Review Article

Peroral endoscopic myotomy (POEM) for achalasia

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Abstract: Achalasia is an uncommon disorder that results from the degeneration of ganglion cells of the myenteric plexus in the lower esophageal wall. It is manifested by a loss of peristalsis in the lower part of the esophagus and failure of the lower esophageal sphincter (LES) to relax. Peroral endoscopic myotomy (POEM) is a minimally invasive intervention that aims to treat achalasia. It is regarded as the endoscopic equivalent of Heller myotomy. POEM is a form of natural orifice transluminal endoscopic surgery that is completed by creating a submucosal tunnel in the lower part of esophagus to reach the inner circular muscle bundles of the LES to perform myotomy, while preserving the outer longitudinal muscle bundles. The result is decreased resting pressure of the LES, facilitating the passage of ingested material. POEM was initially introduced to treat achalasia by targeting the LES. POEM has expanded to include gastric POEM (G-POEM), myotomy of the pyloric sphincter to treat gastroparesis, and per rectal endoscopic myotomy to treat adult Hirschsprung's disease.

Keywords: Achalasia; peroral endoscopic myotomy (POEM)

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Introduction

Achalasia is a rare motility disorder of the esophagus, resulting from the progressive degeneration of ganglion cells in the myenteric plexus in the lower part of esophagus. Achalasia symptoms are due to failed relaxation of the lower esophageal sphincter (LES) associated with loss of peristalsis and impairment of the deglutitive function. Achalasia incidence is approximately 1.6 cases per 100,000 (1) and is usually present between the ages 25–60; however, new onset of achalasia has been reported in pediatric and elderly populations. Men and women are equally affected with achalasia. The etiology of primary achalasia is unknown, although genetic susceptibility combined with a latent infection of Herpes Simplex Virus (HSV) is suspected to trigger inflammatory changes and a cascading autoimmune process (2). Other diseases can mimic achalasia, causing secondary achalasia such as Chagas disease (3), amyloidosis (4), sarcoidosis (5), neurofibromatosis (6), Fabry disease (7), multiple endocrine neoplasia type 2B (8), and juvenile Sjögren syndrome (9,10).

Achalasia is an insidious disease; patients present with symptoms for an average of 4.7 years prior to diagnosis (11). Longstanding achalasia leads to progressive dilatation of the lower esophagus and hypertrophy of the LES (12). Clinical findings may include chest pain (13), weight loss (14), regurgitation and dysphagia (15). Advanced cases are at risk of upper respiratory infections including pneumonia (16), aspiration and lung abscesses (17). Achalasia is diagnosed by a barium swallow and/or manometry (18). Endoscopic evaluation of achalasia is necessary to diagnose conditions that may present as achalasia (pseudoachalasia), for example carcinoma of the gastroesophageal junction (GEJ) (19). *Figure 1* illustrate tight GEJ in patient with achalasia.

Treatment of achalasia is aimed at lowering the resting pressure of the LES (20). This can be achieved by a

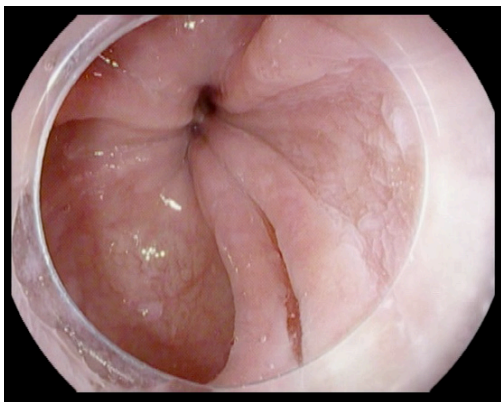

Figure 1 Tight GEJ in a patient with achalasia. GEJ, gastroesophageal junction.

pharmacologic reduction of the muscular resting pressure, botulinum toxin (BT) injection, use of oral nitrates, physical disruption of muscular bundles of LES by laparoscopic myotomy, pneumatic dilation or POEM (18). There is no known treatment to reverse the degenerative process of ganglion cells nor restore normal esophageal function; hence, repeated intervention and long-term follow up is necessary for these patients (21). BT injection is advantageous as a minimally invasive intervention with immediate response in 70–90% of the patients (22-24), but many patients relapse in a few months (25-27). It carries a slight increased risk of perforation (28), ulcers (29) and chest pain (30). Pneumatic dilatation (PD) is forceful mechanical disruption applied to the LES. It is completed by passing a pneumatic balloon with increasing caliber to stretch the circumferential muscle fibers (31). PD should be performed by an experienced endoscopist. Patients undergoing PD should be good surgical candidates due to the risk of perforation requiring surgical intervention (32). PD is the most cost-effective intervention (33) and initial response is high; however, efficacy wanes over time (34). Immediate complications include perforation in 2% and heartburn in 15–35% (34,35).

