Per-oral Endoscopic Myotomy

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Abstract

Per-oral endoscopic myotomy, or POEM, has emerged as the most innovative therapy in achalasia after its introduction in 2008 and the most successful application of NOTES to date. Moreover, it is the prototype for the burgeoning field of tunnel endoscopy. It represents the endoscopic equivalent of laparoscopic Heller myotomy (LHM). POEM has been well validated in terms of impressive efficacy and notable safety and is being now performed all over the world by both surgeons and gastroenterologists. We will describe POEM development, patient evaluation, technique, postprocedural care, complications, accumulating longer-term data, comparison with other achalasia therapy, training concerns, and perspectives for the future.

Keywords

POEM · Achalasia · NOTES · Endoscopic myotomy · Heller myotomy · Submucosal tunnel

Abbreviations

AEs	Adverse events
ASGE	American Society for Gastrointestinal Endoscopy
CSA	Cross-sectional area
EFTR	Endoscopic full-thickness resection

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EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
GEJ	Gastroesophageal junction
GERD	Gastroesophageal reflux disease
HK	Hybrid knife
HM	Heller myotomy
LES	Lower esophageal sphincter
LHM	Laparoscopic Heller myotomy
MCT	Multicenter trial
NOTES	Natural orifice translumenal endoscopic surgery
PBD	Pneumatic balloon dilation
PIVI	Preservation and Incorporation of Valuable Endoscopic Innovations
POEM	Per-oral endoscopic myotomy
POET	Per-oral endoscopic tumor resection
POP	Per-oral pyloromyotomy
PPI	Proton pump inhibitor
STER	Submucosal tunnel endoscopic resection
TT	Triangle-tip

Introduction

Achalasia occurs about equally in both genders and across the age spectrum, with a reported annual incidence and prevalence of about 1/100,000 and 10/100,000 persons, respectively [1]. Patients typically have failure of relaxation of the lower esophageal sphincter (LES) and loss of peristalsis in the esophageal body. This results in dysphagia for liquids and solids, and variable chest pain, regurgitation, and weight loss. The diagnosis is suggested by a typical "bird's-beak" appearance on esophageal barium study and is usually confirmed by esophageal manometry, revealing abnormal relaxation of the LES and variable abnormalities of esophageal body peristalsis.

Development of POEM

Medical treatment of achalasia is generally ineffective and short-lived. More effective therapies are geared toward the weakening or ablation of the LES,

achieved by endoscopy (botulinum toxin injection and large-diameter balloon dilation), surgery (Heller myotomy), or endoscopic surgery (POEM). Until the introduction of per-oral endoscopic myotomy (POEM), Heller myotomy (HM) had been considered the most durable option in achalasia therapy, with a single anterior myotomy extending to the gastric cardia [2]. HM may be performed both laparoscopically and thoracoscopically and is usually combined with fundoplication [3].

Ortega first described a direct endoscopic myotomy in 1980 [4], but this was not adopted by others, perhaps related to concerns about reproducibility and safety. The Apollo group, a group that had been formed in the early 2000s to study NOTES applications, described endoscopic myotomy in a porcine model utilizing a needle knife to selectively cut the esophageal circular muscle layer after an initial mucosal incision 5 cm above the gastroesophageal junction (GEJ) after creation of a submucosal tunnel using a dilation balloon [5].

Inoue performed the first POEM in a human in 2008 and coined the term "POEM." His first

series of 17 subjects noted relief of dysphagia in most subjects with diminished LES pressure and no notable complications [6]. POEM was first performed outside Japan (at Winthrop University Hospital in the USA) in 2009 [7] and subsequently spread to many parts of the world. This was documented by the IPOEMS survey, an international survey sponsored by the Natural Orifice Surgery Consortium for Advancement and Research (NOSCAR) in 2012 [8]. Twenty centers were performing POEM worldwide in 2012. Sixteen of these centers (80%), including all high-volume centers (>30 POEMs), 7 from North America, 5 from Asia, and 4 from Europe, with a total number of 841 POEMs, participated in a comprehensive survey that detailed all aspects of POEM. The documented success led to a burgeoning increase in POEM operators and volume such that an estimated 4000 POEMs have been performed, with two Asian centers performing over 1000 each [9–11].

Within a few years of POEM's initial introduction, the NOSCAR POEM White Paper and the ASGE POEM PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) were published [12, 13]. These publications establish POEM not only as a primary therapy for achalasia patients without antecedent treatment, but also for those achalasia patients with prior endoscopic intervention (botulinum toxin injection and pneumatic dilation), prior HM, or previous POEM [14]. It was also determined that POEM was appropriate therapy for patients with spastic disorders of the esophagus and even "end-stage" achalasia patients with a sigmoid esophagus. A 2016 ASGE technology status evaluation report on POEM followed the comprehensive 2014 White Paper and 2015 PIVI documents, extending the literature review and assessment further to the current state of the art for this procedure [15].

