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Evolution and evidence-based adaptations in techniques for peroral endoscopic myotomy for achalasia

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Abstract

Achalasia is an esophageal motility disorder characterized by impaired lower esophageal sphincter (LES) relaxation and failed peristalsis. Common clinical manifestations include dysphagia to solid and liquid foods, chest pain, regurgitation, and weight loss, resulting in significant morbidity and healthcare burden. Historically, surgical Heller myotomy and pneumatic dilation were the first-line therapeutic options for achalasia. This convention was shaken in 2009 when Inoue and colleagues introduced an endoscopic approach to dissect the muscle fibers of the LES, known as peroral endoscopic myotomy (POEM). Since incorporation of POEM into standard practice, the overall myotomy technique has remained unchanged; however, adaptations in the thickness and length of myotomy have evolved. Full-thickness myotomy is recognized to have similar clinical success and faster procedure times compared with selective circular muscle myotomy. Although myotomy length for type 1 and type 2 achalasia has classically been >6 cm, recent studies demonstrated similar outcomes with reduction of myotomy length to <3 cm. Length of myotomy for type 3 achalasia has been tailored to treat the entire length of spastic muscle segment, and the modality to gauge the optimal thickness and length of myotomy in this group has yet to be established. In addition to changes in POEM technique, the postoperative management of POEM has also changed, favoring reduced post-procedure imaging, antibiotic use, and hospitalizations. (*Gastrointest Endosc* 2022;96:189–96.)

Achalasia is an esophageal motility disorder characterized by impaired relaxation of the lower esophageal sphincter (LES) and failed peristalsis. Through the evolution of esophageal high-resolution manometry (HRM), 3 distinct subtypes of achalasia have been characterized: type 1, characterized by abnormal median integrated relaxation pressure and absence of peristalsis; type 2, characterized by abnormal median integrated relaxation pressure and absence of peristalsis with at least 20% of swallows exhibiting panesophageal pressurization; and type 3, or spastic, characterized by abnormal median integrated relaxation pressure without any evidence of peristalsis and at least 20% of swallows with premature or spastic contractions (Fig. 1).^{1–3} Because treatments to reverse the disease mechanism are not available, current management aims to promote esophageal emptying and alleviate clinical symptoms by reducing pressure and resistance at the gastroesophageal junction (GEJ). Current first-line therapeutic options for achalasia are surgical Heller myotomy (HM), pneumatic dilation, and peroral endoscopic myotomy (POEM).^{2,4,5}

For years HM and pneumatic dilation were the first-line therapeutic options for all types of achalasia. POEM emerged in 2009 when Inoue et al⁶ demonstrated that an endoscopic approach to dissect the muscle fibers of the LES was a minimally invasive yet efficacious therapeutic option for achalasia treatment. Since its introduction, POEM has been shown to perform comparably with HM in multiple studies including randomized trials and network meta-analyses.⁷⁻¹⁰ More recent studies highlight that POEM outperforms other strategies in type 3 achalasia and may outperform HM in types 1 and 2 achalasia.¹⁰ With POEM incorporated into standard practice, efforts have focused on improving clinical outcomes, reducing rates of post-POEM GERD, and limiting overall procedure time through adaptations in procedure techniques, such as myotomy thickness and length. This review aims to examine the evolution of POEM to its current form, with an emphasis on how POEM technique may be tailored among achalasia subtypes.

INTRODUCTION OF POEM

The first reported cases of endoscopic myotomy to treat achalasia were described in 1980 by Fisichella et al¹¹ and Ortega et al.¹² In their study, 17 patients underwent endoscopic myotomy of the esophageal rosette. They found that patients who underwent endoscopic myotomy had increased distal esophageal diameter on barium radiograph, improved ability to tolerate solid foods, and increased weight gain.¹² The more current form of POEM was introduced in 2007, when Pasricha et al¹³ performed endoscopic myotomy on swine esophagus, noting a reduction of LES pressure without any evidence of adverse events. Modifying the technique developed by Pasricha et al, Inoue et al⁶ then performed modern-day POEM in patients in 2009. Their myotomy procedure consisted of the creation of an anterior esophageal submucosal tunnel, dissection of circle muscle layers 7 cm proximal to the GEJ, and extending 2 cm distal to the GEJ. Patients who underwent this procedure were found to have excellent clinical success with significant reduction of LES pressure and improved dysphagia.^{6,14} Since its inception in 2009, the technique has remained relatively unchanged. There has been little modification in myotomy orientation, as studies have demonstrated overall similar efficacy between anterior and posterior myotomy.¹⁵ Most changes in POEM are related to thickness and length of esophageal myotomy.

