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POEM from A to Z: current perspectives

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ABBREVIATIONS

AEs: Adverse events
BTI: Botulinum toxin injection
CP: Cricopharyngeal
CT: Computed tomography
DES: Distal esophageal spasm
D-POEM: Diverticular POEM
ED: Endoscopic dilatation
EGJ: Esophagogastric junction

EGJOO: Esophagogastric Junction Outflow Obstruction

EMD: Esophageal motility disorder

EPD: Epiphrenic diverticula

EPT: Endoscopic pyloric treatment

ESD: Endoscopic submucosal dissection

FED: Flexible endoscopic diverticulotomy

GERD: Gastroesophageal reflux disease

GES: Gastric electrical stimulator

GI: Gastrointestinal

G-POEM: Gastric peroral endoscopic myotomy

HRM: High-resolution manometry

LHM: Laparoscopic Heller's myotomy.

NOTES: Natural orifice transluminal endoscopic surgery

OTSC: Over-The-Scope Clip

POEM: Peroral endoscopic myotomy

POEM-F: POEM plus fundoplication

PPIs: Proton pump inhibitors

RCA: Root cause analysis

RCT: Randomized controlled trial

S-POEM: Salvage POEM

ZD: Zenker's diverticulum

Abstract

The "third space endoscopy" or also called "submucosal endoscopy" is a reality we can transfer to our patients since 2010. Various modifications of the submucosal tunneling technique allow access to the submucosa or deeper layers of the gastrointestinal tract. In addition to peroral endoscopic myotomy for the treatment of achalasia, also called esophageal POEM, other variants have emerged that make it possible to treat different esophageal motility disorders, esophageal diverticula, subepithelial tumors of various locations, gastroparesis, reconnection of complete esophageal strictures or even thanks to exceptional endoscopists, pediatric disorders such as Hirschsprung's disease.

Although some technical aspects are yet to be standardized, these procedures are becoming widespread worldwide and will likely become the standard treatment of these pathologies soon.

KEYWORDS: Third space endoscopy. Submucosal endoscopy. Esophageal. Motility disorders.

Introduction

Natural orifice transluminal endoscopic surgery (NOTES) was first described in the animal model by Kalloo *et al.* in 2004, who performed a transgastric endoscopic liver biopsy (1). Early animal experiments by Sumiyama *et al.* allowed valve-like closure by creating a mucosal entry point into the submucosal space and an opening into the peritoneal cavity remote from the mucosal opening (2). In 2007, Pasricha *et al.* were the first who performed an esophageal myotomy via endoscopic submucosal tunneling in porcine models (3). Later on, Inoue *et al.* published the first peroral endoscopic myotomy (POEM) case series in humans in 2010 (4) and from there, you all know the story. Nowadays, the concept of “submucosal endoscopy” or “third-space” endoscopy is accepted worldwide. In addition to the management of achalasia and different esophageal motility disorders (EMD), different technical variants have been developed to treat various entities like esophageal diverticula, esophageal stenosis, gastroparesis, subepithelial tumors or Hirschsprung's disease (Table 1 and Figure 1). In this review, we will focus on the main aspects of the neuro-muscular pathologies that affect to adults, and we will comment them in order of their anatomical location.

Z-POEM

Zenker's diverticulum (ZD) is an outpouching of the mucosal and submucosal layers through Killian's triangle between the inferior constrictor muscle and the cricopharyngeal (CP) muscle. Dysphagia and regurgitation are the main symptoms related to the presence of ZD. Diagnosis of ZD is usually made on a barium swallow and confirmed with upper endoscopy, allowing a more detailed study of the septum and pouch. Surgical treatment, although effective, features high morbidity rates leading to its replacement by flexible endoscopic therapies (5). Endoscopic treatments mainly

focus on sectioning the CP muscle (diverticulotomy).

Flexible endoscopic diverticulotomy (FED) has been traditionally performed by resecting the septum (including the mucosa and underlying muscle) down to the buccopharyngeal fascia. In general, the steps are: 1) Exposition of the septum by using a guidewire, a nasogastric tube, or a dedicated overtube (Diverticuloscope) or just a plastic cap; 2) Resection of the septum, which has been performed with several devices including needle knives, argon plasma coagulation probes, endoscopic submucosal dissection (ESD) knives and scissors; and in two fashions as a line in the center of the septum or in a wedge shape; 3) Defect closure is not universally performed, either with standard clips or, less frequently, with over-the-scope-clips (OTSC).