Patient Evaluation

Patients should be evaluated and prepared as they would be for any elective surgery. Optimally, their esophageal motor disorder is well categorized by a high-resolution esophageal manometry and a timed barium swallow. Upper endoscopy should be performed earlier to exclude malignancy and again at the time of POEM to ensure esophageal clearance and allow lavage with topical antibiotics. Contraindications to the procedure include coagulopathy, severe pulmonary disease, evidence of mediastinal disease inflammation, prior thoracic-esophageal irradiation, and prior esophageal endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD) [8]. Patients should be prepared to stay at least overnight in the hospital.

POEM Technique

A suggested equipment list is presented in Table 6.1. Typically, a diagnostic gastroscope with accessory irrigation channel is used. Although Inoue initially advocated the use of an overtube and an oblique transparent distal cap attachment, most operators presently do not use an overtube routinely, and many utilize a conventional straight ESD cap (Fig. 6.1).

POEM represents an incisionless method to duplicate the traditional surgical myotomy by the ingenious concept of creating a submucosal tunnel that allows one temporary access to the mediastinum and esophageal muscle, including the LES, before the tunnel entrance is securely closed. Thus, the elements of POEM technique are as follows: (1) mucosal incision, (2) submucosal tunnel creation, (3) esophageal myotomy, (4) LES myotomy, and (5) entry point closure (Figs. 6.2 and 6.3). The entry point site varies depending on the indication, but is typically 10–15 cm proximal to the GEJ [6].

As demonstrated in the IPOEMS study, there is no consensus regarding orientation [8]. Some centers perform POEM anteriorly at the 2 o'clock position (in the usual convention of the posterior wall centered at 6 o'clock) as initially advocated by Inoue, although he appears to have recently changed his preferred approach to a posterior approach [11]. Other centers, such as Winthrop in New York and Zongshan in Shanghai, have favored a posterior orientation at

Table 6.1 POEM equipment

Equipment	Model No.
Vio 300D/200D (ERBE Tubingen, Germany) ERBE Jet Pump cartridge	20150-300
Hemostasis Coag grasper (4 mm) (Olympus, Center Valley, PA) Forceps hemostatic (5 mm) (Olympus, Center Valley, PA)	 FD-411UR FD-410LR
Injector single use (Max Force, Olympus, Center Valley, PA)	NM-400U0423
Disposable distal cap attachment 12.4 mm (Olympus)	D-201-11804
Endoscopic knife Triangle-tip knife (Olympus, Center Valley, PA) I-type hybrid knife (ERBE Tubingen, Germany) T-type hybrid knife(ERBE Tubingen, Germany)	 KD640-L 20150-261 20150-260
Decompression 14-gauge IV angiocath catheter Veress needle	
Submucosal injectate Indigo carmine Methylene blue	
Endoscopic suturing device (Overstitch, Austin Tx) Overstitch endoscopic suture system Overstitch cinch Overstitch polypropylene suture Overstitch tissue helix	 ESS-G02-160 CNH-GO1-000 PLY-G02-020 THX-165-028
Hemostatic clips Resolution 360 clip (Boston Scientific, Marlborough, MA) Resolution clip (Boston Scientific, Marlborough, MA) Instinct (Cook Medical, Winston Salem, NC) Quick Clip Pro (Olympus Center Valley, PA) Quick Clip 2 (Olympus Center Valley, PA)	 M00521230 M00522610 INSC-7230S HX-202UR HX-201UR-135
Endoflip catheter (EndoFLIP, Crospon Ltd, Galway, Ireland)	EF-325 N

