Indications and Outcomes of Per Oral Endoscopic Myotomy from Mouth to Anus

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KEYWORDS

- Per oral endoscopic myotomy • POEM • G-POEM • D-POEM • Z-POEM
- Per rectal endoscopic myotomy • PREM • Third space endoscopy

KEY POINTS

- Submucosal endoscopy using a mucosal flap valve is a novel third space endoscopic technique that uses a submucosal tunneling approach to access deeper layers of the gastrointestinal (GI) tract.
- Per oral endoscopic myotomy (POEM) is the index procedure and has shown excellent clinical safety and efficacy for the treatment of achalasia cardia and its subtypes.
- Various modifications in the POEM technique have been described for other spastic disorders of the GI tract.
- G-POEM or endoscopic pyloromyotomy is an upcoming and potentially effective treatment for patients with refractory gastroparesis.
- More recently, diverticular myotomy for Zenker's and esophageal diverticula (Z-POEM and D-POEM), and per-rectal myotomy for Hirschsprung's disease (PREM) have been described and have shown impressive outcomes.
- Third space endoscopy procedures show potential in changing the way these spastic GI conditions can be treated in future.

INTRODUCTION

Third space endoscopy (TSE) or submucosal endoscopy using a mucosal flap valve (SEMF) was first described by Sumiyama and colleagues[1] as a potential peritoneal access route for natural orifice transoral endoscopic surgery (NOTES). The principle involves creation of a submucosal tunnel in the esophagus through a mucosal incision to

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access the deeper muscle layers and peritoneal cavity, after which the mucosal incision is closed using clips (Fig. 1). The advantage of this technique is that because the mucosa and muscularis are breached at different locations, full-thickness perforation is prevented, and procedural safety is enhanced. In the same year, Pasricha and colleagues[2] showed the safety and feasibility of creating a tunnel and subsequent myotomy in the esophagus in porcine models and named it per oral endoscopic myotomy (POEM). POEM was envisioned to be implemented as a minimally invasive treatment for achalasia cardia (AC). Inoue and colleagues[3] reported the first human case series of POEM for patients of AC.

Since its original description, POEM has become an exceedingly popular and effective treatment for AC. Based on this popularity, endoscopists have implemented the SEMF principle for various other spastic disorders of the gastrointestinal (GI) tract. Gastric per oral endoscopic myotomy of the pylorus (G-POEM) has been described for refractory gastroparesis,[4] diverticular myotomy has been described for Zenker's and epiphrenic diverticula (Z-POEM and D-POEM, respectively),[5] and the technique has also been used for rectal myotomy of the spastic segment in patients with Hirschsprung's disease (per rectal endoscopic myotomy [PREM]).[6] This article describes the indications and outcomes of these various types of POEMs (or PREM) procedures from the mouth to the anus.

PER ORAL ENDOSCOPIC MYOTOMY

Indications

AC is a benign progressive motility disorder of the esophagus characterized by loss of esophageal body motility and nonrelaxation of the lower esophageal sphincter (LES) on wet swallows. It forms a part of a group of conditions collectively classified as spastic esophageal disorders (SEDs). The Chicago classification has classified

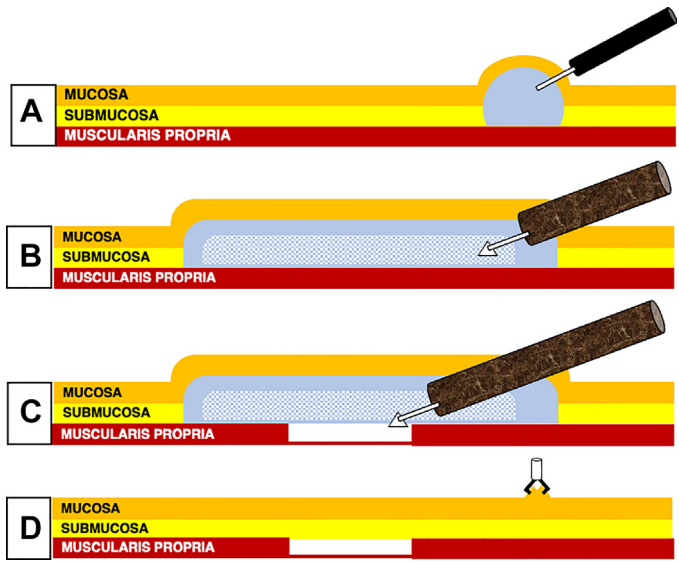

Fig. 1. Schematic showing principle of third space endoscopy: (*A*) layers of gastrointestinal tract represented with creation of submucosal cushion, (*B*) submucosal dissection and tunneling, (*C*) myotomy being performed distal to the site of mucosal incision, and (*D*) closure of mucosa creating sealing of submucosal tunnel thereby preventing bowel leak.

SEDs into AC with its three variant types–I, II, and III based on esophageal high-resolution manometry (HRM), and other SEDs–Jackhammer esophagus (JH), esophagogastric junction outflow obstruction (EGJOO), diffuse esophageal spasm (DES).[7]

Treatment of AC is palliative and is directed toward disruption of the spastic LES, with no therapy presently available to improve esophageal body motility. Surgical LES myotomy was described by Heller in 1913 and remained the mainstay of treatment for several decades until laparoscopic Heller myotomy (LHM) emerged and became the standard of care thereafter. Endoscopic approaches for treatment of AC also include endoscopic pneumatic balloon dilatation (PD) wherein a 30 to 40 mm diameter balloon is used to disrupt the LES, and endoscopic injection of botulinum toxin into the LES. Patients with advanced achalasia with a grossly dilated, nonmotile sigmoid esophagus and with no anticipated benefit by LES relaxation are recommended to undergo esophagectomy. POEM is the newest entrant in the variety of treatment options for AC and provides a minimally invasive option to perform myotomy of the LES (**Fig. 2**).

Indications, Patient Selection, and Contraindications for Per Oral Endoscopic Myotomy

POEM has been proposed as a minimally invasive technique for myotomy as a treatment of AC. It can be performed for all achalasia subtypes. POEM is preferred in patients with type III achalasia and SEDs, as these conditions require a personalized long myotomy.[8]

Common presentations of AC are dysphagia and regurgitation. Clinical evaluation involves calculation of the Eckardt score (ES) which includes four parameters: dysphagia, retrosternal pain, regurgitation, and weight loss; and has been shown to directly correlate with symptom severity. Diagnosis is by esophago-gastroduodenoscopy (EGD), HRM, and sometimes barium swallow and/or a thoracic CT scan. EGD and/or HRM confirm AC, whereas barium swallow or computed tomography (CT) scan can rule out pseudo-achalasia caused by extrinsic compression by