A meta-analysis including 813 patients undergoing FED techniques showed a 91% success rate and an 11.6% adverse event (AE) rate. The recurrence rate was 11% (6). The main limitation of this meta-analysis was the high heterogeneity of the included studies.

The difficulty of determining the depth of cut and perform a complete muscle resection is one of the main limitations of the standard approach. In 2016, Li *et al.* proposed a POEM adaptation that permitted direct septum exposition to facilitate a complete muscle resection, termed Z-POEM (7). This involved a creation of a small tunnel beginning 1 to 3 cm above the septum. This approach has the hypothetical advantage of performing a complete septotomy under direct vision while preserving the mucosal flap, which could reduce the risk of AE. A simpler approach creating the submucosal opening right on top of the septum has been proposed and named Peroral endoscopic septotomy (8) (Figure 2). Extending the myotomy 2 cm into the esophageal *muscularis propria* in the esophageal side has been suggested to decrease the risk of symptom recurrence (9). In some cases, before clip placement, the septum mucosa is further trimmed to prevent the persistence of a mucosal pouch even though the muscle has been resected. The persistence of the pouch has been associated with persistent regurgitation even after dysphagia resolution (10).

Different systematic reviews and meta-analyses of observational studies showed technical and clinical success rates between 90-96% and AE and recurrence rates

around 11% (6,11).

A retrospective comparison of surgical, FED and Z-POEM showed lower AE rates with FESD (2.5%) compared to surgery (30%) and Z-POEM (16.8%). There were no differences in clinical success or recurrence rates (10).

Z-POEM has been successfully applied as a treatment for recurrent ZD after surgical or FED treatments (12). The presence of fibrosis in such cases has led to the development of hybrid techniques resecting the fibrotic area using a FED approach and beginning Z-POEM when submucosal injection is feasible to create a tunnel around the muscle. The results of the ZIPPY study (ClinicalTrials.gov Identifier: NCT04514042), the first multicenter randomized controlled trial (RCT) comparing FED and Z-POEM, are expected to be published soon.

CP-POEM

A CP bar is a radiological finding showing a prominent CP muscle contour in a barium swallow. Diagnosis is complex and ruling out cervical osteophyte and neurological diseases such as dermatomyositis, Parkinson's disease or oculopharyngeal dystrophy is recommended (13). In this regard, video fluoroscopy, endoscopic swallowing evaluation and manometry, ideally with impedance, are recommended (14). Although not always symptomatic, when present, the main symptoms are dysphagia and regurgitation related to impaired CP relaxation (15). Given the absence of a weakness in Killian's triangle, there is no associated ZD in these cases. Some treatment options as botulinum toxin injection (BTI) and dilation that do not solve the problem. CP-POEM that allows complete myotomy is a safe and effective treatment, although the clinical experience is still very limited. The technique features three steps: 1) Create a submucosal opening on top of the bar. This might be challenging due to anatomical lack of space. In addition, the area of the incision has to be carefully selected to allow proper closure in the last step; 2) Perform the myotomy using an ESD knife or scissor. A complete myotomy must be performed and continued 1-2 cm into the esophageal *muscularis propria*; 3) Closure of the submucosal opening with clips.

The largest study to date is a retrospective study including 27 patients showed a 100% technical and clinical success rate with a 7.4% of AEs (16).

Treatment success can be measured using a symptom scale such as the Eckardt score, Dakkak and Bennett Score and, preferably, those focused on oropharyngeal dysphagia such as the Eating Assessment Tool (EAT-10) or the Sydney Swallow questionnaire (17) combined with barium swallow to determine disappearance of the bar; and/or solid state manometry.

D-POEM

The POEM principles have also been proposed as a treatment for non-Zenker esophageal diverticula. Surgery, even in minimally invasive variants such as thoracoscopy or laparoscopy, is associated with high morbidity (8%-23% risk of leaks or fistulas) and mortality (0%-7%) (18), which justifies the growing interest in using third-space endoscopy procedures. Most studies have evaluated the outcomes of diverticular POEM (D-POEM) for epiphrenic diverticula (EPD) (11,19), although case reports treating mid-esophageal (20) and Killian-Jamieson diverticula have also been published (21).