EVOLUTION OF MYOTOMY THICKNESS

The initial POEM technique developed by Inoue et al⁶ consisted of selective myotomy of the circular muscle layer. However, the concept of selective myotomy of the circular muscle layer was challenged as being more difficult, time consuming, and not always possible. One retrospective analysis by Li et al¹⁶ demonstrated similar symptom relief and postprocedure manometry results without significant differences in adverse events when comparing circular myotomy to full-thickness myotomy. Further, mean procedure time was significantly reduced in the full-thickness group compared with the circular myotomy group (56.7 vs 88.2 minutes, $P < .01$). In 2017, Duan et al¹⁷ similarly demonstrated in 123 patients a significantly shorter mean procedure with full-thickness myotomy compared with those who underwent circular myotomy (57.4 vs 63.2 minutes, $P < .05$). As with other studies, they found no significant difference in clinical success and adverse events.¹⁷

Duan et al¹⁷ also assessed pH monitoring results among 19 patients post-POEM; 10 with abnormal acid exposure post-POEM had no difference when comparing myotomy thickness. A meta-analysis by Mota et al¹⁸ examining GERD post-POEM found that a circular/partial myotomy compared with full-thickness myotomy was associated with lower, albeit not statistically significant, incidence of erosive GERD (risk difference, .05; $P = .06$); however, no notable differences of post-POEM GERD based on pH monitoring and symptoms were found. Ultimately, full-thickness myotomy was found to significantly reduce procedure time without increasing incident adverse outcomes such as GERD.

Endoluminal functional lumen imaging probe (EndoFLIP, Medtronic, Dublin, Ireland), a modality that enables clinicians to measure volume-controlled distension throughout the esophagus, has the potential to help guide real-time myotomy thickness to promote therapeutic success. Yoo et al¹⁹ conducted a single-center study showing that a post-POEM distensibility index (DI) on FLIP of $<7 \text{ mm}^2/\text{mm Hg}$ (at 30- or 40-mL fill using an EF 325N catheter, Medtronic, Dublin, Ireland) had a significantly higher rate of incomplete response after POEM ($P = .001$). Kolb et al,²⁰ however, demonstrated a 97% treatment success with $\text{DI} > 2.8 \text{ mm}^2/\text{mm Hg}$ at 60-mL fill using an EF 322N balloon catheter.

More studies are needed to identify optimal FLIP metrics to target during POEM to avoid treatment failure and to promote treatment success as well as to predict risk for adverse outcomes such as post-POEM GERD. For example, a higher DI on FLIP may correlate with a higher incidence of post-POEM GERD. Horsley-Silva et al²¹ found that at 3 months post-POEM, the mean DI at 30-mL fill was significantly higher in those with GERD ($5.66 \text{ mm}^2/\text{mm Hg}$) compared with those without GERD ($4.06 \text{ mm}^2/\text{mm Hg}$; $P = .035$). GERD was uniformly present when the DI was $>6 \text{ mm}^2/\text{mm Hg}$.²¹ Overall, FLIP has the potential to significantly improve the POEM technique moving forward as further research is conducted.