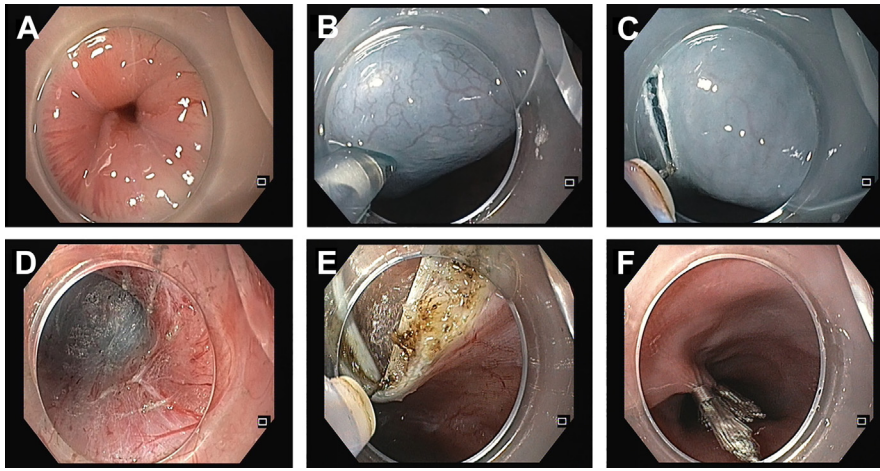

Fig. 2. POEM: (*A*) Tight LES, (*B*) Submucosal cushion, (*C*) mucosal incision, (*D*) submucosal dissection and tunneling, (*E*) full-thickness myotomy using triangular tip J knife, (*F*) mucosal incision closure using endoclips.

mediastinal mass lesions, and to determine the degree of sigmoidization in patients with sigmoid AC. Timed barium swallow is preferred to standard swallow, and the length of the vertical column of barium in the esophagus and the time for esophageal clearance of the barium are important considerations. Sigmoid AC is classified as S1 and S2 depending on degree of sigmoidization and on whether one or two esophageal lumens are visible on a single horizontal CT section (S1 and S2, respectively. Patients with S1 sigmoidization are likely to benefit by POEM (or any other myotomy) whereas S2 is less likely to benefit. Preoperative workup to evaluate fitness for general anesthesia is mandatory before POEM can be planned.

Although absolute contraindications for POEM are very few, several relative contraindications exist, wherein POEM can be technically challenging or potentially difficult to perform. Patients with severe coagulopathy, severe pulmonary disease, cirrhosis with portal hypertension, and conditions that cause severe, extensive fibrosis of the esophageal submucosa are absolute contraindications for POEM.[9] In general, patients unfit for general anesthesia due to comorbid conditions cannot be subjected to POEM. Severe stasis esophagitis and/or esophageal candidiasis are relative contraindications to performing POEM during that session. The esophageal mucosa in these patients is inflamed, friable, and bleeds during incision, is usually adherent to the muscle layer, which makes tunneling technically difficult. Furthermore, secure closure of such a mucosal incision is difficult because clips or sutures can cut through the friable tissues, subjecting the patient to the risk of mucosal dehiscence and mediastinitis. POEM in such situations is best postponed until mucosal inflammation heals. An important contraindication is extensive submucosal fibrosis wherein submucosal elevation cannot be obtained. In such cases, POEM may have to be aborted or deferred for safety concerns. Bing Hu has described a technique of open POEM for such cases with impressive safety and efficacy reported in a single-center case series of over 80 patients;[10] however, the overall acceptance of this technical variation at other centers have been limited.

Outcomes of per oral endoscopic myotomy

POEM has shown excellent short-, medium- and long-term clinical outcomes in various large series and meta-analyses. Outcomes are primarily reported based on improvement in ES.

Short- and Medium-Term Outcomes

Studies on POEM for AC have consistently reported high clinical success rates above 90% (**Table 1**).[11–25] A large multi-center retrospective study from Japan included 1346 patients and reported clinical success rates of 94.7% at 1-year follow-up.[11] Another single-center study from India reporting 400 patients showed 90.9% success rates at 1-year follow-up.[14] A large single-center study of 502 patients reported success rates of 91% at 2 year and 88.5% at 3 year follow-up.[18] Another large international multi-center study involving over 200 subjects reported 91% symptom relief at 2 year follow-up duration.[26]

Long-Term Outcomes

Long-term data on POEM is gradually emerging, with limited studies reporting long-term outcomes. A large single-center study evaluated 10-year sequential follow-up in 610 consecutive patients. The study reports impressive long-term outcomes as identified by Kaplan–Meier clinical success estimates at years 1, 2, 3, 4, 5, 6, and 7 as 98%, 96%, 96%, 94%, 92%, 91%, and 91%, respectively.[25] Other studies have reported similar outcomes. A multicenter retrospective cohort study involving 146

Table 1
Outcomes of per oral endoscopic myotomy in achalasia (select large studies)

Study	Patients (*N*)	Previous Therapy (%)	Mean/Median Follow-Up (months)	Pre-Eckardt Score	Post-Eckardt Score	Treatment Success (%)	Adverse Events (%)	GER (%)
Shiwaku et al.[10]	1346	31	12	6.1	1.1	95.1 at 6 m 94.7 at 1 y	3.7	14.8
Li et al.[11]	564	34.2	49	8	2	94.2 at 1 y 87.1 at 5 y	6.4	37.3
Kumbhari et al.[12]	282	28.6	12	7.8	1	94.3		23.2
Nabi et al.[13]	423	46	17	7	1.2	94 at 1 y 91 at 2 y	4.5	16.8
Shiwaku et al.[14]	100	47	3	5.9	0.8	99	10	28.5
Hungness et al.[15]	112	30	28	7	1	92	2.7	28
Ramchandani et al.[16]	220	41.3	13.4 (149)	7.1	1.25	94 at 6 m 92 at 1 y	6.4	21.6
Inoue et al.[17]	500	39	36	6	1	91 at 1 y 88.5 at 3 y	3.2	16.8 at 2 months, 21 at 3 y
Stavropoulos et al.[18]	100	27	13.3	7.8	0.2	98 at 3 months 96 at 1 y		32
Brewer Gutierrez et al.[19]	146	PD—19.9, Botulinum toxin injection—8.9, Heller's myotomy—8.9	55	7	1	95.2	5.5	Symptomatic reflux—32.1% Reflux esophagitis—16.8%
Wen-Gang Zhang et al.[20]	32	NR	88	7	2	88	22	Symptomatic reflux—38%