Heller myotomy was the primary therapy for achalasia after PD failure, it is usually performed laparoscopically (35-37). Due to the disruptive nature of the intervention, it frequently causes reflux esophagitis and is frequently combined with anti-reflux intervention (37). Heller myotomy is the least cost-effective intervention for achalasia (33), with initial symptom relief in 90% of patients (35); however, it has a long recovery period, in addition to the risk of perforation, bleeding and infection (38).

POEM was first introduced by Ortega JA in 1980. In his initial report, seventeen patients with achalasia were treated by endoscopic myotomy limited to esophageal rosette. In this cohort improvement of symptoms and manometry follow-up was comparable to Heller myotomy (39). The current form of POEM was developed by Inoue in 2008 (40). He utilized a submucosal tunnel to reach the inner circular muscle bundle of the LES to perform the myotomy (41). Following the initial publication, Inoue *et al.* presented their experience in performing POEM on 43 patients for the treatment of achalasia. The authors achieved a comparable outcome to Heller's myotomy (42). POEM is emerging as the treatment of choice for achalasia and is even utilized for prior failed achalasia treatment including laparoscopic surgical myotomy (43). POEM is also applied to treat other motility disorders including spastic esophageal disorders (SED), such as diffuse esophageal spasm, jackhammer esophagus, or type 3 achalasia (44). In a meta-analysis of nine studies with 210 patients, Chandan *et al.* found that POEM was safe and effective in treatment of the SED in over 89% of cases.

Pre-operative evaluation

In the pre-operative evaluation of achalasia, barium swallow, esophageal manometry and EGD should be performed to confirm diagnosis and exclude other conditions (e.g., cancer). High resolution manometry allows tailored treatment based on the type of achalasia.

Patient should be on a clear liquid diet for 2 days before the procedure and NPO the night of the procedure. In some centers, EGD is performed before general anesthesia to remove food remnants and assess for candida esophagitis (45); another approach is to place a nasogastric tube for suction 1 to 2 days prior to the procedure. Oral antifungal treatment can be administered one week prior to the procedure if candidiasis is suspected. A broad-spectrum antibiotic is usually given intravenously the day of the procedure. Anticoagulants and anti-platelet medication should be withheld prior to the intervention.

Technique

A forward viewing scope with a transparent distal cap and triangle or rounded tip knife is used to dissect the submucosal layer and cut the inner circular muscle bundles. A coagulating grasper may be used for hemostasis.

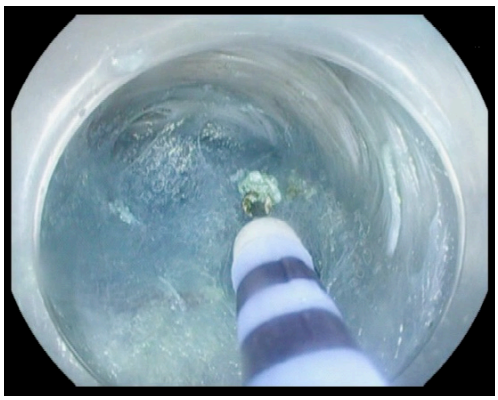

Figure 2 Creation of submucosal tunnel.

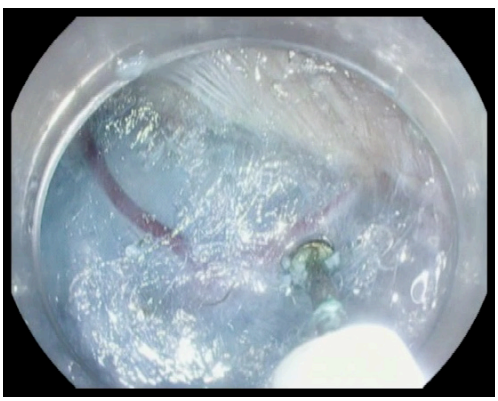

Figure 3 Blood vessel within the submucosa.