EVOLUTION OF MYOTOMY LENGTH

The initial technique of POEM described by Inoue and colleagues¹⁴ in 2009 had a mean esophageal myotomy length of 6.1 cm and stomach myotomy length of 2.0 cm. They found that this length was sufficient enough to relieve LES pressure, because surgical myotomy length in the proximal esophagus is around 6 to 7 cm.²² Thus, the initial recommendation for total POEM myotomy length was a minimum of 7 cm. Over time, and with the advancement of HRM and better appreciation for manometric subtypes of achalasia, the approach to myotomy length has evolved.¹

Type 1 and type 2 achalasia

The original modern-day POEM for types 1 and 2 achalasia was performed with a myotomy length $>6 \text{ cm}$ above the GEJ and an additional 2- to 3-cm extension distal to the GEJ, culminating in a total myotomy length of 8 cm. More recent studies have examined the benefits of a shorter myotomy length. In a retrospective study by Huang et al,²³ 129 patients were divided into short myotomy ($<4 \text{ cm}$ esophageal myotomy) and long myotomy ($>4 \text{ cm}$ esophageal myotomy) groups. Mean total myotomy length in the short myotomy group was 6 cm and in the long myotomy group 11.5 cm. Clinical outcomes were comparable in

both groups, although shorter myotomy length was associated with shorter mean procedure time compared with long myotomy length (46.6 vs 62.1 minutes, $P = .001$). A randomized prospective trial by Nabi et al²⁴ also reviewed myotomy length in the anterior position for types 1 and 2 achalasia in which short myotomy was defined as <3 cm compared with long myotomy defined as >6 cm. The study found short myotomy length to be noninferior to long myotomy in terms of Eckardt score. Furthermore, mean procedural time was shorter in the short myotomy group compared with the long myotomy group (44.0 vs 72.4 minutes, $P < .001$). Thus, short myotomy was posited as potentially cost-effective with reduced risk of insufflation-related adverse events.

A randomized trial by Gu et al²⁵ compared short myotomy (3–4 cm esophageal myotomy) and standard myotomy (7–8 cm esophageal myotomy) in 94 patients with type 2 achalasia who underwent POEM using a posterior approach and similar gastric myotomy length (about 2–3 cm). They found no significant difference in procedural success, postoperative manometry, Eckardt scores, reflux esophagitis, or adverse events between the groups. The short myotomy group, however, had a statistically significant reduction in mean procedure time compared with standard myotomy (31.2 vs 45.6 minutes, $P < .05$) and a significant reduction in esophageal acid exposure.

In addition to length of esophageal myotomy, the length of gastric myotomy has also been studied. Grimes et al²⁶ evaluated 100 patients who had undergone POEM with either a single-scope technique, which used a shorter gastric myotomy of a mean of 2.6 cm, or the double-scope technique, which led to a longer gastric myotomy of a mean of 3.2 cm ($P = .01$). Clinical efficacy was similar in both groups, with no significant differences in adverse events or esophagitis. The authors noted that the endoscopists performing POEM believed the initial gastric myotomy with a single scope was inadequate and that the double-scope technique allowed for more complete gastric myotomy, which may be useful in patients with difficult-to-identify GEJ or altered anatomy (Fig. 2).

In summary, recent studies highlight similar efficacy with short and long esophageal myotomy in both type 1 and type 2 achalasia, with reduced procedure time and potential for reduced adverse events and healthcare costs with short myotomy. Thus, current trends favor a standard short esophageal myotomy <3 cm with a 2-cm extension into the gastric side in patients with type 1 and type 2 achalasia.

It is worth noting that the myotomy lengths in the aforementioned studies are estimates. Currently, there is no established method to calculate the myotomy distance because of resistance of the scope in the submucosal tunnel. Because the measurements on the scope can change dramatically, a strategy for identifying the proximal site for myotomy initiation can be marking the mucosotomy site in relation to the Z-line and beginning calculations thereafter. It is also vital to note that the LES and high pressure zone are typically proximal to the endoscopically visualized Z-line. The endoscopist can confirm the distal extent (gastric side) of the myotomy, established to be 2 cm, using the double-scope technique. With 1 scope in the retroflexed view, the distance between the shaft of the scope and the illuminated light can be used to approximate the length of the gastric myotomy. In addition, another technique that may be used to approximate the length is placement of an endoscopic

clip at the GEJ. Some endoscopists may find this more cumbersome because of the possible need of fluoroscopy and variations in measurements with respirations.

