



Third-Space Endoscopy: Recent Updates

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Abstract

Third space or submucosal space is a potential space which on expansion allows the endoscopist to execute a multitude of therapeutic procedures for various gastrointestinal diseases like achalasia, subepithelial tumors, Zenker's diverticulum, and refractory gastroparesis. Third space was first utilized for performing endoscopic myotomy in cases with achalasia cardia about a decade ago. Since then, the field of submucosal endoscopy has witnessed an exponential growth. The present review focuses on recent advances in the field of third-space endoscopy. With regard to per-oral endoscopic myotomy (POEM) in achalasia cardia, several recent studies have evaluated the long-term outcomes of POEM, compared endoscopic myotomy with pneumatic dilatation (PD) and surgical myotomy, and evaluated the outcomes of short- versus long-esophageal myotomy. In addition, the utility of multiple dose antibiotic prophylaxis to prevent infections after POEM has been questioned. Overall, the results from these studies indicate that POEM is a durable treatment modality, equally effective to Heller's myotomy and superior to PD. With regard to gastric-POEM (G-POEM), recent studies suggest only modest efficacy in cases with refractory gastroparesis. Therefore, quality studies are required to identify predictors of response to optimize the outcomes of G-POEM in these cases. Another third-space endoscopy procedure that has gained popularity is endoscopic division of septum in cases with esophageal diverticula including Zenker's POEM and epiphrenic diverticula POEM (Z-POEM and D-POEM, respectively). The technique of diverticulotomy using the principles of submucosal endoscopy appears safe and effective in short term. Data on term outcomes are awaited and comparative trials with flexible endoscopic myotomy required. Per-rectal endoscopic myotomy (PREM) is the most recent addition to third space endoscopy procedures for the management of short-segment Hirschsprung's disease. Limited data suggest that PREM may be a promising alternative surgery in these cases. However, quality studies with long-term follow-up are required to validate the outcomes of PREM.

Keywords

- ▶ submucosal endoscopy
- ▶ achalasia
- ▶ gastroparesis
- ▶ Zenker's diverticulum

Introduction

Recent advances in therapeutic endoscopy have allowed minimally invasive management of many gastrointestinal

(GI) diseases. Third-space endoscopy or submucosal endoscopy is one such innovation that has amplified the therapeutic armamentarium for various GI diseases like achalasia, refractory gastroparesis, subepithelial lesions, esophageal

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diverticula, and others. Just over a decade old, the field of third-space endoscopy continues to evolve. As such, new pieces of information are being generated and published at a fairly rapid pace.

The purpose of this review is to provide recent updates in third-space endoscopy that may impact the routine clinical practice.

Per-Oral Endoscopic Myotomy

Long-Term Outcomes of Per-Oral Endoscopic Myotomy

Multiple studies have confirmed the safety and efficacy of per-oral endoscopic myotomy (POEM) in achalasia at least during short-term follow-up. More recent studies suggest that the response to POEM may be durable as well.¹⁻⁹ Campagna et al evaluated the outcomes of POEM in 100 patients who completed ≥ 4 years of follow-up.⁶ Clinical success was recorded in 88% and objective evidence of gastroesophageal reflux disease (GERD) found in one-third of cases on long-term follow-up. In another large (610 patients), single-center study by Modayil and colleagues, clinical success at ≥ 5 years was more than 90%, confirming the durability of POEM in cases with achalasia cardia.⁸ Of note, reflux esophagitis (mostly mild) was detected in almost half of the patients in this study. Similar results have been provided in other studies where the clinical success has been reported in 80 to 95% of cases at a mean follow-up of ≥ 4 to 5 years.^{3-5,7}

Short versus Standard Esophageal Myotomy

POEM is an established treatment modality for achalasia and other allied esophageal motility disorders. Updated guidelines and position statements from various GI societies

have incorporated POEM along with pneumatic dilatation (PD) and Heller's myotomy (HM) in the management algorithm for achalasia cardia.¹⁰⁻¹³ Since the initial description of POEM by Inoue and colleagues nearly a decade ago, the technique of POEM has largely remained unchanged.¹⁴ The standard technique of POEM involves a 8- to 10-cm long esophageal myotomy and 2 to 4 cm of gastric myotomy. While, a short gastric myotomy (<1.5–2 cm) has been shown to increase the risk of future relapses,¹⁵ the requirement of a long (8–10 cm) esophageal myotomy has been questioned in recent studies.¹⁶⁻²⁰ Overall, three randomized trials and two retrospective studies have compared the outcomes of short versus standard or long esophageal myotomies in cases with idiopathic achalasia (► **Table 1**). The results from these trials suggest that there is no significant difference in clinical efficacy between the two groups. Moreover, the procedure time was consistently shorter in the short myotomy group in all the studies. In a systematic review and meta-analysis including five studies with 474 patients, there was no difference in clinical success, symptomatic reflux, and overall adverse events between the two groups. However, the incidence of postoperative erosive esophagitis was lower in the short myotomy group (odds ratio [OR] = 0.50, 95% confidence interval [CI]: 0.24–1.03; $p = 0.06$).²¹