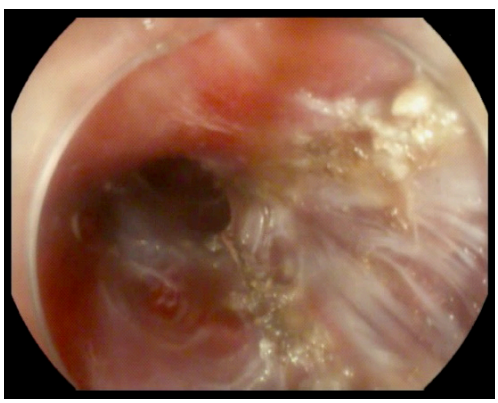

Figure 4 Selective myotomy with preserved longitudinal muscle.

Step 1: mucosal incision

Using a mixture of epinephrine and indigo carmine or methylene blue, a submucosal bleb is raised and a mucosal incision is performed. The incision is done longitudinally with careful dissection of the submucosal fibers around the linear incision to allow the gastroscope to be introduced into the submucosal space. Longitudinal incision facilitates closure with endoscopic clips; in some occasions, a horizontal incision is done to allow suturing of the incision site.

In most cases, submucosal tunnel and myotomy are performed at an anterior position, 2 o'clock, in other cases, a posterior position at 5 o'clock is preferred. A randomized trial comparing the two approaches in 32 patients, found no difference in efficacy nor complications (46). In another study of 448 patients, posterior POEM was associated with fewer adverse events, lower risk of mucosectomy and a shorter incision closure time (47).

In failed surgical attempts or after previous anterior POEM failure, posterior POEM is performed to avoid previous surgical site scarring (48).

Step 2: creating a submucosal tunnel

After creation of the entry site, the endoscope is advanced within the submucosa while preserving the integrity of the mucosa. It is very important to preserve the mucosa since it will be the only remaining barrier between the mediastinum and esophageal lumen after myotomy (*Figure 2*). Typically, dry cut current, forced coagulation current or spry coagulation are used to dissect the submucosa after repeated injection of saline with methylene blue. Larger blood vessels in the submucosa are usually coagulated using hemostatic forceps (*Figure 3*).

The GEJ is identified by multiple methods including visualization of the longitudinal muscle bundles at the GEJ, narrowing of the submucosal space and resistance of advancing the endoscope thought GEJ, followed by expansion of the space in the gastric cardia. The appearance of spiral or comma shaped small blood vessels in the submucosa is another indicator. Once the gastro esophageal junction (GEJ) is identified, the endoscope should be advanced 2 to 3 cm beyond it. On some occasions, prior to tunnel creation, the lower most part of the tunnel is injected 2 cm below the GEJ with indocyanine green to mark the extent of tunnel (40,49).

Step 3: myotomy

Selective myotomy of the inner circular muscle bundles is performed starting 6 cm above the GEJ and extends 2–3 cm below the GEJ (*Figure 4*). The selective myotomy of the

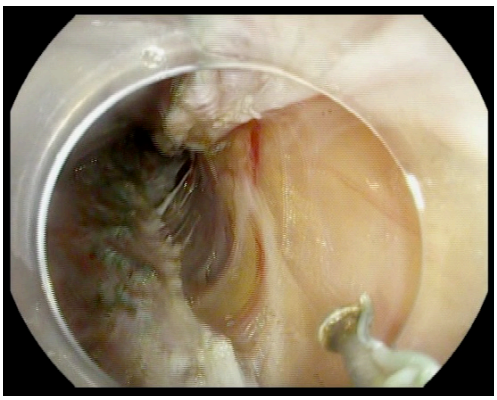

Figure 5 Full thickness myotomy.