Type 3 achalasia

As opposed to types 1 and 2 achalasia, where shorter myotomy is potentially preferred, patients with type 3 achalasia have improved outcomes with longer myotomy.^{27,28} This likely relates to the esophageal body spasticity in type 3 achalasia that can be targeted with proximal extension of the myotomy along the esophageal body. A study by Kane et al²⁷ found that patients with type 3 achalasia who underwent a tailored myotomy using HRM to determine the proximal extent of the myotomy had an overall longer myotomy (15.9 cm vs 12.7 cm, $P = .045$), significantly improved Eckardt scores (1.3 ± 1.5 for nontailored vs $.2 \pm .4$ for tailored, $P = .044$), and overall equivalent procedural success compared with the nontailored myotomy. Along these lines, Kumbhari et al²⁸ compared outcomes of POEM versus HM in patients with type 3 achalasia and found improved clinical outcomes in POEM patients, attributed to the longer myotomy length achieved during POEM. In contrast, a meta-analysis by Chandan et al²⁹ found no statistically significant difference in clinical success based on myotomy length. It is important to note that the meta-analysis reviewed all spastic esophageal disorders including hypercontractile esophagus and distal esophageal spasm and not just patients with type 3 achalasia. Although somewhat mixed, the overall data highlight the potential benefits of tailoring the myotomy for each individual patient with type 3 achalasia. As such, POEM now represents the first-line therapeutic option for type 3 achalasia.

The optimal method to determine the length of myotomy for type 3 achalasia has yet to be determined. Most POEM programs base the length of myotomy according to the length of spastic segment on HRM.³⁰ The spastic segment on manometry is defined as the axial distance between the proximal border of the LES to the proximal border of premature contractions. Serrano et al³¹ performed a study comparing the length of the spastic segment on barium esophagram, esophagoscopy, and HRM and reported an overall discordance among the 3 imaging modalities. They found an average difference in LES position by HRM and esophagoscopy by about 3.9 ± 3.0 cm and an average difference between HRM and spastic length and esophagography by about 4.9 ± 3.2 cm. In our study evaluating spastic segment length on different imaging modalities, we found that the mean spastic segment on HRM was 12.4 cm (standard deviation, 3.9) and the mean spastic segment on barium esophagram was 13.2 cm (standard deviation, 2.7), with a Pearson coefficient of .766.³² In addition to HRM and barium esophagram, some POEM programs also use EUS to measure the thickness of the circular muscle layer in the distal esophagus. To an experienced endosonographer, the circular muscle layer may clearly be more prominent in patients with type 3 achalasia, and these measurements on EUS may help guide the length of the myotomy; however, more research is needed to determine what the optimal cutoff is for increased thickness of the circular muscle layer.

An important consideration, especially for patients with type 3 achalasia, is that of a blown-out myotomy, which is an adverse outcome where a wide-mouthed outpouching or pseudodiverticulum forms in the area of the myotomy. Triggs et al³³ identified significantly

higher rates of blown-out myotomy in patients with type 3 achalasia and those who underwent HM. These findings and anecdotal experiences suggest that a myotomy that is too short in length in type 3 achalasia may lead to a blown-out myotomy. Treatment options for blown-out myotomy are limited and include esophagectomy.³³ In summary, myotomy for type 3 achalasia is an extended length, usually based on the length of the spastic segment on HRM.

POST-POEM GERD

An important issue that remains a pillar of debate among first line-therapeutics for achalasia is postprocedural GERD. When POEM was first established, the concern for GERD was believed to be much higher than is currently present. In a meta-analysis by Schlottmann et al,³⁴ patients who underwent POEM were more likely to develop GERD symptoms (odds ratio, 1.69; 95% confidence interval, 1.33–2.14). A meta-analysis by Repici et al³⁵ found similar findings with abnormal acid exposure of 39% (95% CI, 24.5%–55.8%) in the POEM group compared to 16.8% (95% confidence interval, 10.2%–26.4) in the HM with fundoplication group. A separate meta-analysis by Inoue et al³⁶ identified symptomatic GERD in 8.5% to 19% of patients, endoscopic evidence of erosive esophagitis in 13% to 29.4% of patients, and abnormal pH studies present in 39% to 47.5% of patients. Interestingly, they found the rate of GERD differed depending on the modality of testing used. Ultimately, they found that only .1% of patients needed surgical fundoplication after POEM based on an unpublished study in Japan.³⁷ It is important to note that experts suspect that rates of esophagitis may be overestimated because of endoscopic findings of erythematous changes secondary to the mucosotomy.