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Table 1
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Study	Patients (*N*)	Previous Therapy (%)	Mean/Median Follow-Up (months)	Pre-Eckardt Score	Post-Eckardt Score	Treatment Success (%)	Adverse Events (%)	GER (%)
Teitelbaum et al.[21]	36	NR	65	6.4	1.7	83	NR	Reflux on pH studies (6 m)—38%; At 5 y: Erosive esophagitis—13%, Symptomatic reflux—26%
Werner et al.[22] (POEM vs LHM)	POEM—112, LHM—109	PD—27, Botulinum toxin injection—7, PD and BT—5	24	POEM - 6.8 ± 2 LHM—6.7 ± 2	POEM—2 ± 1.9 LHM—1.8 ± 1.7	POEM—83, LHM—81.7	POEM - 2.6, LHM—7.3	POEM group—3 months—57%, 24 months—44%
Ponds et al.[23] (POEM vs PD)	POEM—64, PD—66	None	24	POEM—med 8 (IQR 6–9), PD—med 7 (IQR 6–9)	POEM—1 (IQR 0–2) PD—1 (IQR 0–2)	POEM—92, PD—54	Serious procedure-related AE, PD—2, POEM - 0	Reflux esophagitis; POEM—41%, PD—7%
Modayil et al.[24]	610	47.9 – PD—17.7, BT—22.5, HM—13.6, POEM—2.8	30	Achalasia—7.6, non-achalasia—7.9	0.5, 1.2	97.6% (1 y), 96.2% (2 y), 95.9% (3 y), 93.8% (4 y), 91.9% (5 y), 91.2% (6 y), 91.2% (7 y)	Clinically significant AEs—3.4	Reflux on pH studies—57.1%, esophagitis on EGD—49.8%, GER symptoms—20.5% at 4 m; Normalization of pH at long term follow-up in 35% of initial positives

patients reported sustained clinical response in 95.2% at >48-month follow-up.[20] A single-center retrospective study of 32 patients reported 88% clinical success at median 88-month follow-up.[21] Two other studies have reported 87.1% and 83% long-term clinical success rates at 4 and 5 years, respectively.[12,22] Although some of these studies indicate that there may be a slight decline in clinical efficacy over the long term, most reported reductions are marginal, and can possibly be attributed to the continued impairment of esophageal body function rather than a recurrence of AC. Similar outcomes have been reported after LHM.

Per oral endoscopic myotomy for spastic esophageal disorders and type III achalasia cardia

POEM is the preferred treatment modality for the management of SEDs including type III AC. A recent systematic review and meta-analysis showed pooled clinical success rates of 89.6% (95% CI 83.5–93.1, 95% PI 83.4–93.7, I2 = 0%) for clinical success and adverse events (AEs) for all SED subtypes. Myotomy length (<10 cm or >10 cm) did not affect the clinical success rates. Furthermore, prior therapeutic intervention also did not affect the primary outcomes.[27] Another systematic review and meta-analysis showed a weighted pooled ratio (WPR) with a 95% confidence interval (CI) for clinical success of 87% (78, 93%), $I^2 = 37\%$; the WPRs for clinical success for type III achalasia, DES, and JH were 92, 88, and 72%, respectively. WPR with 95% CI for AEs was 14% (9, 20%), $I^2 = 0\%$.[28] An international, multicentric, retrospective study of 73 patients subjected to POEM for SEDs and followed up for mean of 234 days showed 93% clinical response and 11% AEs.[29]

Per Oral Endoscopic Myotomy for Pediatric Achalasia

POEM has proven to be a safe and effective modality to treat pediatric AC. A systematic review and meta-analysis of 12 studies included 146 pediatric patients with achalasia. Symptom resolution was seen in 93% patients. Significant reduction in mean ES by 6.88 points (95%CI, 6.28–7.48, $P < .001$) and LES pressure by 20.73 mm Hg (95% CI, 15.76–25.70, $P < .001$) was noted.[30] A single-center study from India evaluating 44 children with AC undergoing POEM reported excellent clinical success rates of 92.8%, 94.4%, 92.3%, and 83.3% at 1-, 2-, 3-, and 4-year follow-up, respectively. Intraoperative AEs were encountered in 25.6% and post-POEM gastro-esophageal reflux (GER) was documented by pH studies in 53.8%.[31]

A major limitation of data reporting outcomes of POEM for pediatric achalasia is that most studies have included patients up to 18 years of age. Most of the unique technical challenges while performing POEM for pediatric AC patients are encountered in a younger population, particularly infants and small-size children. Further subgroup analysis for this age group is therefore desirable.

Per Oral Endoscopic Myotomy for Recurrent Achalasia Cardia and Prior Treatment Failures

POEM has proved to be an effective salvage modality to treat these recurrences. A retrospective comparison of POEM for treatment naïve AC versus prior-treatment-failures showed no significant difference in technical and clinical success rates, complications, and operative times between the two groups.[32] An international multi-center study of 51 patients undergoing POEM for post-Heller's myotomy with recurrent AC showed excellent technical and clinical success rates of 100% and 94%, respectively. AEs were encountered in 13%.[33] A large Chinese single-center retrospective study of >1300 patients including 245 patients with prior treatment failure status showed 'prior treatment' as an independent predictor for clinical failure during follow-up (Hazard ratio 1.90, $P = 0.002$; Cox regression).[34] In another international

multicenter case-controlled study of 181 patients comparing POEM for treatment naïve vs previous failed LHM, success rates, and AE were similar in both groups but post-LHM group showed poorer outcomes during follow-up (81 vs 94%, $p = 0.01$).[35] These results suggest that although POEM is safe and effective in treatment failures, the results may be inferior and may reflect disease progression in these patient groups. A study reporting pediatric achalasia patients revealed comparable results in both groups,[36] also suggesting that duration and natural disease progression could be additional factors responsible for successful outcomes. Endoluminal functional luminal imaging probe (EndoFLIP) has been evaluated as a predictor of response after POEM. A distensibility index (DI) < 7 has been shown to predict incomplete response.[37]

Per Oral Endoscopic Myotomy Compared with Other Treatment Modalities

POEM is the preferred therapy in patients with SEDs and type III AC. As reported in the earlier section, excellent outcomes have been consistently documented in several systematic reviews and metanalyses.[27,28] A retrospective multi-center study comparing POEM versus LHM for type III AC reported significantly superior clinical outcomes (98% vs 80.8%, $P < 0/01$), reduced procedural duration (102 min vs 264 min) and significantly few AEs (6% vs 27%, $P < 0.01$) for POEM as compared with LHM.[38]

For AC types I and II, outcomes of POEM and LHM are comparable. A systematic review and meta-analysis of 74 studies including 7792 patients compared POEM to LHM and reported predicted dysphagia improvement 93.5% for POEM and 91% for LHM at 12 months and 92.7% and 90%, at 24 months, respectively. Incidence of GER, however, was higher in patients undergoing POEM (odds ratio [OR] 1.69, 95% CI 1.33–2.14, $P < 0.0001$).[39]

In a multicenter prospective trial, Werner and colleagues[23] randomized 221 patients to POEM (112) or LHM plus Dor fundoplication (109), and reported comparable clinical success at 2-year follow-up (83.0% POEM and 81.7% LHM [difference, 1.4 percentage points; 95% CI, −8.7 to 11.4; $P = 0.007$ for noninferiority]). GER was more common in the POEM group as measured at 3 months (57% POEM vs 20% LHM, OR 5.74; 95% CI, 2.99 to 11.00) and at 2 years (44% vs 29%, OR 2.00; 95% CI, 1.03 to 3.85). Several other studies have also reported comparable short- and medium-term success rates. POEM achieved shorter operative times, reduced blood loss, and less pain compared with LHM.[38,40–47]

