POEM: Efficacy, Safety, Training, and Competency

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Introduction

Peroral endoscopic myotomy (POEM) is the endoscopic approach of surgical myotomy for patients with spastic esophageal disorders [1]. It uses the concept of natural orifice transluminal endoscopic surgery (NOTES) introduced by the Apollo Group in 2004 [2–4]. Inoue et al. were the first ones to perform POEM in human after initial experimental steps by Pasricha et al. in 2007 [5, 6]. A submucosal esophago-cardial tunnel is created as an operating space, and an endoscopic myotomy is carried out by means of a micro-knife and the tunnel subsequently closed by clips. Due to its minimally invasive character, it appears to be effective and safe even in old or multimorbid patients, regardless of prior therapy undertaken [7–10]. POEM and balloon dilation have replaced other endoscopic treatment modalities such as intersphincteric botulinum toxin A injection [11, 12]. Multiple studies during the last 5 years have proven the clinical value of POEM [13]. However, the POEM procedure can be a challenge for even advanced endoscopists. Serious adverse events can arise, and endoscopists starting with POEM should be well trained to handle these complications endoscopically or minimally invasive and avoid open surgery. These include bleeding, perforation, pneumothorax, pneumomediastinum, pneumoperitoneum, as well as infections such as mediastinitis and abscess formation [14, 15].

Appropriate training and continuous practice are crucial for success of this procedure. With this chapter, we would like to give a short overview on efficacy, safety, training, and competency in POEM.

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Efficacy of POEM

POEM Versus Heller Myotomy

POEM has shown to be highly effective in the management of achalasia in several short-term follow-up studies. Its technical success does not seem to differ significantly from that of Heller myotomy (HM) [16]. Table 19.1 shows a summary of different series comparing the efficacy of POEM in comparison to Heller myotomy (HM) in a non-randomized retrospective fashion [17]. We did not find any results of a prospective direct comparison until july 2019. Beside the management of achalasia, preliminary data suggest that POEM is an effective option for the management of spastic

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Table 19.1 Non-randomized comparisons for laparoscopic Heller myotomy (LHM) versus peroral endoscopic myotomy (POEM)

Study, year	Number of patients	Follow-up in month	Posttreatment reflux, %	Efficacy, %
Peng, 2017 [25]	POEM 13 LHM 18	54.2	No significant difference in GERD	POEM 83.3 LHM 83
Leeds, 2017 [26]	POEM 12 LHM 11	>6	Not reported	POEM 82 LHM 66
Chan, 2016 [27]	POEM 33 LHM 23	>6	POEM 15 LHM 26	POEM 100 LHM 87
Schneider, 2016 [28]	POEM 42 LHM 84	12	Not reported	POEM 91 LHM 84
Sanaka, 2016 [16]	POEM 36 LHM 142	2	Not reported	No significant difference in HREM after 2 months (p >0.05)
Kumbhari, 2015 [29]	POEM 49 LHM 26	9	POEM 39 LHM 46	POEM 98
Bhayani, 2014 [30]	POEM 37 LHM 64	6	POEM 39 LHM 32	POEM 100 LHM 92
Teitelbaum, 2013 [23]	POEM 17 LHM 12	Not reported	POEM 17 LHM 31	POEM 100 LHM 87

From Kahrilas et al. [31]
HREM high-resolution manometry

esophageal disorder. It permits an adapted myotomy according to HR-manometric changes and radiologic findings even in the mid- and proximal esophagus which is usually longer compared to classical achalasia [18–21].

The majority of studies define technical success as a post-procedure Eckardt score of ≤3, decreased lower esophageal sphincter pressure, and improved esophageal emptying [22–24]. Crespin et al. conducted a systematic review including 1299 POEM procedures. Median follow-up was 13 months (range 3–24). Pre- and post-POEM Eckardt scores and lower esophageal sphincter pressures differed significantly with a reported technical and clinical success of 80–100% [13]. The most frequently reported complications were mucosal perforation or mucosotomies (circumscript minimal defects), subcutaneous emphysema, pneumoperitoneum, pneumothorax, pneumomediastinum, pleural effusion, and pneumonia (see Table 19.1).