A recent single-center prospective trial by Modayil et al⁷ evaluated 610 patients who underwent POEM between 2009 and 2019. They found that at a median follow-up of 30 months, 58% of patients reported some reflux symptoms, with 20.5% reporting symptoms more than once weekly. Interestingly, they found that objective evidence of reflux decreased over time after POEM, suggesting improvement in gastroesophageal physiology over the long term.

One factor associated with post-POEM GERD is a gastric myotomy extension to >4 cm in the cardia. In a retrospective multicenter study performed in Japan, muscle incision >4 cm in the posterior gastric cardia was associated with higher rates of erosive esophagitis.³⁶ Another factor associated with worsening GERD is the incision of sling/oblique muscles in the gastric cardia. These findings were identified in a single-center study from Japan, which found that the incision of the sling fibers may lead to erosive esophagitis. Given these findings, the GERD post-POEM consensus authors recommend anterior or posterior myotomy to preserve the oblique muscle fibers and a short gastric myotomy length of 2 to 3 cm (Fig. 3).³⁶

Additionally, as previously mentioned, differences in myotomy thickness have been associated with different rates of post-POEM GERD. In a meta-analysis by Mota et al,¹⁸ full-thickness myotomy was associated with marginally significant rates of GERD when compared with circular myotomy ($P = .06$). Nonetheless, it is important to note that the

circular muscle layer becomes thinner in thickness at the GEJ and despite attempts at selective cutting may result in spontaneous disruption of the longitudinal muscle layer at this level (Fig. 4).¹⁸

Aside from differences in technique, studies examining risk factors for post-POEM GERD have been limited. Arevalo et al³⁷ conducted a retrospective analysis of 46 patients who underwent pre- and post-POEM evaluation to evaluate acid exposure time and rates of esophagitis. They found abnormal esophageal exposure in 15 of 36 patients and a positive correlation between abnormal acid exposure post-POEM and preoperative esophagitis (Pearson correlation = .418, $P = .02$). They also found that higher preoperative Eckardt scores were associated with the presence of esophagitis post-POEM ($P = .016$). Modayil et al⁷ in a single-center prospective study found higher rates of post-POEM GERD in their patient population, attributed to complete LES myotomy, broad inclusive criteria such as patients with rare episodes of reflux, and finally a large proportion of their cohort at high risk for reflux, including 26% of patients with a body mass index $>30 \text{ kg/m}^2$.

Given the likelihood of abnormal acid exposure time post-POEM or complaints of GERD, there have been attempts at developing POEM with endoscopic fundoplication. In a case series by Inoue et al in 2019,³⁸ 21 patients underwent POEM with fundoplication. They found that the procedure was technically successful without any adverse events, although long-term data were limited. Similarly, in a study by Brewer Gutierrez et al,³⁹ 12 patients who had post-POEM GERD underwent transoral incisionless fundoplication (TIF). The authors found improvement in frequency of reflux symptoms and a decreased number of patients on twice-daily proton pump inhibitors, and 7 patients underwent pH studies and showed significant reduction in acid exposure time ($P = .04$). The feasibility of single-session POEM-transoral incisionless fundoplication was evaluated by Benias et al⁴⁰ when the procedure was performed in 5 patients. There were no adverse events reported, and pH testing performed at 6 months showed no evidence of reflux in 4 of 5 patients. They found that POEM-transoral incisionless fundoplication may potentially be done during the same session to help reduce rates of post-POEM GERD, although this remains an area of debate with concerns surrounding increased risk of postprocedure leak and adverse events.⁴⁰

NONTECHNIQUE CONSIDERATIONS OF POEM

Immediate postoperative management of POEM patients has also been rapidly evolving. Multiple studies have evaluated the routine use of esophagram post-POEM. A study by El Khoury et al⁴¹ showed that routine esophagram post-POEM had a 100% sensitivity and 45% specificity in identifying clinically significant adverse events. In a retrospective analysis by Reddy et al⁴² reviewing 170 post-POEM esophagrams on postprocedural day 1, abnormal findings were present in 98 patients, with only 5 patients having esophageal leak or dissection. Reddy et al⁴² found both false positives and false negatives for diagnosis of esophageal leak, questioning the utility of routine esophagram.

