroplasty [23].

Early reports, of this procedure, including one multicenter study, have shown symptom improvement or relief in around 86% of patients and normalization of radionuclide exam in between 47 and 80% of patients [24]. While long-term outcomes are unknown, it appears that the POP procedure may prove to be an important tool in the management of these difficult patients.

Another reported procedure is endoscopic cricomyotomy. Cervical dysphagia due to cricopharyngeal spasm or hypertrophy is an annoying condition, not uncommon in the elderly population. Because it is a benign condition and surgical treatments are rather invasive, treatment is seldom offered to these patients, leaving them to suffer with their decreased quality of life. Endoscopic cricomyotomy has been described using a POEM-like approach, making the mucosal incision in the posterior pharynx, tunneling to the cricopharyngeal muscle, and dividing the muscle well onto the normal proximal esophagus. Good results have been reported in small studies [25].

There are numerous other anecdotal reports of use of submucosal tunneling to treat a variety of conditions, including recalcitrant strictures, congenital cartilage rings, muscularis propria biopsies, and even rectal myotomy for adult Hirschsprung disease [26, 27]. It is clear that the success of POEM has opened the door to a whole brave new world of working in this new "third space"—neither endolumenal nor extralumenal—but providing direct access to the origins of many digestive diseases.

Submucosal Endoscopy in Tumor Resection: Full Thickness and Beyond

Endoscopic resection of gastrointestinal lesions is a rapidly evolving field. The first endoscopic polypectomies for colorectal lesions were described in 1974, and the strip biopsy technique of mucosectomies was described by Tada et al. in 1984. In 1992 cap-fitted EMR (endoscopic mucosal resection) was first described. With the development of the IT (insulated tip) knife in the late 1990s, endoscopic submucosal dissection (ESD) techniques began to thrive, and larger mucosal lesions could be resected en bloc [28]. With knowledge granted from ESD practice, new techniques [29, 30] for tumor resection based on navigation within the submucosa, such as the endoscopic submucosal excavation technique (ESE) and submucosal tunneling endoscopic resection (STER) approaches, were made possible. More recently, the full-thickness resection device (FTRD), which is a combination of a modified over-the-scope-clip (OTSC) system with an electrocautery snare, has emerged as a new method for purely endoscopic full-thickness resection [31].

The endoscopic submucosal excavation (ESE) is an ESD that goes beyond the submucosa. Briefly, the steps of the procedure are the following: normal saline is injected into the submucosa; a precutting incision at the mucosal and submucosal layers around the lesion is performed. After that, a circumferential incision as deep as necessary to isolate the tumor at the MP or serosal level is done. The final resection is usually done with a snare. If a full-thickness viscerotomy results, it can be closed with regular titanium clips, over-the-scope clips, or suturing devices with similar outcomes. This approach is less technically demanding compared with the submucosal tunneling, but there are inherent issues with a full-thickness defect, including loss of working space, peritoneal soiling, and need for an airtight closure of the incision [29].

The submucosal tunneling endoscopic resection (STER) technique is a challenging procedure with a long learning curve. However, in this technique the mucosa is not breached at the resection level, decreasing soiling, losing working space, and facilitating closure. Briefly, the steps of the procedure include: submucosal injection, mucosotomy about 5 cm proximal to the tumor, SM tunnel development, and approach of the lesion with ESD instrumentation [32]. The lesion is resected and the mucosal incision is closed with clips. Lu et al. [33] published a study comparing ESE and STER for resection of esophageal and cardial submucosal tumors less than 3 cm in diameter. Thirty-five patients had ESE and 42 patients had STER. The complete resection and perforation rates were similar for the two techniques, but air leakage symptoms (subcutaneous and mediastinal emphysema) were more frequently in the ESE group when the resected tumor was more than 1 cm of diameter. They concluded that for SMT >1 cm, the STER procedure was preferred. In one of the largest series published to date, Ye et al. [34] described the use of the STER technique in 85 patients with subepithelial tumors. Sixty were located in the esophagus, 16 in the cardia, and 9 in the stomach. All tumors were less than 3 cm in diameter. A 100% resection rate was obtained and eight patients had complications (9.4%), in all cases related to air leakage (pneumoperitoneum, subcutaneous emphysema, pneumothorax). The odds for complications was higher in tumors located in the deep muscularis propria layer.

The location of the submucosal lesion has a major role in the choice of technique for removal (Table 16.2). Tumors located in the esophagus or cardia may favor the STER approach. In the stomach, the STER technique can be performed if the lesion is in the lesser curvature of gastric body and the greater curvature of gastric antrum. In other areas, like the anterior and posterior body, the submucosal excavation technique or the full-thickness resection device (FTDR) can be the best approach. In the colon, FTDR is the most common technique. The FTDR device may be used for mucosal lesions, such as non-lifting or recurrent adenomas and early cancers. A limitation of the FTDR device is the size of the lesion, which has to be accommodated into a dedicated endoscopic cap before resection with a snare. In one study, 18 out of 24 lesions (75%) were resected en bloc [35].