**Fig. 6.1** Disposable distal cap attachment courtesy Olympus America (Center Valley, PA)

Fig. 6.2 Per-oral endoscopic myotomy technique (© S.N. Stavropoulos, Winthrop University Hospital, 2012). **a** Submucosal injection, and mucosal entry. **b** Creation of the submucosal tunnel. **c** Esophageal myotomy. **d** Lower esophageal sphincter and gastric cardia myotomy. **e** Closure of the mucosal incision
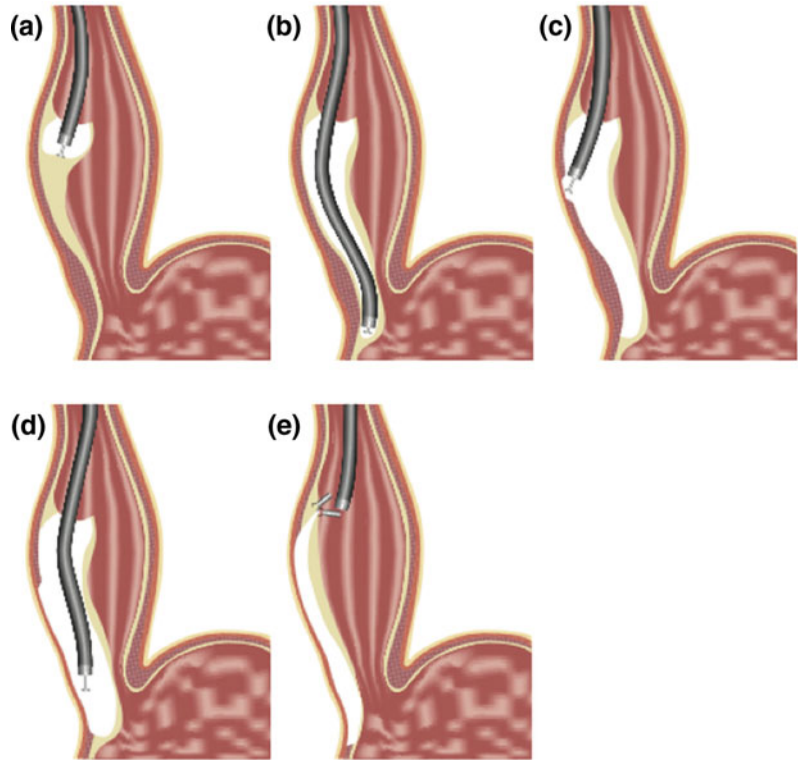
the 5 o'clock position. Various theoretical advantages have been proposed for one approach over the other. Since the posterior approach may cut some of the more powerful sling fibers of the LES compared to anterior myotomy, which is limited to the shorter and weaker clasp fibers, we have argued as early as 2013 that "one could speculate that centers employing a posterolateral approach (5 o'clock orientation), thus cutting a portion of the posterior sling fibers, may achieve higher efficacy in dysphagia relief but possibly at the cost of increased reflux" [8, 16].

It should be noted that in certain situations an anterior or posterior orientation is forced by a prior HM (in which case a posterior approach is selected to avoid postsurgical changes/scarring), or lesions such as ulcerations due to food stasis, pulsion diverticula, and severe angulation of the lumen. No prospective, randomized, comparative data have been published to date. Our group is currently near completion of enrollment of patients in a single-center, randomized study comparing anterior and posterior orientation.

We recently presented preliminary data from a retrospective comparison of anterior and posterior POEMs in our large, single-operator series using data from a prospectively maintained database [17]. In this study, we analyzed all POEMs performed at our center from October 2009 to October/2015, 248 consecutive POEMs (120 anterior, 128 posterior), all successfully completed, with no aborted POEMs or surgical conversions. No learning curve bias was expected as we performed a similar percentage of anterior POEMs in the first 3 years of our series (48/91, 53%), as in the last 2 years (72/157 46%). There were no differences in the Eckardt score, including failures (post-POEM Eckardt score >3, 5/110 anterior vs. 4/117 posterior, $p = NS$), accidental mucosal injuries (including non-transmural minor blanching, 29% vs. 23%), or prolonged stay of >5 days (one patient in each group). There was no difference in significant adverse events (AEs), but it should be noted that there was a paucity of such events in our series, with no leaks, no tunnel bleeds, and no
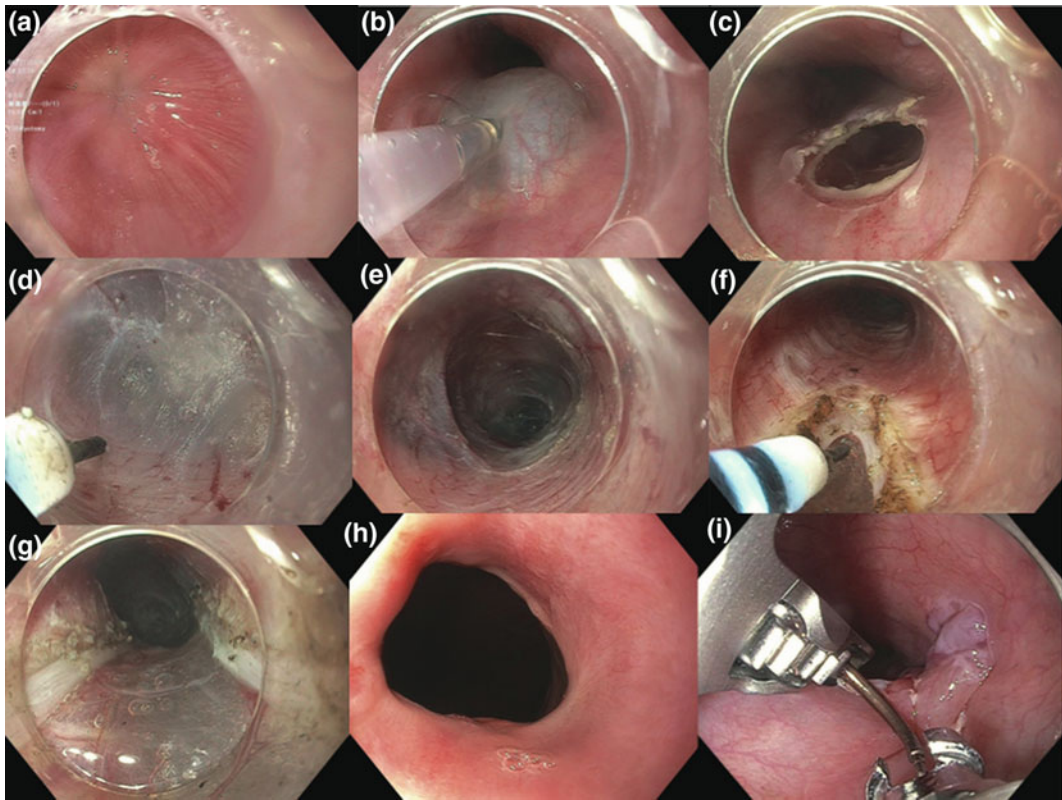
Fig. 6.3 Per-oral endoscopic myotomy endoscopic steps. **a** Tight GEJ prior to POEM. **b** Submucosal injection is performed with saline stained with methylene blue. **c** Mucosotomy is performed along the right posterior wall of the esophagus in the 5 o' clock orientation. **d** Submucosal dissection is performed with hybrid knife. **e** Submucosal tunnel is extended into the gastric cardia, and a completed submucosal tunnel is seen. **f** Myotomy is initiated 2 cm below site of mucosotomy. **g** Complete full-thickness myotomy is performed. **h** Patulous GEJ after POEM. **i** Mucosotomy closed with endoscopic suturing device