Studies have also evaluated the feasibility and safety of same-day discharge. In a retrospective analysis by Cloutier et al,⁴³ 72 of 91 patients were discharged on the same day after POEM and 14 patients were discharged the following day. Only 5 patients required

prolonged hospitalization. A study by Zhang et al⁴⁴ evaluated the safety of same-day discharge in certain subtype of patients: American Society of Anesthesiologists class I to III, no intraprocedural adverse events, secure mucosal closure, controlled postprocedure pain and nausea, and tolerating a clear liquid diet. The patients were monitored for 4 hours postprocedure. In the 17 patients who met the selection criteria, 14 patients were safely discharged the same day. Two patients were admitted because of postprocedure pain and nausea, and 1 was admitted because of intraprocedural concerns. The study demonstrated that same-day discharge may be considered for some patients.⁴⁴

Another point of consideration is the routine use of antibiotics post-POEM. In a randomized control trial by Maselli et al,⁴⁵ patients were divided into 2 groups: 1 group had a single dose of cefazolin preprocedure and 1 group had preprocedure cefazolin and 3 days of amoxicillin/clavulanate postprocedure. They found that no patient in either group developed postoperative fevers and no difference in white blood cell count or inflammatory markers. Their study suggests that short-term antibiotic prophylaxis may not be indicated.

CONCLUSION

POEM has now become a standard excellent endoscopic treatment option for patients with type 1 and type 2 achalasia and is the first-line therapy option for patients with type 3 achalasia. Since its inception, the POEM technique has been modified with respect to myotomy location, length, and thickness, with the goal of optimizing clinical success and reducing adverse events (Table 1). Currently, a shorter length myotomy for types 1 and 2 achalasia and full-thickness myotomy have been shown to have similar clinical success and faster procedure times compared with a longer myotomy length and circular muscle dissection. Post-POEM GERD rates are reduced with shorter gastric myotomy, which also avoids damage to the sling fibers.

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Abbreviations:

DI	distensibility index
FLIP	functional lumen imaging probe
GEJ	gastroesophageal junction
HM	Heller myotomy
HRM	high-resolution manometry
LES	lower esophageal sphincter