POEM and PD have been less frequently compared. A meta-analysis including 66 studies and >6000 patients compared POEM to PD. Superior clinical success rates were reported for POEM as compared with PD at 12, 24, and 36 months (92.9%, vs 76.9%, $P = 0.001$; 90.6% vs 74.8%, $P = 0.004$; and 88.4% vs 72.2%, $P = 0.006$, respectively). Pooled OR for GER was higher with POEM (symptomatic—2.95, $P = 0.02$ and endoscopic—6.98, $P = 0.001$) whereas esophageal perforation (0.3% vs 0.6%, $P = 0.8$) and significant bleeding (0.4% vs 0.7%, $P = 0.56$) were comparable in both groups.[48] A randomized study comparing PD to POEM in 133 patients showed significant superior clinical success with POEM as compared with PD (92 vs 54%, $p < 0.01$) despite no differences in the integrated relaxation pressures (IRP) or median barium column height in both groups. GER was significantly more frequent after POEM (41 vs 7%, $p = 0.002$).[24] Two other studies have reported 91.8% versus 68% ($p = 0.002$) and 92.3 vs 57.5% ($p < 0.0001$) clinical success after POEM and PD, respectively. Higher frequency of GER symptoms at 1-year follow-up was reported after POEM as compared with PD.[49,50]

A network meta-analysis of 19 studies including 5 randomized trials and 4407 patients comparing POEM to LHM and PD reported highest dysphagia remission rates

after POEM as compared with LHM and PD (risk ratio [RR] = 1.21; 95% credible intervals [CIs] = 1.04–1.47 and RR = 1.40; 95% CIs = 1.14–1.79, respectively). However, higher postoperative GER was observed after POEM as compared with LHM and PD (RR = 1.75; 95% CIs = 1.35–2.03 and RR = 1.36; 95% CIs = 1.18–1.68, respectively). No major differences were seen between the LHM and PD arms.[51]

Gastro-esophageal reflux after per oral endoscopic myotomy

Incidence of post-POEM GER has been reported as high as 40-60% in recent literature.[11,13,22,23,25,39,51] GER is more frequent after POEM as compared with LHM or PD. An extensive meta-analysis of 74 studies (>7000 patients) compared POEM to LHM and reported higher risk of developing GER after POEM than after LHM on all measurable parameters–GER symptoms (OR 1.69, 95% CI 1.33–2.14, $P < 0.0001$), endoscopic evidence of erosive esophagitis (EE) (OR 9.31, 95% CI 4.71–18.85, $P < 0.0001$), and abnormal esophageal acid exposure (EAE) on pH testing (OR 4.30, 95% CI 2.96–6.27, $P < 0.0001$).39 Another meta-analysis evaluating 17 and 28 studies with 1542 and 2581 patients of POEM and LHM reported higher abnormal EAE (pooled rate estimate 39% vs 16.8%) and esophagitis (29.4% vs 7.6%) for POEM and LHM, respectively.[52] The Werner study reported a significantly higher incidence of GER in the POEM group as compared with LHM (57% vs 20%; OR, 5.74; 95% CI, 2.99 to 11.00 at 3 months and 44% vs 29%; OR, 2.00; 95% CI, 1.03 to 3.85 at 24 months, respectively). However, incidence of severe grade C/D esophagitis was low in both groups.[23]

POEM experts have described technical modifications to minimize GER occurrence after POEM. Gastric length of myotomy should be limited to <2 cm (ideally observed and confirmed by double endoscope transillumination technique), and the myotomy should be performed in a manner that spares the sling fibers of the LES, especially while performing a posterior myotomy.[53,54] In the absence of double scope transillumination, other measures should be undertaken to ensure the optimal length and direction of myotomy. Tanaka and colleagues[55] have reported the consistent presence of two perforator vessels identified during posterior POEM that mark the boundary between the circular and sling muscle fibers. The second perforating vessels also form the optimal limit of dissection on the gastric side. Maintaining the myotomy direction to the right of these perforators minimizes risk to the sling fibers and may help prevent GER. These techniques collectively can be termed as anti-reflux measures during POEM.

Other factors that have been implicated for post-POEM GER include length of esophageal myotomy–a shorter myotomy could reduce GER; however, reports are conflicting.[56–58] Similarly, anterior versus posterior approach and selective circular versus full-thickness myotomy have failed to show consistently significant differences in post-POEM GER.[59,60] Teitelbaum and colleagues[61] have reported that a DI < 6 mm^2/mm Hg was predictive of lower risk for GER.

A distinct peculiarity of post-POEM GER is that although most studies report high rates of abnormal EAE, endoscopic evidence of EE or symptomatic GER is significantly less frequent. Also, most GER is mild and easily treatable using proton pump inhibitors (PPI).[62,63] In the study by Kumbhari and colleagues,[13] although abnormal EAE was reported in 57.8%, EE was noted in only 23.2% and severe Grade C/D GER was seen in only 5.6%. In another multicenter Japanese study, GER was documented in 63% on pH but symptoms were observed in 14.8% and severe Grade C/D EE was seen in only 6.2%.[11] Repici and colleagues[52] reported GER in 39% on pH although EE, severe esophagitis, and symptoms were reported in 29.4%, 4.47%, and 19%, respectively. The Werner study confirmed that although GER was more frequent after POEM compared with LHM at 3 months, GER after LHM gradually

increased so that the difference was less significant at 2 years. Furthermore, at 2 years, severe esophagitis was infrequent and was comparable in both groups (5 and 6%, respectively).[23] A single-center study comparing POEM with LHM reported significant EAE post-POEM (48.4% vs 13.6%, $P < 0.001$), although symptomatic GER was not significantly different in the two groups (28% vs 14.9%, $P = 0.38$).[40] A retrospective cohort study evaluating long-term outcomes of post-POEM GER in 68 patients reported >50% GER at 12-month follow-up; however, GER was mild and PPI responsive in >95% of patients and no GER-related AEs were noted at 5-year follow-up.[64] Similar outcomes have been reported in a study with long-term follow-up.[25] Therefore, although POEM does seem to predispose to GER, the majority of cases are mild, nonerosive, and responsive to PPI therapy.

Anti-reflux Procedures after Per Oral Endoscopic Myotomy. Anti-reflux procedures have been reported for treatment of refractory post-POEM GER. Second-stage transoral incisionless fundoplication (TIF) for symptomatic post-POEM GER was reported in 5 patients. All patients could discontinue PPI at a mean of 27 months of follow-up.[65,66] There have been few case reports of subsequent laparoscopic fundoplication following POEM.[62]

Inoue and colleagues[67] reported safety and feasibility of a novel endoscopic partial fundoplication performed in conjunction with POEM (POEM + F) as a potential minimally invasive option to prevent post-POEM GER. The procedure involves performing a standard anterior full-thickness POEM at 12 o'clock followed by entry into the peritoneal cavity by dissecting and opening the overlying serosa over the gastric myotomy. The gastric fundus is folded and fixed to the distal end of the myotomy using endoclips and endoloop to create a partial wrap. At 3-month follow-up, an intact wrap was shown in 19/21 patients. Results of POEM + F were also evaluated at 1-year follow-up in a single-arm study published from the authors' group. Wrap integrity was confirmed in 82.6% and GER was identified in 11.1% patients at median 1-year follow-up, much lower than that reported for most POEM studies.[68] Longer-term outcomes are under evaluation.