POEM after Heller Myotomy

Zhang, Stavropoulos and colleagues from Mineola, NY, followed 318 patients for at least 3 months after POEM, performed between October 2009 and October 2016 [9]. They compared efficacy and safety of POEM in 46 patients with prior Heller myotomy (HM) and the remaining 272 patients without myotomy pretreatment. Patients with prior HM had longer disease history, more advanced disease, more type I and less type II achalasia, and lower before-POEM Eckardt scores. Procedure parameters and follow-up results (clinical success rate, Eckardt score, LES pressure, GERD score, esophagitis, and pH testing) showed no significant difference between the two groups [9].

POEM Long-Term Data

There are only few long-term data exceeding 5-years follow-up at present [9, 10, 32–36]. The group led by P.H. Zhou recently analyzed a collective of 564 patients having undergone a POEM procedure between August 2010 and December 2012 in Shanghai, China [36]. Major perioperative adverse events occurred in 36 patients (6.4%). After a median follow-up of 49 months (range, 3–68), the Eckardt score and lower esophageal sphincter (LES) pressure were significantly decreased (median Eckardt score, 2 vs. 8 [p <0.05]; median LES pressure,

11.9 vs. 29.7 mm Hg [p <0.05]). Fifteen failures occurred within 3 months, 23 between 3 months and 3 years, and 10 after 3 years. The estimated clinical success rates at 1, 2, 3, 4, and 5 years were 94.2%, 92.2%, 91.1%, 88.6%, and 87.1%, respectively. Multivariate Cox regression revealed long disease duration (≥10 years) and history of prior interventions to be risk factors for recurrence. Clinical reflux occurred in 37.3% of patients (155/416). The authors concluded that POEM is a highly safe and effective treatment for esophageal achalasia with favorable long-term outcomes [36]. Teitelbaum and Swanstrom analyzed their long-term data on 36 patients who had undergone a POEM procedure from October 2010 to February 2012 in Portland, Oregon. Current symptom scores were obtained from 29 patients at a median follow-up of 65 months. In the 23 patients with achalasia, Eckardt scores were significantly improved from preoperative baseline (mean preoperative 6.4, mean current 1.7; p <0.001). Nineteen patients (83%) with achalasia had a symptomatic success (Eckardt ≤3) and none required re-treatment for symptoms. Eckardt scores were dramatically improved at 6 months and maintained at 2 years. However, there was a small but significant worsening of symptoms between 2 and 5 years. Of the 5 patients with EGJ outflow obstruction, all had current Eckardt scores ≤3, but two needed re-intervention for persistent or recurrent symptoms, one with a laparoscopic Heller myotomy and another with an endoscopic cricomyotomy and proximal esophageal myotomy extension. At 6-month follow-up, repeat manometry showed decreased EGJ relaxation pressures, and esophagram demonstrated improved emptying. 24-h pH monitoring showed abnormal distal esophageal acid exposure in 38% of patients. Fifteen patients underwent endoscopy at 5 years, revealing erosive esophagitis in two (13%), new hiatal hernia in two, and new non-dysplastic Barrett's esophagus in one. The authors concluded that POEM resulted in a successful palliation of symptoms in the majority of patients after 5 years, though the results confirmed the importance of a systematic long-term follow-up in all patients.

Adverse Events

As Peter Cotton et al. state: The most feared negative outcome is when something "goes wrong" and the patient experiences a "complication" [37]. This term has unfortunate medicolegal connotations and is perhaps better avoided. Describing these deviations from the plan as "unplanned events" fits nicely with the principles of informed consent, but the term "adverse events" (AEs) is in common parlance [37].

Adverse events with POEM have to be classified in intra- and post-procedural AEs [15]. Pre-interventional AEs such as aspiration pneumonia in achalasia should be excluded prior to the procedure. There is up to now no consensus on a standard classification of AEs associated with the procedure [8, 10, 15, 32, 38–45].

In general, the POEM procedure can be seen as safe procedure in the hands of an expert endoscopist at a specialized referral center [8, 10, 32, 38–45]. Until 2015 only 1 death in about 4000 procedures had been reported [45]. Inoue et al. presented in 2015 a large cohort study of 500 POEM procedures [32]. Adverse events were observed in 3.2% of patients. However, complication rates in small series are not clear yet.