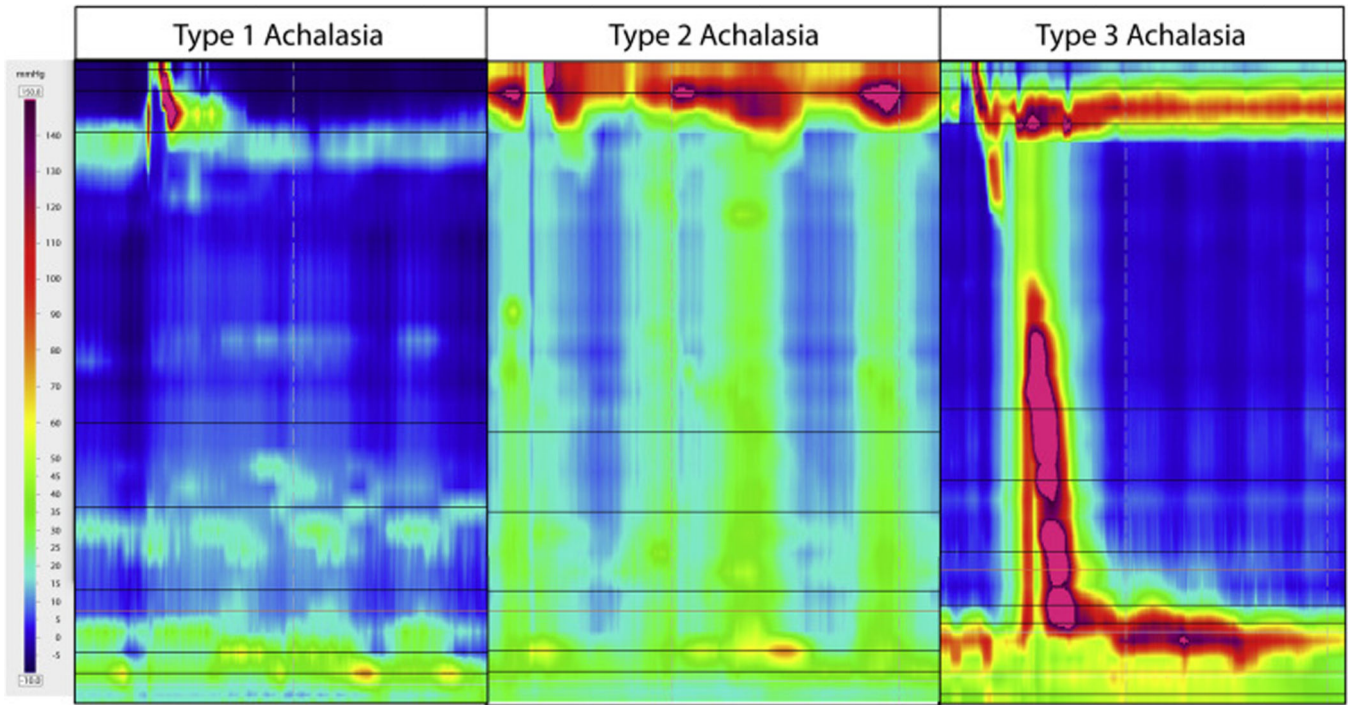
POEM peroral endoscopic myotomy

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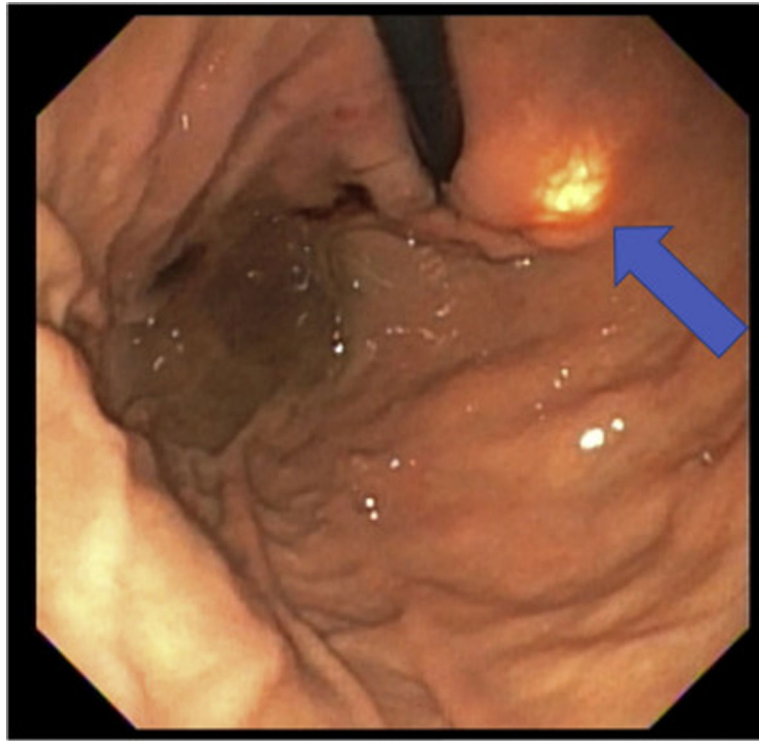
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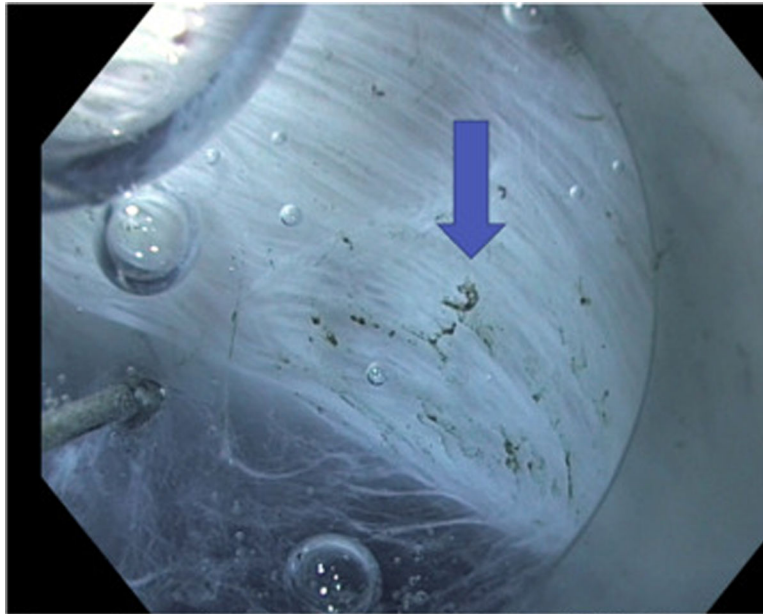
Courtesy of Center for Esophageal Diseases at University of California San Diego