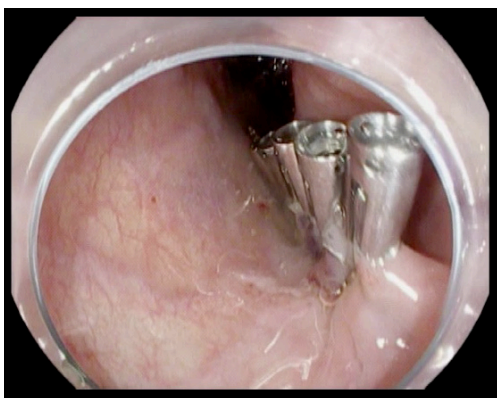

Figure 6 Clip closure of the entry site.

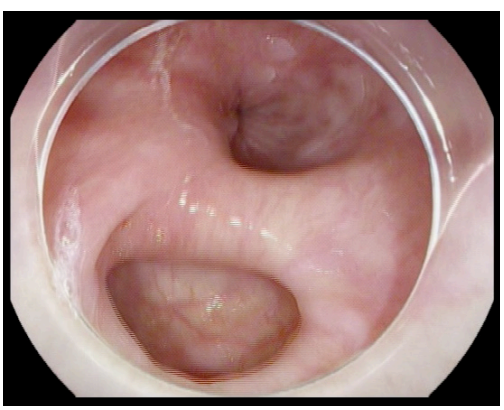

Figure 7 Esophageal diverticulum in a patient with achalasia.

inner circular layer while preserving the longitudinal outer layer may be difficult to achieve and is time consuming. The longitudinal outer muscle layer is very thin and fragile making selective myotomy difficult. May endoscopists advocate for full thickness myotomy (*Figure 5*). In a study of 103 patients comparing the selective myotomy of inner circular bundles versus full-thickness myotomy, it was found that short-term relief and clinical outcome of both methods were comparable (50). Full-thickness myotomy significantly reduced the procedure time without increase in adverse events or reflux (50). However, 24-hour pH study in the same trial showed that abnormal esophageal acid exposure was higher in the full-thickness myotomy group when compared to the selective myotomy group; although not statistically significant (P>0.05) (50).

Step 4: closure of mucosal incision

After successful completion of the myotomy, careful inspection of the submucosal tunnel should be performed. The endoscopist should ensure that any active bleeding is controlled prior to closure. The esophageal mucosa is then inspected and any incidental tear, mucosectomy, should be closed. Closure of the initial mucosal incision can be performed with endoscopic clips or endoscopic suturing devices (*Figure 6*).

Post-operative care

A gastrografin swallow study with fluoroscopy should be obtained to confirm the absence of any leakage. A soft diet can be started on day 2 post operatively and continue for 10–14 days before starting a regular diet. Intravenous antibiotics should be stopped on day 3 and switched to oral antibiotics for a total of 7 days. Proton pump inhibitors should be prescribed for a minimum of 14 days.

Follow-up

A 3–6-month post-procedure follow-up should include EGD, manometry and a pH study to evaluate the patient's outcome and assess any complications.

Contraindications

Contraindications to the procedure include severe esophagitis, significant coagulation disorder, advanced liver cirrhosis and submucosal fibrosis from prior radiation. Large esophageal diverticulum is considered a relative contraindication depending on the location and the extent of the diverticulum (*Figure 7* illustrate esophageal diverticulum in a patient with achalasia).

Table 1 Severity of dysphagia assessed by the dysphagia score and the Eckardt score (52)

Eckardt score	Weight loss, kg	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

Table 2 Long-term efficacy of peroral endoscopic myotomy

Study	Total subject number	Follow-up (months)	Eckardt score (before/after)	LES pressure (mmHg) (before/after)	Clinical GERD (symptomatic or PPI use)	Major adverse events	Clinical success
Inoue *et al.* (55)	500	36	6.0/1.7	25.4/13.4	21.3%	3.2%	88.5%
Sharata *et al.* (51)	100	20.1	6/1	22.2/11.7	19.1%	6%	97%
Minami *et al.* (57)	28	16	6.7/0.7	71.2/21	21.4%	0%	100%
Teitelbaum *et al.* (58)	41	15	7/1	28/11	15%	2%	92%
Von Renteln *et al.* (59)	70	12	6.9/1	27.6/8.9	29%	0%	82.4%
Liu *et al.* (60)	82	18 (6–26)	7.4/1.8	N/A	15.9%	12.2%	96.3%
Hernández-Mondragón *et al.* (61)	68	36	9/2	24.3/11.2	50%	0%	95%
Khashab (62)	50	9	6.9/1.9	NA	16.1%	20%	84.9%
Zhang (63)	32	27	7.2/1.4	39.2/19.0	90.6%	0%	90.6%
Khashab (64)	73	7.7	6.73/1.13	NA	NA	0%	93.2%

GERD, gastro-esophageal reflux disease; LES, lower esophageal sphincter; PPI, proton pump inhibitor; NA, not available.