Single Center and Multicenter Analysis of AEs in POEM

Haito-Chavez published in 2017 an international multicenter study on adverse events in association with POEM performed in a total of 1826 patients at 12 tertiary care academic centers between 2009 and 2015 [8]. All authors were expert endoscopists and pioneers in the field of POEM. They found 156 AEs occurring in 137 of 1826 patients (7.5% of patients). Mild, moderate, and severe AEs had a frequency of 116 (6.4%), 31 (1.7%), and 9 (0.5%), respectively. An AE was defined as any symptomatic event related to the POEM procedure itself or to anesthesia, requiring temporary stop of the procedure and/or further action to solve the event and/or to treat the symptoms [8]. Any event that prevented completion and/or resulted in prolongation of hospital stay required another procedure, or subsequent

medical consultation was considered as AEs as well. The ASGE lexicon's severity grading system was used to grade the AEs [37]. Incidental findings of capnoperitoneum, capnothorax, or capnomediastinum on post-procedure imaging and subcutaneous emphysema were not considered AEs. The authors included different multivariate analyses to find out predictors for AEs. They analyzed factors related to the patient including age, gender, Charlson comorbidity index, American Society of Anesthesiologists (ASA) class, history of antiplatelet or anticoagulation, immunosuppression drug or steroid use, and previous therapies including botulinum toxin injection, pneumatic dilation, and LHM. There was no significant association between these patient-related predictors and occurrence of AEs.

Multivariate analysis demonstrated that sigmoid-type esophagus (odds ratio (OR) 2.28, $p = 0.05$), endoscopist experience <20 cases (OR 1.98, $p = 0.04$), use of a triangular tip knife (OR 3.22, $p = 0.05$), and use of an electrosurgical current different than spray coagulation (OR 3.09, $p = 0.02$) were significantly associated with the occurrence of AEs [8].

The most common time of presentation of AEs was intraprocedural in 89 patients (57.1%). A total of 64 (41.0%) AEs presented during the first 48 h, and only 3 (1.9%) AEs presented after 48 h. The most common AEs that presented during the first 48 h were esophageal leak ($n = 13$), submucosal hematoma ($n = 10$) (Fig. 19.1a, b), and pneumonia ($n = 8$). A total of 51 (2.8%) inadvertent mucosotomies occurred, mostly closed by clips (Fig. 19.2a, b). Only three AEs occurred after 48 h. There was one case of empyema requiring thoracotomy and chest tube insertion. The two remaining cases were one patient with pneumonia and one patient with delayed bleeding, both of whom were treated conservatively [8].

As discussed most of the AEs were graded as mild in 116 (6.4%), followed by moderate and severe in 31 (1.7%) and 9 (0.5%), respectively.

Among the nine severe AEs, two were esophageal leaks, two bleeding episodes during tunneling (one resulted in conversion to LHM and one resulted in intensive care unit admission), one perforation, one aspiration pneumonia, one empyema, one capnomediastinum, and one severe cardiac arrhythmia. There were two patients with heavy bleeding during tunneling; one patient with secondary bleeding could not be managed endoscopically and required balloon tamponade with a Sengstaken–Blakemore tube. The second patient experienced intraprocedural bleeding with extensive submucosal hematoma that rendered completion of POEM impossible. LHM was performed successfully during the same session [8].