Currently, there is a debate about whether ARP should be offered prophylactically at every POEM or whether it should be reserved for those who develop refractory GER following POEM. This presently remains an unanswered question. Toshimori and colleagues[69] have described an endoscopic fundoplication (POEF) performed as a second stage following a posterior POEM. Accurate pre-POEM identification of patients who are at risk of developing GER in the post-POEM period could help provide insights into these decisions.

In conclusion, POEM has shown excellent outcomes in all achalasia subtypes and SEDs. It is effective for naïve as well as recurrent AC after failed initial therapy. Outcomes of POEM are comparable to LHM and are superior to PD. Post-POEM GER occurs in a significant number of patients, although most of it is mild, nonerosive, and responsive to PPI therapy. ARPs for post-POEM GER have been described and are currently under evaluation.

GASTRIC PER ORAL ENDOSCOPIC MYOTOMY

Gastroparesis is a motility disorder defined as a clinical syndrome and objective evidence of delayed gastric emptying in the absence of mechanical obstruction. Characteristic features of gastroparesis include early satiety, postprandial nausea, vomiting, bloating, and abdominal pain.[70,71] Gastroparesis has shown to have a significant impact on morbidity and mortality, especially in diabetics making it crucial to manage

this condition appropriately.[71] Dietary modifications such as consuming small frequent low residue meals are not efficacious in all patients. Pharmacotherapy in the form of metoclopramide has been recommended for gastroparesis; however, data on its long-term efficacy are limited and are limited by its black box warning due to the risk of tardive dyskinesia.[72] Endoscopic management for gastroparesis has been studied more recently. Two randomized controlled trials showed that intra-pyloric botulinum toxin injection improved gastric emptying. However, symptom benefit was not evident. Therefore, intra-pyloric botulinum toxin injection is not recommended for the management of gastroparesis.[73] Endoscopic transpyloric stenting showed short-term efficacy but was limited by frequent stent migration up to 48%. The procedure therefore, has been considered as a temporizing measure to treat hospitalized patients, or to identify patients who may respond to durable pylorus-directed therapies.[74] Surgical or laparoscopic pyloroplasty is effective, however these procedures are invasive and can be associated with significant morbidity.[75]

This inspired Kawai and colleagues[76] to envision endoscopic myotomy of the pyloric sphincter based on the principles of SEMF which was subsequently performed and reported by Khashab and colleagues[4] G-POEM involves submucosal tunneling at the pylorus followed by a full-thickness short (2–3 cm) myotomy of the pyloric ring (**Fig. 3**).[8]

Currently, G-POEM has been performed and reported for medically refractory gastroparesis of all etiologies.

Outcomes of gastric per oral endoscopic myotomy

Technical Success

Data on G-POEM is still growing and is currently limited to observational studies and one randomized, sham-controlled trial (**Table 2**).[77–90] G-POEM is a complex procedure based on surgical principles and the mean procedure time for G-POEM ranges from 33 to 119 min indicative of its variable learning curve.[91] Procedure time has reduced as procedural proficiency has improved and was reported to be 43 min (34–56.5) in a 2022 multicenter study.[89] Technical success rates reported for G-POEM are high. A meta-analysis of ten studies of 292 patients from multiple

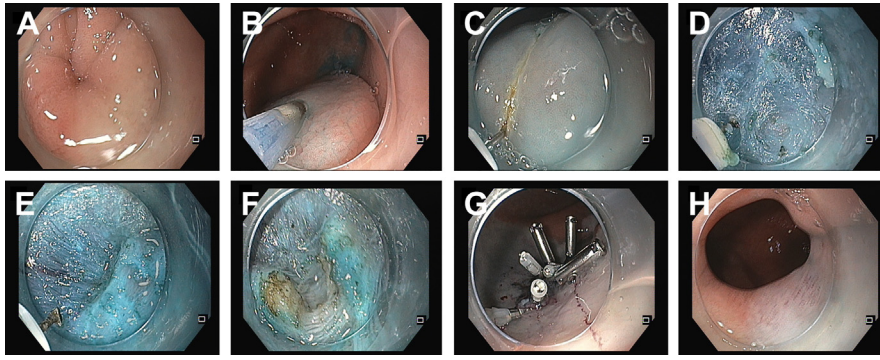

Fig. 3. G-POEM: (*A*) tight pyloric opening, (*B*) mucosal injection and submucosal cushion approximately 5 cm proximal to pyloric ring on posterior gastric wall, (*C*) mucosal incision, (*D*) submucosal dissection and tunneling perpendicular to circular muscle fibers, (*E*) duodenal mucosa visualized rising vertically beyond the pyloric ring, (*F*) short full-thickness pyloromyotomy, (*G*) mucosal incision closed using endoclips, and (*H*) opened-up pylorus.

Table 2
Outcomes for gastric per oral endoscopic myotomy

Study	Patients (N)	Technical Success (%)	Procedure Time (min)	Clinical Success (%)	Adverse Events	Follow-up (months)
Shlomovitz et al.[79]	7	100	90–120	6/7 (86)	1 bleeding (clips)	6.5 ± 2.1
Mekaroonkamol et al.[80]	3	100	74 (55–93)	3/3 (100)	None	3
Rodriguez et al.[81]	47	100	41.2 ± 28.5	31/47—(66)	1 death (cardiac disease, unrelated to procedure)	3
Dacha et al.[82]	16	100	49.7 ± 22.1	13/16 (81)	None	6
Gonzalez et al.,[83] 2017	29	100	47 (32–118)	3 m—23/29 (79%); 6 m—20/29 (69%)	1 bleeding (clips), 1 abscess (conservatively managed)	10 ± 6.4
Khashab et al.,[84] 2018	30	100	72 (35–223)	26/30 (86)	1 capnoperitoneum, 1 ulcer	5.5
Gonzalez et al.[85]	12	100	51 (32–105)	10/12 (85)	2 capnoperitoneum	5
Kahaleh et al.[86]	33	100	77.6 (37–255)	28/33 (85)	1 bleeding (clips), 1 ulcer	11.5
Xu et al.[87]	16	100	45.25 ± 12.96	13/16 (81.25)	NR	14.5
Mekaroonkamol et al.[88]	30	100	NR	23/30 (76.7)	NR	18
Malik et al.[89]	13	100	119 ± 23	GCSI and GES revealed statistically insignificant improvements; 11/13 patients reported feeling somewhat better on questionnaire	1 pulmonary embolism	6
Abdefatah et al.[90]	97	100	50 ± 13	73/97 (81.1%)	2 mild, 2 moderate—1 tension capnoperitoneum (needle decompression), 1 bleeding ulcer (endoscopic treatment)	36

Vosoughi et al.[91]	80	100	43 (34–56.5)	45/80 (56)	3 Capnoperitoneum (needle decompression), 1 mucosotomy, 1 thermal mucosal injury (clips)	12
Martinek et al.[92]	21	95.23 (20/21), 1 G-POEM unable to be completed due to severe SM fibrosis	76 ± 41	At 6 months—14/20 (70) vs 4/19 (22) in sham group. Patients from sham group when crossed over to G-POEM—9/12 (75)	2 serious AE related to procedure in G-POEM group—1 pyloric ulcer (required hospitalization managed conservatively), 1 mucosal injury (managed conservatively)	6

centers in 3 countries reported a 100% technical success rate.[91] These studies included patients who had undergone prior treatments including botulinum toxin injections (28.1%), gastric electrical stimulator (12.6%), transpyloric stenting (1.4%) and dilation (0.3%), and laparoscopic pyloric surgery (1.4%) which did not affect technical success. Similarly, a study on 80 patients reported a 100% technical success after patients had undergone botulinum toxin injection (35%) or transpyloric stenting (20%).[89]

Clinical Success

Clinical success with G-POEM has been reported in the form of symptomatic improvement, objective improvement in gastric emptying, and overall quality of life.