Outcomes of POEM for achalasia

POEM aims primarily to treat achalasia. The intervention is successful and efficacious for the management of symptoms with a success rate of 82–100% (45,51). Outcomes of the intervention to treat achalasia is assessed subjectively and objectively by multiple methods. The most used tool to assess outcomes is the Eckardt score, which is a subjective assessment of pre and post-intervention symptoms (see *Table 1*). Clinical success is defined as a post-intervention Eckardt score of 3 or lower or a reduction of LES by 50% or more (45). Other measures to assess clinical improvement such as quality of life (53), or a barium swallow (54) also show similar favorable outcomes after POEM.

Intermediate to long-term outcome using the Eckardt score was studied in Japan and the USA. Both studies observed 90% clinical success at 24-month after the intervention (55,56) (*Table 2*).

When compared to Laparoscopic Heller Myotomy (LHM) (*Table 3*), POEM was shown to have similar safety and efficacy (65). In one meta-analysis of 486 patients who received POEM, it was found that they had a similar reduction of Eckardt score compared to LHM. In another meta-analysis of over 7,000 patients including over 70 cohort studies, POEM was more effective than LHM, improving dysphagia (66) at 12-, 24-, 30- (56) and 60-month (61), although POEM was found to have higher incidents of new gastro-esophageal reflux disease (GERD). New suggested approaches include combining POEM with anti-reflux measures (67); in this series, patients who underwent POEM and transoral incisional fundoplication (TIF) found

Table 3 Peroral endoscopic myotomy compared with laparoscopic Heller myotomy

Point of comparison	POEM	LHM
Body scar	No	Yes
Selective inner bundle myotomy	Yes	No
Feasibility for repeat if first attempt fails	Yes	No
Disruption of esophageal hiatus	No	Yes
Post-operative GERD	20–30%	15%
Concurrent anti GERD procedure	Possible (TIF)	Yes fundoplication
Ability to extend myotomy to proximal esophageal body	Possible and easy	Difficult
Cost	Low to intermediate	High
Clinical response	Excellent	Good
Hospital stay	Short	Long

POEM, peroral endoscopic myotomy; LHM, Laparoscopic Heller Myotomy; GERD, gastro-esophageal reflux disease; TIF, transoral incisional fundoplication.

to have improved symptoms of esophagitis and lower need for long-term proton pump inhibitor (PPI) use. POEM improved all dimensions of health-related quality of life in one study of 143 patients. Perbtani *et al.*, showed significant improvement of SF-36 survey scores in a long-term follow-up study (16.4 months with a range of 12 to 40 months). The survey was obtained before and after POEM and it showed a strong association of Eckardt score improvements in all health-related quality of life (68).

POEM for recurrent achalasia

POEM is also a feasible and safe option for treatment of recurrent achalasia. Patients who failed in previous endoscopic or laparoscopic attempts underwent successful POEM and had a favorable clinical response with an Eckardt score of 3 or less (69-71). Sharata *et al.* reported the outcomes of POEM in 40 achalasia patients who failed a prior BT or pneumatic dilation. POEM resulted in a favorable outcome with an Eckardt score 3 or less. Of note, previous treatment with PD and or BT was not associated with increased intra- or post-operative adverse events (69). Another study of twenty-one patients found a similar outcome after POEM in patients who failed prior repeated BT and PD therapy (70). Orenstein *et al.*, reported the outcome of POEM in a forty-one patients with achalasia who previously failed endoscopic treatment or surgery (LHM). In Both group, there was no difference in POEM outcome or adverse events (71). however submucosal fibrosis from repeated BT and PD rendered dissection more difficult (49). In a retrospective multi-center study which compared the POEM outcomes of ninety patients with prior LHM compared to ninety patients without previous intervention, the adverse event rate was similar; however, clinical success was lower in the group who previously received LHM (94% *vs.* 81%) (72). Another study that looked at repeated POEM in patients with previously failed POEM found average Eckardt score improved from 4.3 to 1.64 (73).