Figure 1.
Manometry findings in different subtypes of achalasia.



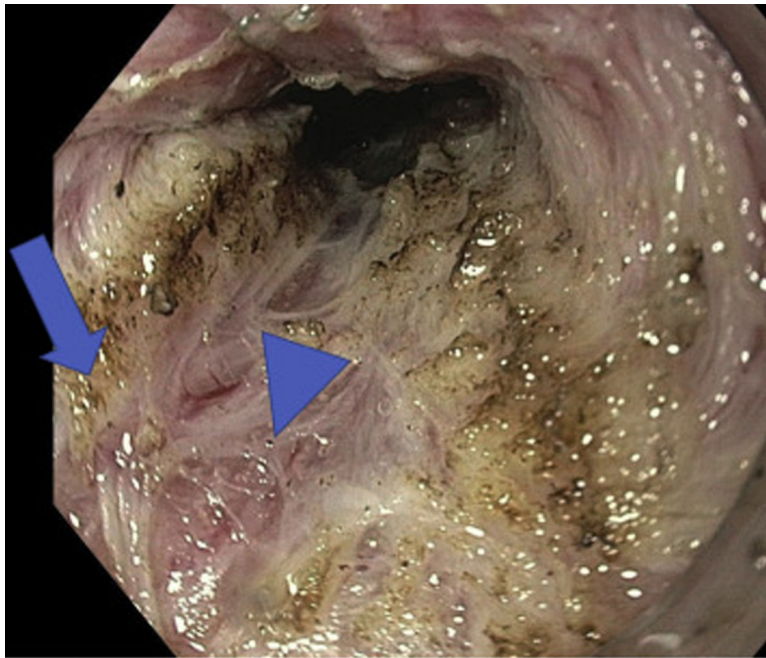
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Figure 2. Double-scope technique, which is the most accurate way to determine proper tunnel extension to the gastric side and orientation. The GIF-XP endoscope (Olympus, Tokyo, Japan) is seen in the retroflexed view, along with the light illuminated by the upper endoscope (*arrow*) in the submucosal tunnel.



Courtesy of Center for Esophageal Diseases at University of California San Diego

Figure 3. Web of spindle-like veins (*arrow*) that are one of the indicators that submucosal tunnel has reached the gastric side.



Courtesy of Center for Esophageal Diseases at University of California San Diego

Figure 4. Selective myotomy of the circular muscle layer (*arrow*) with the spontaneous splaying of the longitudinal muscle layer (*arrowhead*).

TABLE 1.

Current trends in peroral endoscopic myotomy method

Trends	Type 1 achalasia	Type 2 achalasia	Type 3 achalasia
Myotomy length	Shorter myotomy length favored	Shorter myotomy length favored	Length of spastic segment
Esophageal myotomy length, cm	3–4	3–4	Tailored to esophageal spastic segment
Gastric myotomy length, cm	2	2	2
Myotomy thickness	Full-thickness myotomy favored	Full-thickness myotomy favored	Full-thickness myotomy favored