Symptoms. Symptomatic improvement has been assessed with standardized subjective criteria namely Gastric Cardinal Symptom Index (GCSI) comprising three symptoms: (1) post-prandial fullness/early satiety, (2) nausea/vomiting, and (3) bloating.[92] A randomized sham-controlled trial reported a 71% clinical success rate in the G-POEM group and 22% in the sham group. GCSI scores were reduced by 2.4 (95% CI 2–2.8) in the G-POEM group compared with 0.7 (95% CI 0–1.2) in the sham group.[90]

Uemura and colleagues[93] compared pre and post-G-POEM GCSI scores in patients across 10 studies and 281 patients in their meta-analysis of observational studies. All studies showed a decreased GCSI score, and the pooled mean difference was a statistically significant reduction of 1.76 points (95% CI 1.43, 2.08, $p = 0.0002$). This was consistent with findings reported by other reviews evaluating the effect of G-POEM on GCSI.[91,94] An international prospective trial reported a reduction in GCSI by 1.2 ± 1.3, $p < 0.001$ at 12 months, and a clinical success rate of 56.3% (95% CI 44.8–66.7).[89] Studies reported GCSI scores at different times in the follow-up period; however, an improvement in these scores was seen at 3, 6, 12, and 18 months.[93]

Abdominal pain is not assessed in the GCSI but can be a common symptom of gastroparesis. A study showed improvement in abdominal pain in 56% to 73% of patients following G-POEM when followed up for a mean of 11.5 months.[86]

Gastric Emptying Studies. Objective evaluation of gastric emptying using a 4-hour gastric emptying scintigraphy (GES) was also a marker of clinical success of G-POEM in several studies. Some variability has been reported in GES results with improvement seen in 70-100% of the study population.[87] One randomized sham-controlled trial showed a significant decrease in 4-h gastric retention in the G-POEM group compared with no change in the sham group. There was no correlation between GCSI and gastric retention at 3 months ($r = 0.15$, 95% CI –0.18 to 0.42).[90]

Ten observational studies individually showed an improvement in GES. When pooled together, they revealed a 26.28% (95% CI 19.74–32.83, $p < 0.0001$) reduction in gastric retention at 4 h following G-POEM.[93] Mohan and colleagues[95] reported an 85.1% pooled clinical success rate based on improvement in 4-h GES. This study also showed comparable improvement in 4-h GES with G-POEM (85.1%) and surgery (84%), ($p = 0.91$).

Other Outcomes. Endoscopic functional luminal imaging probe (EndoFLIP) measurements have revealed increased length, cross-sectional area (CSA), and distensibility of the pylorus in patients following G-POEM.[90] However, only increased CSA has been associated with better clinical outcomes.[87] Studies have also shown improvement

in quality-of-life (assessed by SF36 questionnaires) in 70-78% of patients. In addition, emergency room visits, gastroparesis-related hospitalization rate, and anti-emetic use significantly reduced following G-POEM as compared with controls.[86]

Patient Selection for Gastric Per Oral Endoscopic Myotomy

Gastroparesis is a complex clinical disorder and both impaired gastric dysmotility and pylorospasm play a variable role in its pathophysiology.[96] Impaired gastric motility is likely the predominant mechanism in diabetic gastroparesis, whereas pylorospasm may be an important factor in postoperative (after vagal injury or vagotomy) gastroparesis. Therefore, analyzing outcomes for G-POEM based on etiology of gastroparesis becomes crucial. Data regarding G-POEM are still emerging and are quite varied across studies. Predictors of poor outcomes after G-POEM identified are diabetes,[79,81] female gender,[81] higher BMI, history of psychiatric or pain medication use.[88] However, Mekaroonkamol and colleagues[86] reported similar benefits with G-POEM in diabetics and nondiabetics. Moreover, among diabetics, the baseline HbA1c levels did not influence outcomes. Longer duration of gastroparesis before G-POEM may have inferior outcomes at 12 months; however, this has not shown to influence outcomes at 1 month or 6 months. Vosoughi and colleagues[89] in their multicenter prospective study of 80 patients reported comparable clinical success with G-POEM at 12 months regardless of the demographics, etiology, and duration of gastroparesis. Investigators identified that a baseline GCSI score greater than 2.6 (OR = 3.23, $p = 0.04$) and a baseline gastric retention >20% at 4 hours (OR = 3.65, $p = 0.03$) was an independent predictor of clinical success at 12 months. Benefits of G-POEM were shown to be evident at 1-month post-procedure. Patients who had clinical improvement at 1-month post-procedure were significantly more likely (OR 8.75 [95% CI 2.9–26.38], $p < 0.001$) to have a sustained benefit at 12 months. A scoring system has been developed to predict clinical response to G-POEM based on symptom subsets among the GCSI and results of GES study (**Table 3**). It was validated in 46 patients and showed 93.3% sensitivity, 56.3% specificity, 80% PPV, 81.8% NPV, and 80.4% accuracy. Patients with a score >/2 were more likely to be responders at 3 years than those with a score < 2 (80% and 18%, respectively, $p = 0.0004$).[97]

Gastric Per Oral Endoscopic Myotomy versus Other Treatment Modalities

In medically refractory gastroparesis, G-POEM can be compared with gastric electrical stimulators and surgery. G-POEM has shown a 60% lower risk of clinical recurrence along with a higher 24-month clinical response rate (76.6% vs 53.7%).[86,98] G-POEM (4.3%) had fewer AEs than electric stimulators (26.1%), $p = 0.1$, and was effective across all types of gastroparesis whereas electric stimulators had limited

Table 3
Gastric per oral endoscopic myotomy patient selection predictive model scoring system

Criterion	Score
Nausea subscale < 2	+ 1
Satiety subscale >/4	+ 1
Bloating subscale > 3.5	+ 1
Retention at 4 hours > 50% on GES	+ 1

Data from Labonde A, Lades G, Debourdeau A, et al. Gastric peroral endoscopic myotomy in refractory gastroparesis: long-term outcomes and predictive score to improve patient selection. Gastrointest Endosc. 2022;96(3):500-508.e2.