surgical/IR interventions. Posterior POEM was significantly faster overall (97 min anterior, 79 min posterior, $p = 0.0007$) including a faster closure (suturing 177, clips 71) (9.6 min anterior, 7.9 min posterior, $p = 0.02$). More patients had pain requiring narcotics in posterior POEM (17% anterior vs. 27% posterior, $p = 0.007$). There was a trend for less acid exposure in anterior POEM: +BRAVO studies (21/58 (36%) anterior vs. 29/58 (50%) posterior, $p = 0.13$) and reflux esophagitis (22/57 (38%) anterior vs. 33/60 (55%) posterior, $p = 0.076$).

Once orientation and location is selected, the submucosal space is expanded by saline injection to allow the endoscope to enter. An incision is made in the esophageal mucosa over this saline cushion, and a tunnel is begun with an electro-surgical knife inserted through the instrument channel. When the tunnel is deep and wide enough to permit introduction of the cap-fitted endoscope, it is then inserted and tunneling is continued with electrocautery distally toward the stomach. Usually, epinephrine is not utilized to avoid ischemia of the mucosal flap that may lead to necrosis. The endoscope is advanced as submucosal dissection is continued, and a tunnel is created within the submucosa from the middle esophagus to the gastric cardia. Meticulous care is taken not to tear the mucosal "roof" (or "floor," depending on the approach) of the submucosal tunnel.

The myotomy is generally performed after the tunnel creation, but recently, a technique has
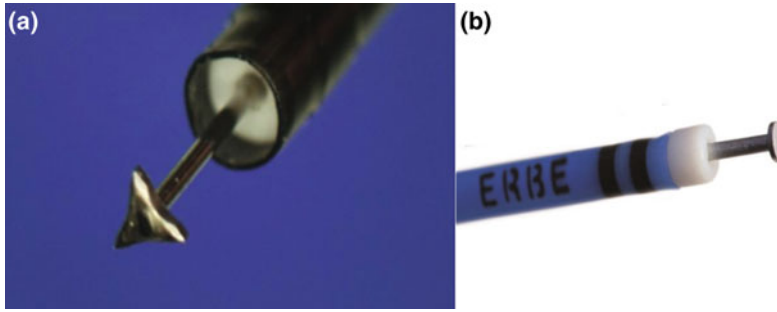
Fig. 6.4 **a** Triangle-tip knife. Courtesy Olympus America (Center Valley, PA). **b** Hybrid knife. Courtesy ERBE (Tubingen, Germany)

been described where the submucosa and muscularis are dissected simultaneously, possibly resulting in shorter procedure times [18, 19]. Some operators prefer the triangle-tip (TT) knife (Olympus, Center Valley, PA, Fig. 6.4a), while others, such as our group at Winthrop and the Shanghai group, prefer the multifunctional hybrid knife (HK) that can perform submucosal injection and dissection (ERBE, Tubingen, Germany, Fig. 6.4b). In their randomized controlled trial of 100 patients comparing POEM performed with the TT knife versus the HK [20], the Shanghai group reported that the HK produced significant decreases in POEM procedure time (22.9 vs. 35.9 min) ($p < 0.0001$) and fewer minor bleeding episodes, with no differences in complications or treatment success. This improvement in procedure times was mostly attributed to fewer exchanges of accessories. Similar results were also reported in a case–control study comparing the TT knife and the HK [21].