The results of these studies suggest that a short esophageal myotomy may be sufficient in cases with type-I and -II achalasia. However, caution is advised while extrapolating the results to type-III achalasia and other nonachalasia spastic esophageal motility disorders where long esophageal myotomies are recommended.^{22,23} Similarly, the impact of length of esophageal myotomy on the incidence of postoperative GERD needs further evaluation.

Table 1 Short versus standard esophageal myotomy in achalasia cardia

Study (year)	Study design	n (S vs. L)	Myotomy length (cm)	Procedure duration Mean (SD/ range)	Adverse events (%)	Erosive esophagitis (%)	Reflux symptoms (%)	pH GERD (%)	Success (%)	Follow-up in months (range)
Khashab et al (2018) ²²	RCT	62 58	7 (total) 12	43.6 (17.0) 54.8 (17.3)	NR	35 vs. 33.9% (not known how assessed)			100 98.3	6 6
Li et al (2019) ¹⁷	R	63 63	6–8 (tunnel) 10–14	39.5 (21–74) 49.2 (23–120)	9.5 33.3	9.5 12.7	9.5 12.7	NR	98.2 98.2	20.1 (6–48) 23.6 (6–48)
Huang et al (2020) ¹⁸	R	36 74	≤ 7 (total) >7	46.6 (18.5) 62.1 (25.2)	8.3 8.1	2.8 5.4	NR	NR	94.4 91.9	26.8 (8–54.3) 29.5 (6–58.8)
Gu et al (2021) ¹⁹	RCT	46 48	3–4 (esophageal) 7–8	31.2 (15.3) 45.6 (16.2)	0 2.2	8.7 14.6	15.2 22.9	23.9 43.8	95.6 93.8	12 12
Nabi et al 20 (2021)	RCT	34 37	≤ 3 (esophageal) ≥ 6	44.03 (13.78) 72.43 (27.28)	11.8 10.8	32.3 48.6	NR	25.9 40	93.5 97	12 12

Abbreviations: GERD, gastroesophageal reflux disease; L, long; NR, not reported; R, retrospective; RCT, randomized controlled trial; S, short; SD, standard deviation.

Per-Oral Endoscopic Myotomy versus Pneumatic Dilatation

PD and Heller's myotomy (HM) have been the mainstay of treatment in achalasia cardia for several decades. Several randomized trials have concluded that the outcomes of graded dilatation are similar to HM.²⁴ With the introduction of POEM, the focus of recent research has diverted toward comparative evaluation of POEM with other treatment modalities. Several retrospective studies have concluded the superiority of POEM over PD.²⁵⁻²⁸ In a recent meta-analysis including 66 studies, clinical success with POEM was superior to PD at 12, 24, and 36 months (92.9, vs. 76.9% $p = 0.001$; 90.6 vs. 74.8%, $p = 0.004$; 88.4 vs. 72.2%, $p = 0.006$, respectively). In the only randomized trial published till date, 133 patients with achalasia were randomized to POEM or PD.²⁹ The primary outcome of this study was clinical success (Eckardt's score ≤ 3) at 2 years of follow-up. Clinical success was significantly higher in the POEM group (92 vs. 54%). However, reflux esophagitis was also significantly higher in the POEM arm (41 vs. 7%). Some of the limitations of this otherwise well-conducted randomized trial are worth mentioning.³⁰ PD was performed using 30- to 35-mm balloons instead of 30- to 35- to 40-mm balloons. Younger patients may require additional dilatation using a larger (40 mm) balloon for optimum response. Despite of lower clinical success, the barium emptying was intriguingly better in the PD arm, generating questions regarding the mechanisms of failure in the dilatation arm. Nevertheless, this randomized trial is the most robust comparison between the two modalities.