In the future, we can anticipate that different techniques for full-thickness endoscopic resections will have clear indications taking into consideration anatomic site, size, and histology of tumors. It seems unlikely that the same technique and device will prove to be superior for use in removing all esophageal, gastric, or colonic tumors. Submucosal tunneling will most likely be part of the repertoire. Robotized endoscopic platforms with emphasis in surgical tasks and easier manipulation will have a pivotal role in enabling more physicians, not only highly specialized surgical endoscopists, to perform endoscopic full-thickness resections [13, 15, 16].

The Role of Submucosal Endoscopy for Diagnosis of Disorders of the Muscularis Propria and Myenteric Neurons

Comprehensive histological evaluation of motility disorders in the gastrointestinal tract, such as achalasia, gastroparesis, and Hirschsprung disease, has been limited due to difficulties in tissue acquisition in layers deeper than the mucosa. Assertive methods of tissue sampling, such as the double EMR technique and full-thickness resections, are needed [36].

Table 16.2 Comparison between STERcopic submucosal excavation (ESE), and OTSC (over-the-scope clip)

Author/year	# of patients	Location	Pathology	Mean size (mm)	Technique	% en bloc resection	Complications
Huang et al.	35	14 fundus 21 corpus	25 GISTs 7 leiomyomas 2 schwannomas	28	ESE	100	None reported
Guo et al.	23	11 fundus, 9 corpus, 3 antrum	19 GISTs 4 leiomyomas	12	OTSC	100	2 localized peritonitis
Lu et al. (2014)	83	56 esophagus, 27 cardia	74 leiomyomas 9 GISTs	12	STER-45 ESE-38	STER-97 ESE-92	STER-SE/ME-1/45 ESE-SE/ME–5/38
Feng et al.	48	40 fundus, 7 corpus, 1 antrum	43 GISTs, 4 leiomyomas, and 1 schwannoma	15, 9	ESE	100	5 PP
Li et al. (2015)	32	3 fundus close to the cardia 12 corpus close to the cardia 6 lesser curvature corpus 11 greater curvature of antrum	11 GISTs, 18 leiomyomas, 3 others	23	STER	100	1 bleeding, 6 PP, 3 PTX, and SE
Zhou et al. (2015)	21	Esophagogastric junction	6 GISTs, 15 leiomyomas	23	STER	100%	9 ME and SE
Ye et al. (2014)	85	60 esophagus, 16 cardia, 9 stomach	19 GISTs, 65 leiomyomas, 1 calcifying fibrous tumor	19.2	STER	85%	6PTX, 8SE, 4PP

Abbreviations: *GIST* gastrointestinal stromal tumor, *SE* subcutaneous emphysema, *ME* mediastinal emphysema, *PTX* pneumothorax, *PP* pneumoperitoneum

Recently, optical biopsy methods have been developed, aiming to provide analysis at a cellular level in GI endoscopy. Numerous studies on the application of technologies such as optical coherence tomography (OTC), endocytoscopy, and confocal laser endomicroscopy have been published in the evaluation of mucosal diseases [37–39]. At the submucosa, endocytoscopy and confocal laser endomicroscopy have been tested to evaluate the muscularis propria and myenteric plexus with encouraging results, thus potentially replacing the current cumbersome methods to obtain deep-layer samples in the GI tract. For example, Sato et al. [40] used endocytoscopy, a technique in which there is a ×380 magnification and methylene blue staining, to evaluate the muscular cells in seven achalasia patients undergoing POEM procedure. After submucosal tunnel creation and completion of the myotomy, the GIF-Y0002 endoscope (prototype from Olympus Co.) was used to perform the optical biopsies. No abnormalities in the muscular layer were found in endocytoscopy and similar results were found on conventional biopsy. The nerve plexuses were not visualized in this setting because of a lack of neuron-specific fluorescent stain available for safe use in humans. Neuroenteric plexus visualization remains a future perspective in submucosal endocytoscopy.

The use of probe-based confocal laser endomicroscopy (pCLE, Cellvizio technology, Mauna Kea, Paris, France) in the submucosa has been tested in the porcine model. Ohya et al. [41] studied two ex vivo and six in vivo pigs, in which a submucosal tunnel was developed and neuron-like cells were stained with a fluorescent neuronal molecular probe (available for animal use). The author then developed specific sites for inspection with pCLE and posterior histologic evaluation. The muscularis propria was visualized in all cases and neuron-like cells were identified in 41.7% of the sites with pCLE.

Conclusions

Submucosal endoscopy is the basis for a diverse set of exciting procedures and techniques, including myotomy, tumor resection, NOTES, and optical biopsy. With several indications today, the ability to work in the potential space of the submucosal plane may still be somewhat novel, but the potential is enormous and the future is bright for those willing to extend this path in advanced surgical endoscopy [42–47].

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