The incision site may be closed effectively with either clips or endoscopic sutures. Our group published data of a retrospective comparison of clips and suturing indicating similar closure times and cost for suturing versus clips [22]. Another US surgical group using much smaller numbers in a retrospective analysis of only 5 cases per group reported very long closure times with suturing (mean of 33 min), which, in their analysis, resulted in higher overall cost for suturing despite similar equipment cost to clips [23].

Infection is prevented by meticulous removal of retained food from the esophagus prior to beginning the tunnel, secure closure of the esophagotomy, and prophylactic systemic antibiotics. Many centers also perform antibiotic lavage of the tunnel prior to closure as recommended by Inoue [6].

There is significant variation in technique between POEM operators in terms of entry point (site and orientation), myotomy length, submucosal injection, mode of dissection, myotomy depth, and closure methods, all of which may vary depending upon procedure indication, operator preference, local expertise, etc. In addition, ancillary procedures to confirm adequate myotomy length may vary [24]. For instance, a myotomy of 5 cm length should suffice for most patients with Chicago Classification Achalasia types I and II, but an extended myotomy ranging to at least 15 cm may be necessary in type III achalasia patients, diffuse esophageal spasm, and jackhammer esophagus [25, 26].

A greater curvature (extended gastric) myotomy may be considered in subjects with prior HM or POEM [27]. Extension of the myotomy to the cardia is important, even without prior Heller procedure, to ensure complete LES ablation. A variety of indicators that suggest that the GEJ or cardia has been reached include the following: (1) endoscopic measurements (using the markers on the endoscope to measure depth of insertion from the incisors); (2) narrowing of the submucosal space at the GEJ with resistance to endoscope insertion caused by the LES, followed by prompt expansion of the submucosal space in the

cardia with increased overall vascularity of the submucosa; (3) slender palisade vessels along the mucosal flap, indicating the distal-most aspect of the esophagus; (4) spindle-like veins on the surface of the muscularis propria near the GEJ; (5) large-caliber, arborizing, perforating vessels in the cardia (usually branches of the left gastric artery); (6) aberrant inner longitudinal muscle bundles at the GEJ originating from circular muscle fibers and inserting into circular muscle fibers after a short course of 2–3 cm; and (7) visualization of a blue hue on intraluminal inspection of the mucosa of the cardia (due to the blue color of the injectate) [12].

A transillumination auxiliary technique, initially described by Baldaque-Silva and colleagues, allows confirmation that the tunnel was extended into the cardia by inserting an ultrathin endoscope transnasally in parallel with the orally inserted gastroscope used to perform the POEM procedure. The ultrathin scope is advanced to the level of the stomach and placed in the retroflexed position with visualization of the cardia, while the gastroscope is kept within the tunnel with its tip at the tunnel terminus. The light intensity of the thin endoscope is diminished, and the light from the gastroscope within the submucosal tunnel is identified, thereby confirming its position in the cardia [28]. Inoue's group compared this technique to conventional identification of the cardia by the indicators listed above in a prospective randomized controlled trial with 100 consecutive achalasia patients undergoing POEM. POEM was completed with high rates of technical and clinical success in both groups, with low adverse events, but the double-scope transillumination group had myotomy extension in 34% of cases, which led to an increase in the length of the cardiomyotomy from 2.6 to 3.2 cm ($p = 0.01$) [29]. Despite the extension of the myotomy in a third of the patients in the transillumination group, suggesting that the final length of the cardiomyotomy of the control group may have not been of adequate length in a third of patients, there were no differences in clinical success rates, and no differences in postprocedure gastroesophageal reflux disease (GERD), thus raising doubts about the clinical utility of the

double-scope method. Some drawbacks of this technique are that it may require two operators, is cumbersome, requires a second endoscopy tower and endoscope, and adds significant time to the procedure (17 min in this study). However, this technique may be beneficial for difficult cases such as those on patients with sigmoid end-stage achalasia or for operators early on the POEM learning curve.

Another technique for reliably identifying an adequate myotomy extension into the cardia involves the use of fluoroscopy. Kumbhari reported using either a hemoclip attached to the GEJ or the fluoroscopically guided placement of a 19-gauge needle on the skin at the level of the GEJ to help accurately assess the length of the myotomy in 24 consecutive patients undergoing the POEM procedure. Based on the fluoroscopic information, the submucosal tunnel was extended in 21% of patients, with minor increases in procedure time (4 min for the hemoclip group and 2 min for the 19-gauge needle group) [30]. Another group has also reported on the use of fluoroscopy to ensure proper orientation and extension of the tunnel into the cardia particularly in challenging cases with sigmoid esophagus [31].