EPD are rare (prevalence 0.02% (22)), located in the distal third of the esophagus and mostly asymptomatic. Treatment is only indicated when they produce symptoms with a quality-of-life impairment such as dysphagia, significant regurgitation or chest pain associated with swallowing. EPD are categorized as "pulsion diverticula" based on their pathophysiology, or as "pseudodiverticula" or "false diverticula" since they lack muscular layer. In 75%-80% of the cases, they are associated with an EMD (18). Hence, an adequate preoperative study including endoscopy, high-resolution manometry (HRM) and barium study is essential to size the diverticulum and tailor the length of the myotomy.

The D-POEM technique is not standardized and varies from center to center (20,23,24). The procedure is performed under general anesthesia and the steps are similar to POEM: 1) mucosal incision 1-4 cm above the septum to enter the submucosa; 2) creation of a submucosal tunnel to isolate the septum; 3) progress the esophageal submucosal tunnel until the base of the diverticulum and distally up to 2-3 cm into the gastric cavity if motor disorder associated; 4) myotomy of the septum; 5) myotomy of the lower esophageal sphincter in patients with abnormal relaxation; 6)

closure of the mucosal incision with hemoclips. Some authors have reported a modified approach named salvage POEM (S-POEM) in patients with associated achalasia and/or spastic motility disorders with excellent results (19,25,26). They propose performing a myotomy of the LES and/or the associated spastic segment without treating the septum to simplify the procedure and reduce the risk of AEs. A subset of patients may not improve clinically because the diverticular pouch remains intact. To overcome this problem, some authors have proposed the pouch endoscopic resection and suturing (27) or eversion of the diverticular lumen with OTSC (28).

Evidence about D-POEM stems from retrospective and uncontrolled series of small sample size summarized in four recent meta-analyses (11,20,29,30). These meta-analyses indicate that the technical and clinical success rate is approximately 90%-100%, with a very low risk of recurrence (< 5-10%) and a favorable safety profile compared to surgery (\approx < 10% risk of serious AEs) (11,20,29,30). Perforation represents the most frequent serious AE, followed by bleeding (11). Both can usually be controlled with conservative management or endoscopic treatment. It should be noted that no randomized data is available and that procedures were performed in highly specialized centers.

In conclusion, D-POEM emerges as a very promising and safe technique in experienced hands, but prospective studies with long-term follow-up are required to validate its role as a first-line treatment for non-Zenker esophageal diverticula.

E-POEM

Esophageal POEM or simply POEM refers to endoscopic peroral myotomy initially applied in achalasia and later implemented in different EMD. The procedure has entered European (31), American (32) and Asian (33) guidelines for achalasia treatment as a first-line therapy at the same level of endoscopic dilatation (ED) and laparoscopic Heller's myotomy (LHM). However, it is a fact that the centers that have incorporated the technique have relegated the other treatment options to very specific cases. Table 2 summarizes the comprehensive adequation of LHM, POEM and ED to different clinical scenarios (34–45).

Preoperative work-up

Anamnesis should define whether the EMD sufficiently explains the patient's symptoms. An optimal definition of the underlying EMD is the key to success. Work-up should include HRM, endoscopy and barium swallow \pm computed tomography (CT) scan in case of suspected underlying neoplasia (31). Esophageal impedance planimetry (EndoFLIP[®]) is a promising novel diagnostic technique, particularly in borderline EMDs (46).

POEM procedure

POEM has well-defined steps: 1) endoscopic cleansing and anatomical landmarks definition, 2) mucosotomy, 3) Tunneling, 4) myotomy and 5) mucosotomy closure. It was initially described through the anterior orientation and performing an 8 cm myotomy (6 cm in the esophagus, 2 cm in the stomach) of the circular muscle selectively (4). Later, most groups have shifted to the posterior orientation due to shorter and easier procedures with less inadvertent mucosotomy rate and same clinical success and reflux rate (47–49). Theoretically, any orientation could be performed (50), in fact, a second tunnel with a different orientation is an alternative in patients with submucosal fibrosis found in the initial tunnel (51). Full-thickness myotomy reduces the procedure duration without impairing clinical success nor increasing reflux (52). Also, the length of esophageal myotomy is not standardized, and shorter myotomies for type I and II achalasia have been successfully reported (53). Otherwise, for EMD different to the previous, myotomy should be tailored by work-up study findings (54). Stomach myotomy length could have direct implications in post POEM reflux, and long gastric myotomy (> 2-3 cm) has been associated with a higher risk of postprocedural GERD (55,56). Several techniques have been described such as the double scope, but lately, the identification of the second penetrating vessel in the submucosal space can help detect the end of tunneling (57), and orientating the myotomy to the right side of this second penetrating vessel helps preservation of the sling fibers (58) (Figure 3).