Per-Oral Endoscopic Myotomy versus Heller's Myotomy

Endoscopic and surgical myotomies have been compared one randomized study and several retrospective cohort studies.³¹⁻⁴¹ Overall, the bulk of data suggest that both modalities provide with similar clinical success. A recent systematic review and meta-analysis comparing both the modalities concluded that POEM is more effective than laparoscopic Heller's myotomy (LHM) in relieving dysphagia in short term.⁴² The downside of POEM is higher reflux rates as compared with HM with fundoplication.^{42,43} A noteworthy flaw of the published systematic reviews is lack of randomized trials which impedes the generation of firm conclusions. Werner and colleagues conducted a noninferiority randomized trial including 221 patients.³⁸ In this randomized trial, POEM was noninferior to LHM plus Dor's fundoplication in controlling symptoms of achalasia at 2 years (83 vs. 81.7%). Gastroesophageal reflux was more common among patients who underwent POEM (44 vs. 29%).

Per-Oral Endoscopic Myotomy and Prophylactic Antibiotics

Infectious complications are uncommon after POEM. Nevertheless, prophylactic antibiotics are commonly administered for a variable duration to prevent infection-related adverse events after POEM and other third-space endoscopy

procedures. In the absence of quality evidence, considerable variations exist with regard to the duration of antibiotic prophylaxis. In a first, Repici and colleagues evaluated the role of prophylactic antibiotics in preventing infectious complications after POEM. In this study, the authors randomized 124 patients to single-dose antibiotic (intravenous [IV] cefazolin) or multiple-dose antibiotic (IV cefazolin on day 1 followed by oral amoxicillin/clavulanate for 3-days) groups. None of the patients developed fever in either groups. There was no difference between the groups with regard to systemic inflammation (white blood cells and C-reactive protein), immune response (interleukin [IL]-6, IL-1b, and tumor necrosis factor [TNF]-a), and microbial translocation (lipopolysaccharide binding protein and sCD14). Blood cultures were transiently positive in three patients including one in single-dose group and two in multiple-dose group. Overall, the results of this randomized trial question the utility of multiple doses of antibiotics to prevent infections after POEM. Besides this study, several ongoing trials are evaluating the role of prophylactic antibiotics in this setting (NCT03784365 and NCT03404739). If similar results are reproduced in these trials, single shot of antibiotic prophylaxis would allow reduction in the antibiotic usage in these cases.

Gastric Per-Oral Endoscopic Myotomy

Gastroparesis is a chronic debilitating disease characterized by a myriad of symptoms like nausea, vomiting, early satiety, abdominal discomfort, and others. In about a quarter of patients, gastroparesis may be refractory to nutritional and pharmacological therapies. The ideal management strategies are not clear in this subgroup. Per-oral endoscopic pyloromyotomy or gastric POEM (G-POEM) is a recent addition to the endoscopic armamentarium for the management of refractory gastroparesis.⁴⁴⁻⁴⁷ Overall, the pooled clinical response rate of G-POEM in the initial studies was 84% (95% CI: 77-89%).⁴⁸ However, the limitations of the initial studies include small sample size, retrospective design, and short follow-up periods. More recently, Vosoughi and colleagues evaluated the outcomes of G-POEM in a well-conducted, prospective, multicenter study.⁴⁵ This study included 80 patients with refractory gastroparesis. The clinical success at 12 months was 56% (95% CI: 44.8-66.7). The independent predictors of clinical success were baseline gastric cardinal symptom index (GCSI) score >2.6 , baseline gastric retention $>20\%$ at 4 hours and early response to G-POEM at 1-month. In concordance to this trial, the clinical response in another multicenter study from France was 66% at 1-year.⁴⁷ Overall, the results from the more recent studies highlight that G-POEM has a modest efficacy in cases with refractory gastroparesis. (Table 2)

In an attempt to address the suboptimal outcomes with the conventional G-POEM which involves single pyloromyotomy, Abdelfatah and colleagues evaluated the short-term outcomes with double pyloromyotomy.⁴⁹ The clinical response was better in the double myotomy (86%) group as compared with single myotomy (67%). The shortcomings of

this study is retrospective design and short follow-up duration (6 months).

In conclusion, the enthusiasm generated with initial studies which depicted a relatively high clinical success (80–85%) has been somewhat dampened by some of the newer studies. The disparate outcomes in recent studies also underscore the need of quality trials with long-term follow-up and recognition of preoperative predictors of clinical response. Whether, Endo-functional lumen imaging probe (FLIP) will improve the preoperative prediction of clinical response remains to be seen in future studies.