Adequacy of LES ablation may also be assessed by real-time measurement of the GEJ distensibility with a balloon-based imaging probe (EndoFLIP, Crospon Ltd, Galway, Ireland) that uses impedance planimetry and can been used during the procedure to assess the adequacy of the myotomy via measurements that include GEJ cross-sectional area (CSA), minimal diameter, compliance, and distensibility [32–36].

Patients are kept nil per os until a water-soluble contrast study is performed when the patient is awake to exclude a leak, though it has little bearing on ultimate efficacy [37]. Most patients can be discharged soon after the tolerance of food.

POEM Efficacy

The NOSCAR POEM White Paper compiled results from 14 early series through early 2014 with follow-up periods ranging from 3 to

Table 6.2 POEM series with efficacy data

Location	Year	# of patients	Mean age (years)	Mean follow-up (months)	Eckardt score (pre/post)	LES pressure (pre/post) (mmHg)	Post-POEM ctimed barium esophagram	Efficacy (%)
Portland, Oregon [41]	2014	100	58 (18–83)	21.5	6/1	44.3/19.6	In 55 pts Median emptying at 1 min 93%: 100% emptying 100%: 80%–100% emptying	96
Chicago, Illinois [42]	2014	41	45	15	7/1	28/11	In 16 pts Median height 1 min 6 $\pm$ 4 cm 2 min 6 $\pm$ 4 cm 5 min 5 $\pm$ 3 cm ($p < 0.001$)	92
Rome, Italy [43]	2014	100	48 (18–75)	11	8.1/1.1	41.4/19		94.5
Mineola, New York [40]	2015	93	52 (18–93)	22	78/0.44	43/18		96
Europe MCT [44]	2015	80	44.9 (9–88)	29	7.7/1.5	31.9/10.1	In 32 pts 93.75%: >70% emptying at 5 min	78.5

12 months, with generally excellent results [12]. There was a significant decrease in the Eckardt score to ≤ 3 in 90–100% of patients, the primary clinical success criterion traditionally used in achalasia trials. Somewhat more modest 12-month results were reported by an early European multicenter series which noted only an 82% clinical response, perhaps reflecting early learning curves, since there were a small number of early procedures submitted by each of the participating centers [38].

A meta-analysis of more than 1000 patients showed POEM short-term success of 93% in terms of Eckardt scores and LES pressures [39]. Four more recent Western series from pioneering centers reflected excellent early midterm results, with a 90+% efficacy at 11- to 22-month follow-up (Table 6.2) [40–43]. Another attempt to present midterm POEM results utilized a multicenter methodology combining patients from 3 centers (Hamburg, Rome, Portland) that had completed a minimum of 24 months of follow-up (mean 29 months) [44]. This was a small study with only 79 patients and likely included patients from Hamburg that had also been included in the multicenter European series reviewed above. This 3-center study demonstrated similar modest efficacy results, with an initial high clinical success of 94% at 3–6 months, decreasing to 88% at 12–18 months and to 78% at ≥ 2 years (mean 29 mos, range 24–41). As was the case with the European multicenter trial (MCT) reviewed above, these more modest results were attributed by the authors to a learning curve effect, since half of the failures occurred in the first 10 patients from each of the 3 contributing centers.

In a recent publication of outcomes from the series with the longest follow-up to date, Inoue's series of 500 patients, 88% clinical success was reported at 3 years post-POEM [30]. However, it should be noted that there were substantial missing follow-up data (Eckardt score available in only 61 out of the 105 patients that had completed at least 3 years of follow-up) and that the patient population in this Asian series, as compared to US series, consisted of significantly younger patients with much less advanced/end-stage disease and prior Botox or Heller treatments, conditions that can result in more complicated POEM procedures [45].

GEJ-integrated relaxation pressures and barium passage have been shown to be improved post-POEM correlating with clinical parameters

[46]. POEM has demonstrated success for achalasia patients of all ages, those with prior endoscopic and surgical interventions, sigmoid esophagus, and spastic esophageal disorders [8, 11, 14, 26, 27, 39–44, 47]. POEM appears effective in relieving chest pain as well as dysphagia in achalasia and non-achalasia esophageal motility disorders, but POEM results may be somewhat more modest in spastic disorders compared to classic achalasia [26, 41, 48].

POEM Adverse Events

POEM has a superlative safety record with only one death attributed to POEM as a late complication (cachexia) reported in a recent systematic review of AEs [49]. Adverse events are uncommon and typically diminish with experience [8, 12, 13]. In the recent large series of 500 POEMs reported by Inoue, the AE rate was 3.2%, and all were mild/moderate [47]. These results were identical to the rate of AEs reported in the IPOEMS survey of pioneering centers [8].

