Submucosal Surgery: Pyloromyotomy and Tumor Enucleation

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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.

E. Shlomovitz (✉) • O.M. Crespin
Division of General Surgery, University Health Network, Toronto, Canada
e-mail: eran.shlomovitz@uhn.ca

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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)

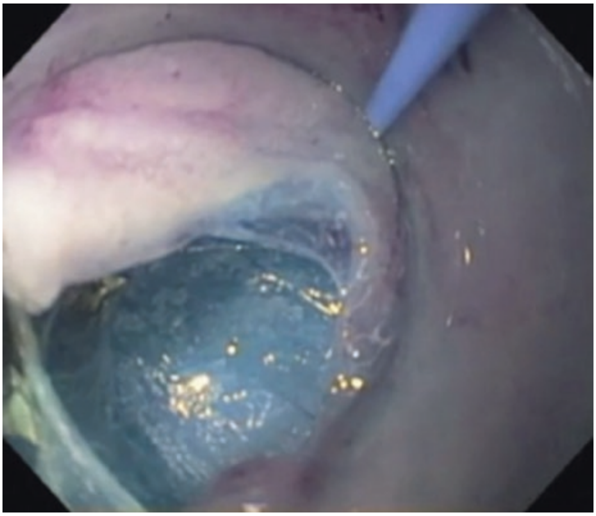

Fig. 15.1 Initial longitudinal mucosal incision is performed following submucosal injection of a lifting solution.The submucosal space stained with the dilute methylene blue solution can be seen

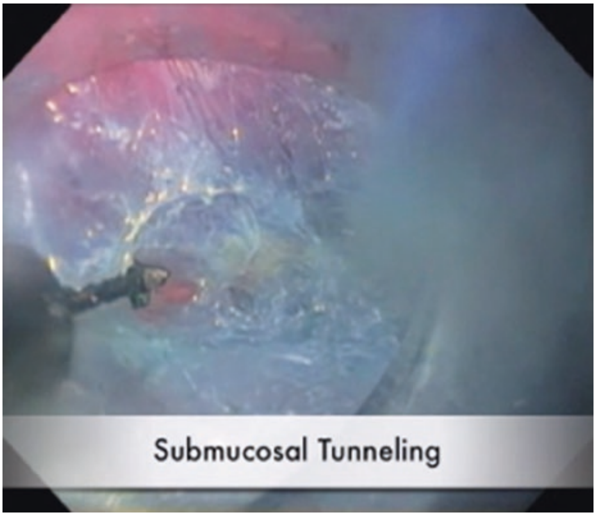

Fig. 15.2 The submucosal dissection is perfomed in the deep submucosal space to avoid injury to the overlying mucosal flap which can be appreciated at the upper portion of the image

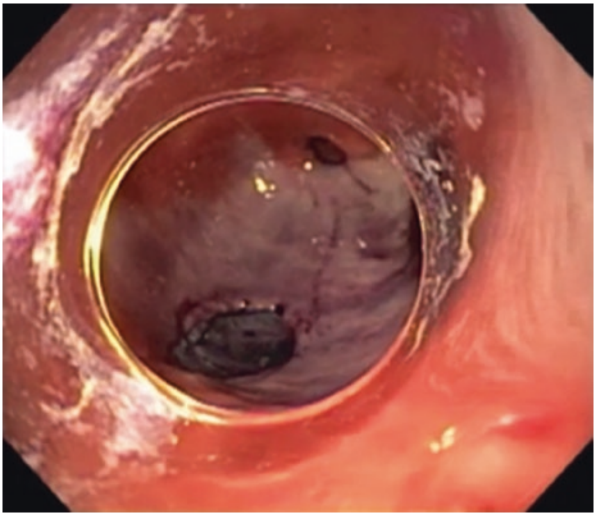

Fig. 15.3 Luminal view of the completed submucosal tunnel extending from the mucosotomy to the pylorus. Pallor of the mucosa is related to the dilute epinephrine which is mixed into the lifting solution

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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