Indication and outcomes

POEM is the only treatment equally effective for the three achalasia subtypes, with an optimal response in the short and long term (34,35,38,39). Also, POEM has been performed for non-achalasia EMD such as distal esophageal spasm (DES), jackhammer

esophagus and Esophagogastric Junction Outflow Obstruction (EGJOO) with favorable results (94.1%, 75% and 93.3% respectively) (40). Moreover, POEM is feasible for symptomatic EMDs not gathered in the Chicago Classification (41,42). ED is confined to the esophagogastric junction (EGJ), and LHM cannot readily reach mid or cervical esophagus, yielding 80% success in DES (59). Thus, the only treatment fitting all the EMDs is POEM.

POEM can be performed after failure of any other treatments. Previous BTI or ED do not seem to diminish clinical success (60), but they can lead to fibrosis (61). After previous POEM or LHM, symptom release is less frequent than in naïve patients, but still a >75% response has been described, superior to repeating ED and LHM (60% and 29% response rate) (43).

POEM has been compared to LHM for achalasia in an RCT (44). 2-year clinical response was slightly superior for POEM (83 vs 81.7%). Another RCT compared POEM to a double step ED with a clinical response favoring POEM at 2 years (92 vs 54%, $p < 0.01$ and OR 12.3). Serious AEs were only described in ED group (62).

Adverse events

POEM is a safe procedure, and large series show less than 1% severe AEs (45). Mild, moderate and severe AEs had a frequency of 6.4%, 1.7% and 0.5% respectively. Most of them were intraprocedural (57.1%), whilst 41% presented in the first 48h, and only 1.9% appeared after 2 days. Inadvertent mucosotomy was the most common of the intraprocedural, follow by gas-related AEs and bleeding. During the first 48h esophageal leak, submucosal hematoma and pneumonia were orderly the most frequent. Overall, one patient needed conversion to LHM because of severe bleeding and another needed surgery for drainage of an esophageal leak (45). Compared to LHM and ED, POEM was least likely to lead to perforation, need for re-intervention, need for surgery, or serious AEs (63).

Gastroesophageal reflux disease (GERD)

GERD is a common AE after POEM (64,65). However, GERD related symptoms are infrequent, 8.2% to 16.8% of the patients (66,67), most of them respond to PPIs (68) and the GERD Questionnaire score globally diminishes in studies based on QoL (69). Two meta-analysis had deemed POEM to be more prompt to GERD when compared to

LHM (36,37) and a network meta-analysis found that the approach less related to GERD is ED (63). Werner's RCT, though, only found more POEM related GERD at the initial evaluation, but 2 years after both POEM and LHM the 24h acid exposure was equal (altered in 30% of patients), and grade D esophagitis was found in 3 patients of LHM group vs 0 after POEM (44). Likewise, a recent systematic review support that GERD tends to be similar between endoscopic and surgical myotomy in the long-term (70). Barrett's esophagus and stenosis have been reported after POEM as rare events (71).

There are not established prePOEM GERD risk factors (48), although excessive gastric myotomy and dissection of the collar sling fibers may increase the frequency of GERD after POEM, thus, it is recommended to avoid exceeding a gastric myotomy longer than 2-3 cm (68). Other strategies such as anterior, selective and short myotomies remain to be studied in a combined fashion. Recently, POEM plus fundoplication (POEM-F) has been proposed to avoid GERD in uncontrolled case series, with promising results when the endoscopic fundoplication persists in time (72). The necessity of surgical fundoplication after POEM is rare (68), and in cases of refractory reflux, endoscopic techniques can also be applied (73).

G-POEM

Gastroparesis refers to a set of symptoms that are associated with delayed gastric emptying in the absence of mechanical obstruction. The pathophysiology of gastroparesis is complex and partially elucidated, including pyloric sphincter dysfunction, as well as impaired gastric accommodation, antrum hypomotility, insufficient fundic hypotonia, desynchronization of the stomach with the antrum, and probably visceral hypersensitivity (74–76).