Per-Oral Endoscopic Myotomy for Esophageal Diverticula: Zenker's diverticulum and Epiphrenic diverticulum

Esophageal diverticula (ED) are uncommon with a reported prevalence of 0.06 to 4%. The three main types of ED include pharyngoesophageal diverticulum or the Zenker's diverticulum (ZD), epiphrenic diverticulum, and midesophageal or Rokitansky's diverticulum. The management of ZD has evolved from rigid endoscopic septotomy to flexible endoscopic division of cricopharyngeal septum. However, recurrences may occur in up to one-third patients on long-term follow-up.⁵⁰ Incomplete septotomy has been proposed as

one of the major reasons for symptomatic recurrence after flexible endoscopic septotomy. Recently, third-space endoscopy has been used for the management of ZD and termed as Z-POEM or submucosal tunneling endoscopic division of septum (STESD).^{51–56} Zenker's per-oral endoscopic myotomy (Z-POEM) allows for complete division of septum without undue risk of mucosal perforation. This in turn may reduce the risk of future recurrences. In recent studies, the clinical success with Z-POEM has been reported in more than 90% of cases (► **Table 3**).^{51,52} In a multicenter comparative study, clinical success was comparable between Z-POEM and flexible septotomy ((92.7 vs. 86.7%).⁵³ Of note, long-term follow-up studies are lacking with regard to Z-POEM. In addition, randomized studies are required before concluding the superiority of Z-POEM over flexible endoscopic septotomy (**Table 3**).

Besides ZD, endoscopic division of septum has also been utilized in cases with epiphrenic diverticula and termed as diverticular per-oral endoscopic myotomy (D-POEM).^{57–60} The technique of D-POEM has been described in detail by the authors of this review.⁶¹ The standard technique of D-POEM involves division of diverticulum septum along with lower esophageal sphincter (LES) myotomy in cases with coexisting achalasia cardia. Alternatively, LES myotomy alone has also been found to be successful in relieving symptoms in cases with epiphrenic diverticula.^{59,62} The fact that majority

Table 2 Recent studies evaluating the outcomes of G-POEM in refractory gastroparesis

Study (year)	n	Technical success (%)	Clinical success (%)	Follow-up (mo)	Adverse events (%)
Pioppo et al (2021) ⁴⁴	102 (G-POEM:39, surgery: 63)	100 100	92.3 82.5	5.5 15.6	13 33.3
Vosoughi et al (2021) ⁴⁵	80	100	56	12	6
Gregor et al (2021) ⁴⁶	52	100	6 months: 58 12 months: 48	12	5.8
Ragi et al (2021) ⁴⁷	76	99.2	65.8	12	6

Abbreviation: G-POEM, gastric per-oral endoscopic myotomy.

Table 3 Recent studies depicting the outcome of Z-POEM in cases with Zenker's diverticulum

Study (year)	Study design	n	Size (cm)	Clinical success (%)	Adverse events (%)	Follow-up
Yang et al (2020) ⁵¹	R, multicenter	75	3.1	92	6.7	291 days (IQR: 104–436)
Elkholy et al (2021) ⁵²	R, multicenter	24	4 (2–7)	95.8	None	10 months (IQR: 6–24)
Al Ghamdi et al (2021) ⁵³	R, multicenter	245 (Z-POEM: 119, FES: 86, rigid 40)	3.5, 2.9, 3.6	Z-POEM: 92.7, FES: 86.7, rigid: 89.2	Z-POEM: 16.8, FES: 2.3, rigid: 30	282 ± 300 days
Budnicka et al (2021) ⁵⁴	R, multicenter	22	3	90.9	13.6	266 days (IQR: 213–306)
Kahaleh et al (2021) ⁵⁵	R, multicenter	101 (Z-POEM: 52, septotomy: 49)	NR	Z-POEM: 92, septotomy: 84	Z-POEM: 9.6, septotomy: 30.6	3.4 months 7.9 months
Sanaei et al (2021) ⁵⁶	R, multicenter	32 (previously treated)	NR	96.7	12.5	166 days (IQR: 39–566)

Abbreviations: IQR, interquartile range; NR, not reported; R, retrospective; FES, flexible endoscopic septotomy; Z-POEM, Zenker's per-oral endoscopic myotomy.

of these diverticula have coexistent esophageal motility disorder with nonrelaxing LES supports this hypothesis. However, comparative trials are required between these two techniques.