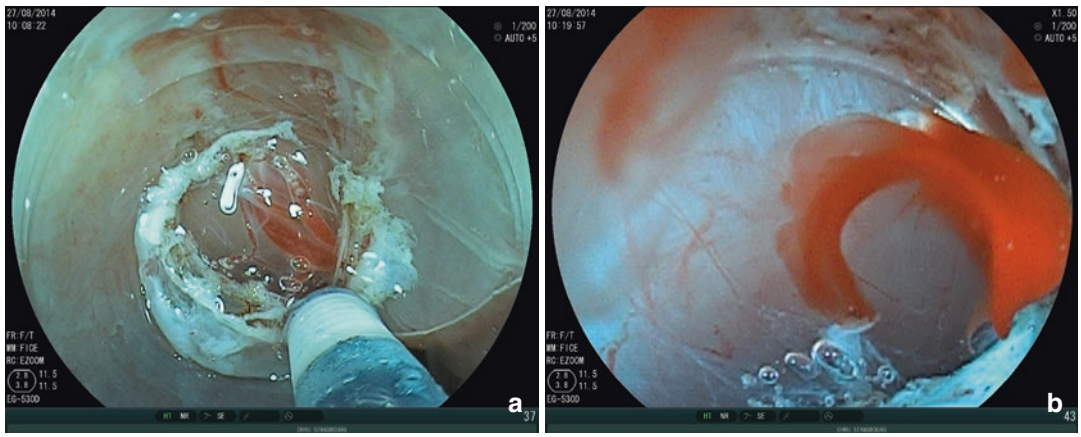

Fig. 19.1 Submucosal vessels at the enterance site appearing after mucosal incision (**a**). Bleeding submucosal vessel after transsection during mucosal incision for tunnel creation (**b**)

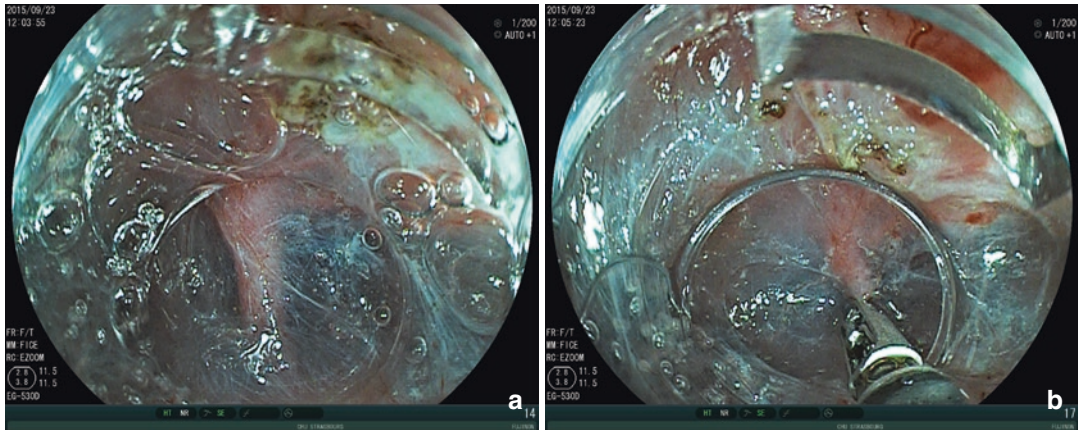

Fig. 19.2 2 mm arterial vessel crossing the submucosal tunnel. Soft or low wattage Forced Coagulation using a coag-grasper over 3-5 mm before transsection of the vessel

Among the 13 patients who presented with esophageal leak, there were two with severe esophageal leaks; one of them required surgery (washout surgery and drainage), while the second patient was treated with endoclipping. However, this latter patient progressed with a pleural effusion requiring insertion of a chest tube and then progressed with empyema requiring thoracotomy and drainage.

Overall inadvertent mucosotomy was the most common intraprocedural AE occurring in 51 patients, followed by insufflation related AEs in 28 patients (22 capnoperitoneum, 4 capnothorax, 1 pneumothorax, and 1 capnomediastinum), and bleeding during tunneling in 6 patients [8].

Other successful treatment of the 13 esophageal leaks included stent placement (n = 2) and endoscopically assisted vacuum therapy (n = 1). Three patients presented with contained leak into the submucosal tunnel and responded to conservative management.

Zhang and Zhou et al. presented their retrospective single-center analysis on only major perioperative adverse events (mAE) in 1680 patients who underwent POEM between August 2010 and July 2015 at Zhongshan Hospital, Shanghai, China [38]. They identified a total of 55 patients experiencing major adverse events (3.3%): they found delayed mucosal barrier failure (n = 13; 0.8%), delayed bleeding (n = 3; 0.2%), hydrothorax (n = 8; 0.5%), pneumothorax (n = 25; 1.5%), and miscellaneous (n = 6; 0.4%). Four patients (0.2%) required ICU admission. No surgical conversion occurred, and 30-day mortality was zero. In stepwise multivariate regression, institution experience of <1 year (odds ratio [OR] 3.85; 95%CI 1.49–9.95), air insufflation (OR 3.41; 95%CI 1.37–8.50), and mucosal edema (OR 2.01; 95%CI 1.14–3.53) were identified as related risk factors. After introducing CO_2 insufflation, the major Adverse Event rate declined to 1.9% (95%CI 1.2–2.7%) and seemed to plateau after 3.5 years at ~1%. The authors concluded that POEM appeared to be a safe procedure. Major adverse events were rare and could usually be managed effectively.