The treatment of gastroparesis is complex, without a clear pharmacological alternative. There are "non-pyloric" therapies, such as gastrostomy and placement of a gastric electrical stimulator (GES), which are intended to improve symptoms. GES, which appeared to be a very promising therapy, has shown a high rate of long-term complications (77).

Endoscopic treatment of pylorospasm aims to reduce the pressure gradient across the pyloric sphincter, thereby improving gastric emptying. Among the "pyloric" therapies, BTI, balloon dilatation-pyloroplasty, and transpyloric stent placement, have shown transient efficacy, moderate or not superior to placebo, and a non-negligible risk of AEs (78–82), although BTI is used to predict response to pyloric therapies.

On the other hand, gastric peroral endoscopic myotomy (G-POEM) has been postulated in recent years as an effective therapeutic alternative for the treatment of refractory gastroparesis (83,84). The G-POEM procedure consists of making a mucosotomy around 3-5 cm near the pylorus, tunneling through the submucosal space, identification of the pyloric ring, pyloric myotomy (which may be accompanied by a small myotomy of the adjacent antral muscle) and the closure of the mucosotomy.

Several studies demonstrated 100% technical success of G-POEM, with less than 0.5% serious AEs, although clinical success is variable (56-83.9%), and the 1-year clinical response is about 56-66% (85–96).

A multicenter prospective observational study showed that patients with baseline gastric retention >20% at 4 hours pre-intervention and with more severe symptoms from baseline are independent predictors of clinical success for G-POEM at 12 months (88). Contrary to other studies, a RCT recently published showed better results in diabetic patients compared to post-surgical or idiopathic, but data are limited to 41 patients. The enrolment was stopped after the interim analysis due to a G-POEM success rate of 71% versus 22% in the *sham* arm ($p=0.005$). Twelve patients crossed over to G-POEM with 9 of them (75%) achieving treatment success (97). Despite the studies carried out, it has not yet been established how to choose the best approach for each patient, the best time to treat them and the best selection criteria. Traditional surgical management options include pyloromyotomy or the partial gastrectomy (77). Until more evidence is available, the European Society of Gastrointestinal endoscopy suggest using G-POEM in the setting of research studies (98). Table 3 shows the pros and cons of the different non-pharmacological treatment options available.

Discussion

The “third space endoscopy” or also called “submucosal endoscopy is a subspecialty of endoscopy already established in multiple centers around the world. Some procedures such as POEM in achalasia and other EMD are in the first line of treatment for these pathologies and will probably appear as the treatment of choice in the updates to the main clinical guidelines. In achalasia, most of the technical and management aspects are clearly defined, although there are still areas for improvement (51). However, in other pathologies, the possibility of treatment by submucosal endoscopy needs to be defined both at a technical level and positioned in the therapeutic algorithms.

In Zenker's diverticula, flexible endoscopy techniques will probably be positioned as the procedure of choice, but the technical steps to follow will have to be better defined to minimize or eliminate the remaining pouch (11). The advantages of Z-POEM over traditional endoscopic FED need to be elucidated before assuming its hypothetical benefits.

One of the main problems of CP achalasia is the clinicians' poor knowledge of this pathophysiology and the difficulties in its diagnosis. It seems appropriate that this pathology is managed by specialized centers, since the closure of the entrance mucosotomy is challenging (32).

There is also limited experience in the management of middle and EPD, but the endoscopic approach in experienced hands seems clearly superior to the surgical alternative (23). As in Zenker's diverticulum, the mucosal pouch may ultimately causes persistent symptoms that are not relieved by septotomy or the management of the underlying EMD.

Regarding G-POEM, its clinical efficacy is limited to approximately 65% of patients and we are still not able to select adequately which are the ideal candidates to access this treatment (88,89).

Another aspect that should be implemented is the training in this type of procedures, which is far from being standardized. A recent meta-analysis suggests that approximately 25 cases are required to master POEM (99), but this number can be even higher for non-ESD experts (100).

Despite these difficulties, the spectrum of pathologies covered by submucosal endoscopy is increasing, and the lines with conventional surgery are being diluted on

many occasions. We are creating a new endoscopy field that could be called “flexible surgical endoscopy”, and its boundaries need to be defined in the future with a multidisciplinary approach.