Per-Rectal Endoscopic Myotomy

Hirschsprung's disease (HD) is a congenital motility disorder of intestine characterized by the absence of enteric ganglion cells.⁶³ HD usually involves distal colon (rectosigmoid, 80–85%) and results in functional obstruction of large bowel. The standard of care for the management of HD is surgical resection of abnormally innervated segment of colon. Endorectal pull through and Duhamel's pull through procedures are the most commonly performed surgical procedures.⁶⁴ Recently, endoscopic management (utilizing the principles of third space endoscopy) has shown encouraging results in these cases.^{65–67} The technique of per-rectal endoscopic myotomy (PREM) as described by Bapaye and colleagues is discussed here.⁶⁵ The first and foremost step involves mapping of aganglionic segment by analyzing serial biopsies obtained using the technique of band assisted endoscopic mucosal resection (EMR) described by Nabi and colleagues.^{68,69} Although band EMR can be performed along different orientations along the rectosigmoid colon, posterior site should be avoided to circumvent submucosal fibrosis during posterior myotomy. The actual procedure is performed under general anesthesia with the patient in a semi-jackknife position. Overall, the steps of PREM are similar to esophageal POEM for achalasia cardia and include submucosal lifting injection just inside the anorectal junction, mucosal incision, submucosal tunneling, and myotomy followed by closure of incision. It is important to carefully preserve external anal sphincter to avoid postoperative fecal incontinence.

Bapaye and colleagues initially reported PREM in an adult patient with short-segment HD.⁶⁵ Subsequently, the authors reported the outcomes of PREM in nine patients with short-segment HD.⁶⁷ The mean age of patients was 7.5 ± 5.2 years and the average length of aganglionic segment was 6.3 cm. The procedure was successfully performed in all the cases with a mean operative time of 96.1 minutes. At a median follow-up of 17 months (range: 9–58 months), improvement in stool frequency was noted in all the cases. Anal stenosis was reported in one patient. There were no other major adverse events. Of note, fecal incontinence was not reported in any case. There are several potential advantages of PREM. The procedure is essentially similar to esophageal POEM and therefore, should not be technically challenging for those already performing third-space endoscopy procedures. However, the data on outcomes of PREM are limited to case reports and small case series. Therefore, quality studies with larger sample size and longer follow-up are required before adopting PREM in cases with HD.

Conclusion

Third-space endoscopy is a field under progress. Multiple therapeutic endoscopic procedures have been unwrapped

Table 4 Summary of recent updates in third space endoscopy

POEM in achalasia	
1.	Short and long esophageal myotomy provide with similar clinical success in type-I and -II achalasia
2.	Single-dose antibiotic prophylaxis may be sufficient in cases undergoing POEM for achalasia
3.	POEM is superior to pneumatic dilatation and equivalent to LHM with fundoplication. However, the incidence of GERD is higher after POEM
4.	POEM is a durable treatment modality in achalasia with efficacy of >90% at ≥4-years
G-POEM in refractory gastroparesis	
1.	G-POEM has modest efficacy in cases with refractory gastroparesis
2.	Double pyloromyotomy may potentially improve the outcomes with G-POEM. Randomized trials with long-term follow-up are required
POEM in esophageal diverticula	
1.	Z-POEM is a promising alternative to flexible endoscopic septotomy in Zenker's diverticulum
2.	D-POEM is effective in cases with epiphrenic diverticula. Septotomy may not be required in cases with co-existing esophageal motility disorders. However, comparative trials are required
PREM	
1.	PREM appears promising in cases with short segment Hirschsprung's disease. Quality studies are required before PREM can be recommended in routine clinical practice

Abbreviations: GERD, gastroesophageal reflux disease; G-POEM, gastric per-oral endoscopic myotomy; PREM, per-rectal endoscopic myotomy; Z-POEM, Zenker's per-oral endoscopic myotomy; D-POEM, diverticular per-oral endoscopic myotomy.

under the umbrella of submucosal endoscopy. Ample data are available regarding the safety and efficacy of some of the third-space procedures like POEM for achalasia and submucosal tunneling endoscopic resection (STER) for subepithelial tumors. On the other hand, several gaps exist in the current understanding with regard to others like G-POEM and PREM. Recent studies indicate that G-POEM may not be as effective as initially thought in cases with refractory gastroparesis and therefore, it is paramount to evaluate the predictors for clinical efficacy. Similarly, more data are required before incorporating PREM in the management algorithm for HD. Z-POEM appears promising in cases with ZD. However, randomized comparison trials are required between the time tested flexible endoscopic myotomy and Z-POEM. ► **Table 4** summarizes recent developments in the field of third-space endoscopy.

Conflict of Interest

None declared.

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