benefit in patients with idiopathic gastroparesis.[98] G-POEM has shown comparable clinical success to surgical pyloroplasty based on GCSI scores (75.8% vs 77.3%, $p = 0.81$) and improvement in 4-h gastric emptying studies (85.1% vs 84%, $p = 0.91$).[95,99]

Adverse Events

G-POEM has been reported to have a low rate of AE at approximately 6-11%.[89,91,95] The most common AEs following G-POEM are bleeding (32%), abdominal pain (30%), and capnoperitoneum (24%). In one randomized sham-controlled study, seven AE were reported in the G-POEM group compared with three in the sham group. Of these seven, three were related to the G-POEM procedure, gastric ulcer ($n = 1$), mucosal injury ($n = 1$), and delayed dumping syndrome ($n = 1$).[90] Bleeding can usually be managed with proton pump inhibitor therapy and/or endoscopic therapy. Capnoperitoneum is often managed conservatively and resolves spontaneously and rarely needle decompression can be used to treat severe cases.[86] Two deaths have been reported in G-POEM-related studies; however, none of them were related to the procedure.[93]

Data on G-POEM has grown over the last few years as it continues to get incorporated in clinical practice. G-POEM has shown robust efficacy in gastroparesis of all etiologies. Results with G-POEM are comparable to surgical pyloroplasty and are superior to gastric electrical stimulators with an excellent short- and long-term safety profile. Appropriate patient selection is crucial to improve clinical success rates and the development and validation of predictive models is essential.

DIVERTICULAR PER ORAL ENDOSCOPIC MYOTOMY

Diverticular or D-POEM is an inclusive term for endoscopic myotomy performed for esophageal diverticula (ED). It has been reported for Zenker's diverticula, epiphrenic diverticula, and mid esophageal diverticula.

Zenker's Per Oral Endoscopic Myotomy or submucosal tunneling endoscopic septum division

Zenker's diverticulum (ZD) is a rare clinical condition characterized by sac-like herniation of the mucosal and submucosal layers originating from the pharyngoesophageal junction due to a defect in the cricopharyngeus muscle. Traditionally ZD are treated by surgical resection of the diverticulum with cricopharyngeal myotomy; however, morbidity and mortality rates have been reported to be 30% and 3%, respectively.[100–102] Flexible endoscopic cystotomy (FES) soon became the preferred treatment modality which was attributable to its preferable safety profile, shorter procedure time and length of hospital stay.[103] FES however carried the limitation of recurrence rates much higher than surgery (11%) possibly due to incomplete division of the septum.[103,104] This led to the conceptualization of submucosal tunneling endoscopic septum division (STESD or Z-POEM).[5] This technique allowed for a longer septotomy length which is a prognostic marker of septotomy success.[105]

Literature on outcomes after Z-POEM is still emerging (**Table 4**).[106–109] An international multicenter study of 75 patients undergoing Z-POEM for mean ZD size 31.3 ± 1.6 mm reported 97.3% technical and 92% clinical success rates. AEs were low at 6.7% which included bleeding (1) and perforation (4). Length of hospital stay was mean 1.8 ± 0.2 days. Patients were followed up for a mean 291.5 days (interquartile range [IQR] 103.5–436) and one recurrence was noted. Dysphagia scores reduced from mean 1.96 to 0.25 ($P < 0.0001$).[106] Another study of 22 patients with symptomatic ZD (mean size 30 mm [IQR, 24–40]) undergoing Z-POEM reported

Table 4
Diverticular per oral endoscopic myotomy (diverticular per oral endoscopic myotomy and Z-per oral endoscopic myotomy)

Study	Procedure Details	Patients (*N*)	Clinical Success	Adverse Events	Follow-up (Median)
Yang et al.[109]	Z-POEM	75	92%	6.7%	291.5 d (IQR 103.5–436)
Budnicka et al.[110]	Z-POEM	22	90.9%	13.6%	266 d (IQR 213–306)
Sanaei et al.[111]	Z-POEM	32	96.7%	12.5%	166 d (IQR 39–566)
Kahaleh et al.[112]	Z-POEM vs Septotomy	Septotomy—49, Z-POEM—52	Septotomy—84%, Z-POEM—92%	Septotomy—30.6%, Z-POEM—9.6%	Mean, Septotomy—7.9 m, Z-POEM—3.4 m
Yang et al.[114]	D-POEM, esophageal diverticula	11 (ZD—7, Mid esophagus—1, EED—3)	100%	0%	145 d (IQR 126–273)
Nabi et al.[115]	D-POEM, EED	13	84.6%	7.69% (1 AE requiring surgery)	25 m
Zeng et al.[116]	D-POEM	10 (ZD—2, mid-esophagus—5, EED—3)	90%	0%	11 m (IQR 10.25–17.25)
Maydeo et al.[117]	D-POEM	25 (ZD—20, EED—5)	86%	0%	12 m

100% technical and 90.9% clinical success rates. At a mean follow-up duration of 266 days, no recurrences were seen. AEs included mild (2) and severe (1) subcutaneous emphysema.[107]

A recent study of 32 patients looked at outcomes of Z-POEM after failed prior interventions such as surgery (10), rigid (9) and flexible endoscopy (13), Z-POEM (3), and Botulinum toxin injection (1). Overall technical success rate was 93.8%. Two technical failures occurred due to presence of extensive fibrosis preventing the creating of a submucosal tunnel. The clinical success rate after excluding technical failures was 96.7%. Ten patients followed up for at least 12 months and did not have symptom recurrence. AE rate was 12.5% (two inadvertent mucosotomies and two leaks), none of which were severe or fatal.[108]

A multicenter retrospective study compared outcomes of Z-POEM with FES in 101 patients and reported comparable dysphagia relief in both arms although AEs were significantly lower in the Z-POEM group (9.6% vs 30.6%, $p = 0.02$).[110]

Diverticular Per Oral Endoscopic Myotomy

Diverticular per oral endoscopic myotomy (D-POEM) is similar to Z-POEM and has been performed for epiphrenic and mid-esophageal diverticula. Esophageal epiphrenic diverticula (EED) are rare pulsion-type outpouchings at the lower end the esophagus, most commonly occurring in association with AC. Data on outcomes for D-POEM are scarce and include studies with small sample sizes due to the low incidence of EEDs (see **Table 4**).[111–114] Yang and colleagues[111] studied 11 patients undergoing D-POEM for ZD, mid-esophageal and epiphrenic diverticula. Technical success was achieved in 10/11 (91%) and clinical success was reported in 10/10 (100%) patients with mean dysphagia score decreasing from 2.1 to 0.1 ($p < 0.001$). No AEs were reported. A retrospective study of 13 patients who underwent D-POEM for EED reported a technical success rate of 12/13 (92.3%). At 25-month(-median) follow-up, clinical success was achieved in 84.6% cases. Mean integrated relaxation pressures reduced significantly after D-POEM (25.80 ± 13.24 vs 9.40 ± 3.10, $p = 0.001$). There was one AE requiring surgical intervention.[112] A study by Zeng and colleagues[113] reported patients with ZD (2), mid-esophageal diverticulum (5) and EED (3) who underwent D-POEM. Technical success rate was 100%, clinical success achieved in 9/10, symptomatic score reduced from 2.5 to 1 ($p = 0.007$) during a median follow-up of 11 (IQR 10.25–17.25) months. A single-center study reported outcomes of 20 ZDs and 5 EEDs treated by Z-POEM or D-POEM and reported 86% clinical response at 12-month follow-up.[114]

Nevertheless, additional safety data are needed before D-POEM becomes standard of care for all patients with esophageal diverticula. It must be kept in mind that ED is more commonly seen in the elderly, who may harbor significant additional comorbidities. FES is technically easier and quicker compared with D-POEM and therefore the benefits of a more invasive procedure should be carefully weighed against the potential consequences.