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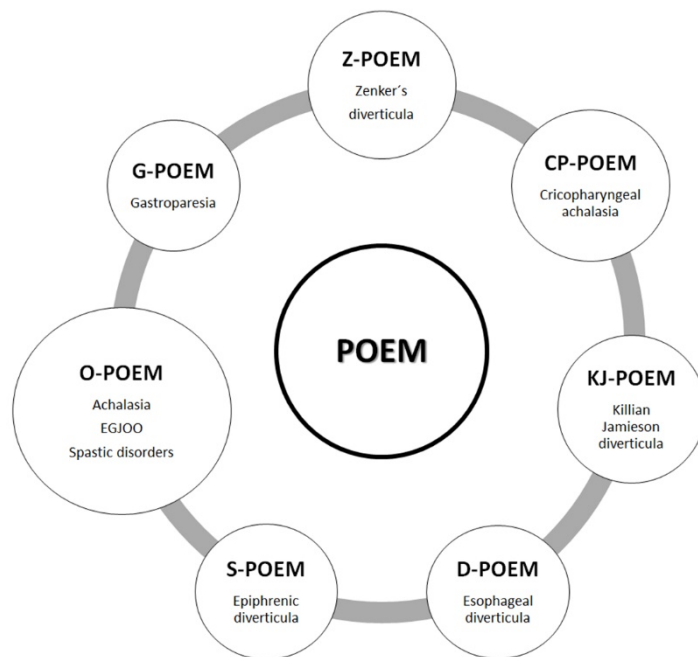


Figure 1: Summary of all variants of POEM. C-POEM: Cricopharyngeal peroral endoscopic myotomy; D-POEM: Diverticulum peroral endoscopic myotomy; EGJOO: Esophagogastric junction outflow obstruction; G-POEM: Gastric peroral endoscopic myotomy (i.e., myotomy of the pyloric ring; KJ-POEM: Killian-Jamieson diverticulum peroral endoscopic myotomy; O-POEM: Open peroral endoscopic myotomy (i.e., myotomy of the lower esophageal sphincter without submucosal tunneling; POEM: Peroral endoscopic myotomy; S-POEM: Salvage peroral endoscopic myotomy (i.e., no septotomy is performed).

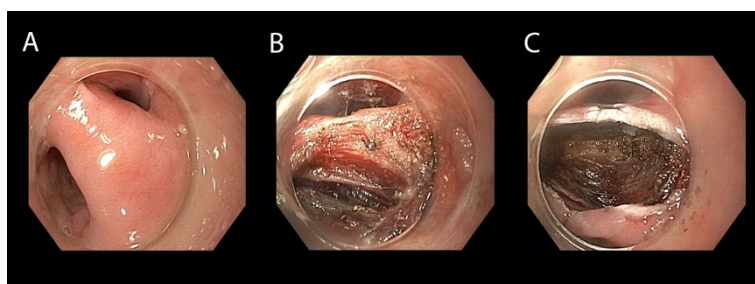


Figure 2: Z-POEM in Zenker's diverticulum. **A.** Zenker's diverticulum. Soft cap centering the diverticular septum; **B.** Z-POEM: tunneling of the diverticular septum with exposure of the hypertrophied cricopharyngeal muscle; **C.** Completed cricopharyngeal myotomy.

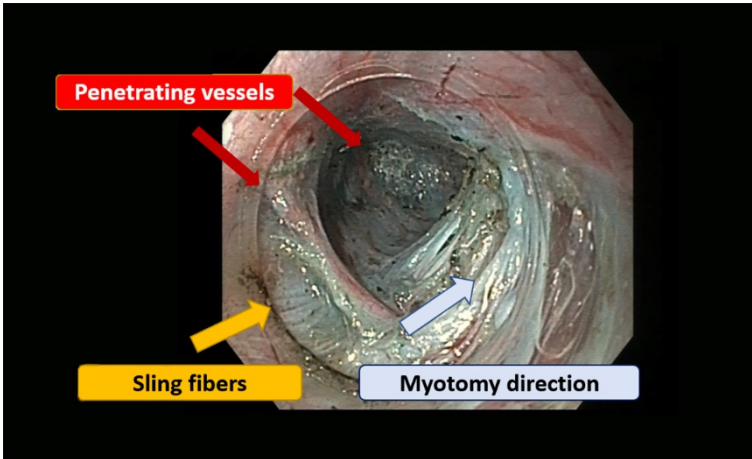


Figure 3: Anatomical landmarks to guide the cardial and subcardial myotomy during POEM.