Adverse events

In experienced hands, POEM is a safe procedure with low post-operative adverse events (74). Adverse events are usually managed medically or endoscopically. In a multi-center international study that included 1,826 patients, adverse events ranging from mild to severe occurred in 137 patients with nine patients experiencing a severe adverse event (75).

Mucosal tear

Mucosal tear during POEM requires closure because it represent a full-thickness esophageal perforation. Mucosal tear has a highest risk of occurrence at level of LES due to narrowing of submucosal space. Mucosal tear tends to expand quickly if not addressed immediately; it is usually closed with endoclips, although glue (76) and over-the-

scope clips are also used (77). Mucosal tear can lead to mediastinitis if not treated (45).

Bleeding

Bleeding during the submucosal dissection is expected and addressed with multiple methods including pressure with gastroscope tip, electrocautery knife or hemostatic forceps. In one study, delayed bleeding occurred in 0.7% (78). Hematemesis after POEM is an emergency; the patient should undergo immediate endoscopy to assess the surgical site.

GERD

GERD is the most common adverse event post-POEM, with a prevalence rate of 20–57% (45). As mentioned above, combing POEM with TIF improved GERD and esophagitis. Other methods to decrease GERD post-POEM include preserving the outer longitudinal muscle bundles and the sling fibers. In comparison to full thickness myotomy, selective myotomy was associated with a lower esophageal acid exposure based on 24 hours manometry study in some published trials (50). Recently it was suggested to limit the extension of the myotomy to only one centimeter beyond GEJ (instead of 3 cm); however, this has not yet been fully studied.

Pneumoperitoneum

Small pneumoperitoneum occurs in 50% of cases and subcutaneous emphysema occurs in 15% (45). Both events resolve spontaneously. Tension pneumoperitoneum is rare and can be assessed clinically by an abdominal exam, it can be addressed with prompt decompression using a large bore needle.

Pneumothorax

Pneumothorax is a rare event, usually left to resolve spontaneously, unless respiratory compromise occurs.

Tailoring POEM to the type of achalasia

Based on esophageal pressurization by high resolution manometry, Chicago Classification (CC v3.0) identify 3 subtypes of achalasia (79):

(I) type I classic: 100% failed peristalsis, swallowing results in no significant change in esophageal pressurization;
(II) type II: 100% failed peristalsis, swallowing results in pan esophageal pressurization with ≥20% of swallows;
(III) type III: swallowing results in abnormal spasms, no normal peristalsis, premature (spastic) contractions with distal contractile integral >450 mmHg-s-cm in ≥20% of swallows.

Standard POEM technique is tailored for type I and type II. Performing the myotomy according to the length of the spastic segment is required in type III. In type III achalasia which is characterized by rapidly propagating pressure due to spastic contractions, POEM was superior to LHM due to longer myotomy 16 *vs.* 8 cm, shorter procedure time (80) and significant better clinical outcome (98.0% *vs.* 80.8%).

POEM training

POEM is a complex procedure, demanding skilled hands to avoid serious complications. Endoscopists should be able to recognize structures beyond mucosa, including vasculature nerves and the anatomy of the mediastinum. It is currently performed in highly specialized centers by experienced endoscopists or surgeons. Initially the endoscopist should observe the procedure performed by experienced operators, familiarize themselves with all equipment needed for the intervention including the tools to control possible adverse events. After that endoscopist should perform POEM on animal models to develop the needed skills. The most commonly used animal model is swine esophagus. Swine esophagus is long which allows submucosal dissection and myotomy, replicating the experience in human. Swine model disadvantages include a soft and avascular submucosal space allowing easier dissection in comparison to human, however, the swine muscle layer is thinner with a higher risk of perforation. Training on animal models should go through two phases, non-survival animal model followed by survival models using the same equipment and principles described for humans. After evaluation of a successful training in the above structured program, endoscopists who can meet the competency requirements can advance to perform POEM in tertiary centers (48).

Acknowledgments

None.

Footnote

Conflicts of Interest: MO Othman MD, is a consultant for Olympus, Boston Scientific, Abbvie and Lumendi. Y Ahmed has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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