PER-RECTAL ENDOSCOPIC MYOTOMY

Hirschsprung's disease (HD) is a congenital disorder characterized by the absence of intrinsic ganglion cells in the submucosal and myenteric plexuses of the hindgut. Single or multistage surgical or laparoscopic pull-through procedures have been the standard of care for HD for several decades. However, there is considerable morbidity associated with these surgeries, especially anal incontinence, fecal soiling, enterocolitis, and poor quality of life.[115,116]

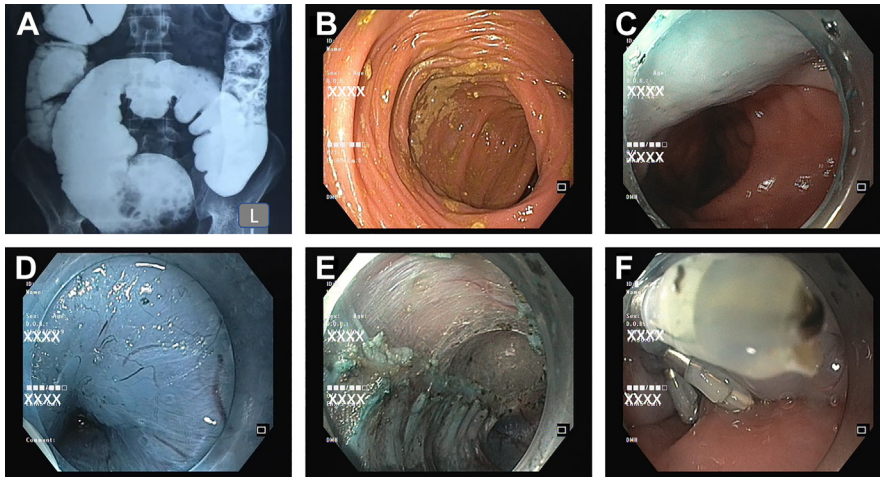

Fig. 4. PREM: (*A*) barium enema showing dilated proximal colon with spastic distal segment in a case of HD, (*B*) endoscopic view of dilated proximal colon, (*C*) submucosal injection and cushion, (*D*) submucosal tunneling in oral direction following horizontal mucosal incision just proximal to anal verge, (*E*) full-thickness myotomy in aboral direction, (*F*) mucosal incision closure using endoclips.

PREM was conceptualized based on the principle of POEM wherein a myotomy of the spastic bowel segment leads to relief of the functional obstruction.[6] Optimal preoperative mapping of the aganglionic segment is mandatory before planning PREM and can be performed using suction EMR biopsies that include the deep submucosal layer in the biopsy specimen.[117,118] The PREM procedure involves creating a retrograde submucosal tunnel starting at the anorectal junction extending proximally of a predetermined length based on the pre-PREM mapping biopsies, and performing a full-thickness myotomy, which must necessarily include the internal anal sphincter (**Fig. 4**).[6,119]

Data on PREM has been limited to case reports and case series. To date, it has been performed for infantile, pediatric, and adult HD.[6,117,120] A case series on nine patients of median age 4 years (range, 1–24) undergoing PREM for HD reported technical success of 100%. Mean aganglionic segment length was 6.3 (±4.4) cm. No periprocedural AE's or new-onset incontinence was observed. Patients were followed up for a median 17 months (IQR 11–35) and stool frequency improved from pre-PREM 1 in 4.4 (±1.5) days to post-PREM 1 in 1.2 (±0.4) days (P = 0.0004). Laxative usage reduced from pre-PREM mean 5.4 UL (±4.9, range 2–18) to post-PREM mean 0.4 UL (±0.7, range 0–2) (P = 0.0002). Laxative could be discontinued in six patients, whereas a dose reduction of > 50% was seen in the remaining three.[119] A recent case report showed safety and efficacy of PREM after failed surgical myectomy (Lynn procedure) for a 9-year-old with HD.[121] Further studies on this topic are necessary to establish the role of PREM in the management of HD.

SUMMARY

In conclusion, the SEMF technique has provided access to the muscle layer of the bowel wall and can be used to perform a minimally invasive endoscopic myotomy of spastic segments in the GI tract. The concept has been used from the esophagus to the anus in the form of various procedures which have been described and named

accordingly. Esophageal POEM is the index procedure in this group and has proved to be an effective procedure for the treatment of AC. It is useful for all AC subtypes and is effective to treat recurrences. Although post-POEM GER remains a concern, the majority of cases are mild, nonerosive and responsive to PPI therapy. G-POEM is an upcoming and potentially effective treatment for patients with refractory gastroparesis. Optimal patient selection remains the current challenge for G-POEM. Z-POEM, D-POEM, and PREM have shown impressive outcomes for patients with ZD, EED, and HD, respectively, although these procedures are relatively new, less studied, and require further evaluation.

CLINICS CARE POINTS

- Submucosal endoscopy using a mucosal flap valve technique provides safe access to the muscle layer of the bowel wall and can be used to perform a minimally invasive endoscopic submucosal tunneling myotomy of spastic segments in the GI tract.
- Tunneling myotomy for spastic gastrointestinal (GI) segments has been described for achalasia cardia (AC) (per oral endoscopic myotomy [POEM]), refractory gastroparesis (G-POEM), Zenker's and esophageal diverticula (Z-POEM and D-POEM, respectively), and Hirschsprung's disease (per-rectal endoscopic myotomy [PREM]).
- POEM is a safe and effective procedure for the treatment of AC. It is useful for all AC subtypes and for treating recurrent AC. Outcomes of POEM are comparable to LHM for AC types I and II and superior to PD. POEM is superior to all other modalities for type III AC and spastic esophageal disorders.
- Gastro-esophageal reflux frequently occurs after POEM, but is mostly mild, nonerosive, and responsive to PPI therapy.
- G-POEM is an upcoming and potentially effective treatment for carefully selected patients with refractory gastroparesis. Optimal patient selection remains the current challenge.
- Z-POEM, D-POEM, and PREM have shown impressive outcomes for patients with Zenker's diverticulum, esophageal epiphrenic diverticula, and Hirschsprung's disease, respectively. They have been newly described and require further evaluation in larger studies.

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