The unusually high rate of AEs reported in an early POEM series that uniquely employed air rather than CO_2 for insufflation, particularly insufflation-related AEs such as symptomatic pneumothorax requiring decompression, tense pneumoperitoneum, and symptomatic subcutaneous emphysema, emphasizes the importance of using CO_2 for insufflation [50]. If CO_2 insufflation is used, insufflation AEs are rare, generally limited to the early learning curve, and mostly consist of capnoperitoneum that can be easily vented during the procedure with an angiocath or Veress needle without any sequelae or morbidity.

Episodes of intraprocedural hemorrhage diminish with experience and are usually easily managed with hemostatic forceps. Accidental mucosal injuries also decrease with experience [51]. They can occur in 10–20% of cases and are usually easily managed with endoscopic closure with minimal or no patient morbidity. Occasionally, closure can be difficult due to large size of the defect, difficult location, or poor tissue characteristics. In such cases, specialized techniques may be required to achieve closure and

avoid risk of leak and mediastinal sepsis [52, 53]. Delayed hemorrhage within the submucosal tunnel has been reported in less than 1–2% of cases and may require reintervention such as reexploration of the tunnel and endoscopic hemostasis or, as has been reported, balloon tamponade [54].

Anesthesia complications are infrequent and usually self-limited. Attention should be paid to avoiding aspiration during induction of anesthesia and intubation, particularly in patients with a very dilated esophagus. Rapid induction should be performed with simultaneous vigorous cricoid pressure in order to avoid aspiration with resultant pulmonary infectious complications.

The most serious AE probably involves leaks, which may result in mediastinal sepsis, and which usually require emergent surgical intervention. Such leaks have been infrequently reported by a small number of centers early in their experience [42, 45, 46]. Tension capnopericardium has also been reported as a complication of POEM, resulting in cardiac arrest and premature termination of the procedure [55]. This patient survived without sequelae and went on to have a Heller–Dor procedure six months later.

GERD After POEM

A concern with POEM is that unlike laparoscopic Heller myotomy, a concomitant reflux procedure is not performed. It is now apparent that GERD is common after POEM, with GERD symptoms in 12–24%, esophagitis in 20–59%, and positive pH studies in 31–50% (Table 6.3) [41, 42, 56]. In fact, dysphagia relief is clearly correlated to LES ablation and subsequent tendency toward GERD as demonstrated in a recent multicenter study [44]. In this study concentrating on longer-term data from subjects with two-year follow-up, 37% had erosive esophagitis, and 37% were on a proton pump inhibitor (PPI) at ≥ 2 year follow-up (mean 29 months, range 24–41). The presence of GERD was the strongest predictor of POEM efficacy. GERD assessment can be complicated by the fact that up to half of the patients with GERD-like symptoms

Table 6.3 POEM series with GERD data including pH studies

Location	GERD symptoms	Erosive esophagitis	+pH study
Chicago, Illinois [42]	15/41 (15%)	13/22 (59%)	4/13 (31%)
Portland, Oregon [41]	12/100 (15%)	20/73 (27%)	26/68 (38%)
Rome, Italy [43]	19/103 (18%)	21/103 (20%)	52/103 (50%)
Mineola, New York [78]	40/174 (23%)	29/86 (34%)	29/84 (36%)

may not have a positive pH study, and conversely, a significant percentage of patients with a positive pH study may not have symptoms. In some of these patients, a falsely positive pH study may result due to stasis or fermentation [57, 58]. The Rome group proposed the term "clinically relevant GERD" for patients who, in addition to having a positive pH study, also have typical GERD symptoms and/or reflux esophagitis. Using this definition, in their comprehensive study of 103 patients, even though 50% had a positive pH study, only 29% had "clinically relevant GERD" [56].

Most patients' GERD is well controlled with PPIs, and the trade-off for dysphagia relief is seemingly worthwhile in terms of overall quality of life [59]. With regard to comparing GERD after POEM to GERD after laparoscopic Heller myotomy (LHM), in a recent retrospective comparison of 64 LHMs and 37 POEMs performed by the same surgical group in Portland, no significant difference was found in positive pH studies (32% in LHM, 39% in POEM).

It should be noted here that the Dor or Toupet "loose" fundoplications performed in achalasia patients in conjunction with a LHM have only modest efficacy. High-quality studies from expert LHM centers have shown abnormal acid exposure rates in 18–42% of patients after LHM with fundoplication [60–62], rates not too dissimilar to those after POEM. Furthermore, these pH data were collected only 6–12 months postoperatively and may be even less favorable on long-term follow-up. One may reasonably wonder why the rate of GERD after POEM is not substantially greater than that after LHM combined with a fundoplication. The explanation may lie in the lack of hiatal dissection during POEM compared to extensive dissection of the hiatus during a standard LHM. This extensive dissection disrupts important "suspensory ligaments" of the esophagus, notably the phrenoesophageal membrane, which thought to contribute to the maintenance of the angle of His and to have an important antireflux function separate from the esophageal sphincter itself. Two recent studies lend support to this hypothesis by demonstrating that a modified LHM with as limited dissection of the hiatus as possible results in much lower rates of GERD even without a fundoplication (9 and 31%, respectively) [63, 64].

Comparative Analysis

There are no published randomized trials to date comparing POEM to LHM or POEM against endoscopic therapies. There are MCTs underway in Europe between POEM, LHM, and pneumatic balloon dilation (PBD). Four studies utilized historical LHM controls to compare with POEM and found comparable excellent clinical results and few complications [45, 65–67]. These studies demonstrated shorter operative times and less blood loss for POEM, less postoperative pain, shorter length of hospital stay, and more rapid return to usual activities. Two meta-analyses with one-year follow-up found similar results, with no notable differences between POEM and LHM [68, 69]. Barium column height was comparable between POEM and LHM subjects [60]. Quality-of-life improvement is comparable between LHM and POEM [59]. A multicenter retrospective comparison of POEM and LHM for type III achalasia noted that POEM allows for a longer myotomy than LHM and found a trend toward better clinical results with POEM [70].

Training

POEM operator numbers have increased greatly since the procedure was introduced, but its performance is still largely limited to larger centers. Questions have been raised as to what constitutes adequate training and performance [8, 12, 13]. Our group's analysis of the first 93 POEMs performed by a single operator found that efficacy was attained at 40 procedures and mastery at 60 [40]. The Portland group found "mastery of POEM technique to be after 20 procedures" (as denoted by decreased procedure time and decreased rate of accidental mucosotomies) [51]. On the other hand, the Northwestern group reported a "learning rate" of 7 POEMs for completing just the submucosal access and myotomy portions of the procedure (insufficient data were reported regarding the entire procedure) [71]. Both of these analyses were by the surgical groups in Portland and Northwestern and were based on 40 or fewer POEMs by multiple operators, raising methodological questions. Another group reported on the importance of preclinical training before performing POEM in humans [72–74]. While it remains unclear exactly how many cases constitute the learning curve for POEM, it is clear that the technical difficulty of the procedure is such that significant experience is required to attain consistent results. This line of thinking may contribute to the observed performance of POEM primarily in larger centers, where this type of experience is more readily available.

Future and Offshoots

The future of POEM appears bright, and garnering longer-term data will likely further validate its dominant niche in achalasia therapy. More importantly, however, POEM has led to an exciting rebirth of NOTES in the form of "short-range," intramural, endoscopic interventions of the GI tract: interventions such as POEM, STER (submucosal tunnel endoscopic resection), EFTR (endoscopic full-thickness resection), and POP (per-oral pyloromyotomy). Whereas traditional NOTES, with its grand vision of deep incursions into the abdominal and chest cavities and major organ resections, failed to gain wide adoption, it planted the seeds for the "new NOTES" procedures, which are thriving and enjoying rapid growth. These "new NOTES" interventions are finally delivering on the great promise of NOTES, replacing traditional surgical procedures with more minimally invasive, scarless ones [73].

POEM developed as a fortuitous offshoot of early traditional NOTES work, but now arguably represents the most successful application of NOTES to date [73, 75]. Two especially promising "new NOTES" applications of submucosal endoscopy are a technique for R0 full-thickness resection of deep seated subepithelial tumors named "POET" for per-oral endoscopic tumor resection by Inoue and colleagues, or "STER" (submucosal tunnel endoscopic resection) by the Shanghai group [76–78]. Another technique has developed as an offshoot of POEM called per-oral pyloromyotomy (POP, also termed by some G-POEM) for the therapy of gastroparesis [79].

Conclusion

POEM was initially performed in 2008 as a novel therapy for achalasia, derived from the evolution of NOTES work, and is now performed globally. POEM is well validated as an achalasia therapy, with documented excellent efficacy and safety. Moreover, it can be equally successful in those with prior intervention, including LHM, and is applicable in a wide range of esophageal motility disorders beyond achalasia, including diffuse esophageal spasm and jackhammer esophagus. Longer-term data, including randomized trials of POEM versus pneumatic dilation and Heller, are awaited. These are expected to confirm the uniformly excellent efficacy of POEM reported by a large number of prospective series, including several series with early midterm data at 1- to 3-year follow-up. The burgeoning field of submucosal endoscopy "new NOTES" interventions is largely predicated upon the spectacular success of POEM.

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