CO_2-Associated Problems and Anesthesiologic Considerations

Already in early series, the need for CO_2 insufflation instead of room air during POEM became evident [46, 47]. CO_2 may inadvertently track into surrounding tissues during POEM, causing systemic CO_2 uptake and tension capnoperitoneum. This in turn may affect cardiorespiratory function. Gas-associated AEs include also pneumomediastinum, subcutaneous emphysema, and

pneumothorax. In a meta-analysis of Akintoye et al., subcutaneous emphysema was found in 7.5%, pneumothorax in 1.2%, pneumomediastinum in 1.1%, and pneumoperitoneum in 6.8% [48]. Important guiding parameters indicating the need for an intervention were significant abdominal distension, increased end-tidal CO_2 and increased peak airway pressure [40]. In cases of tension pneumoperitoneum, a Veress needle (or a 16–18 G intravenous cannula) is inserted through the abdominal wall paraumbilically respecting sterile conditions [15]. A 10–20 ml syringe is filled with saline and connected with the canula, and the plunger is removed. The appearance of bubbles shows a successful drainage of the capnoperitoneum. CO_2 is absorbed about 300 times faster than room air. Only gas-related events requiring an intervention should therefore be categorized as adverse events [15].

The endoscopist should try to reduce the CO_2 gas flow to the necessary minimum. The use of a low-flow CO_2 gas tube has been described helpful in this regard. In case of a pneumothorax with a volume of more than 30%, a thoracic drainage should be introduced for 2 or 3 days. In the rare case of capno-pericardium, a cardiac arrest may occur the way that anesthetists and endoscopists should be aware of this rare but possible complication [49].

Close anesthesiologic supervision of changes in airway pressures and hemodynamics are recommended, and an arterial line for monitoring of arterial blood gases can be considered [15, 50]. Important guiding parameters indicating the need for an intervention include significant abdominal distension, increased end-tidal CO_2, and peak airway pressure. Increasing minute ventilation is usually enough to manage an increase in end-tidal CO_2 levels associated with CO_2 insufflation [40]. Loeser et al. analyzed 173 consecutive POEM patients of a tertiary care single center in Germany over a 4-year period from an anesthesiologic standpoint [50]. During POEM, cardiorespiratory parameters increased from baseline: pmax 15.1 vs 19.8 cm H_2O, $etCO_2$ 4.5 vs 5.5 kPa [34.0 vs 41.6 mmHg], MAP 73.9 vs 99.3 mmHg, and HR 67.6 vs 85.3 min(−1) ($p < 0.001$ for each). Hyperventilation [MV 5.9 vs 9.0 L.min(−1), $p < 0.001$] was applied to counteract iatrogenic hypercapnia. Individuals with tension capnoperitoneum are treated with percutaneous needle decompression (PND; $n = 55$). They had higher peak pmax values [22.8 vs 18.4 cm H_2O, $p < 0.001$] than patients who did not require PND. After PND, pmax [22.8 vs 19.9 cm H_2O, $p = 0.045$] and MAP [98.2 vs 88.6 mmHg, $p = 0.013$] decreased. Adverse events included pneumothorax ($n = 1$), transient myocardial ischemia ($n = 1$), and subcutaneous emphysema ($n = 49$). The latter precluded immediate extubation in eight cases. Postanesthesia care unit (PACU) stay was significantly longer in individuals with subcutaneous emphysema than in those without ($p < 0.001$). The authors concluded that carbon dioxide insufflation during POEM produced systemic CO_2 uptake and increased intra-abdominal pressure. Changes in cardiorespiratory parameters included increased pmax, $etCO_2$, MAP, and HR. Hyperventilation and percutaneous abdominal needle decompression helped to mitigate some of these changes. Subcutaneous emphysema was common in 28.3% of cases and did delay extubation and prolong PACU stay.

Bleeding

Bleeding is a common side effect during any of the different steps of POEM, especially during submucosal tunneling (Figs. 19.1, 19.2, 19.3, and 19.4). Careful stepwise dissection will allow vessels to be visualized and to be prophylactically treated using cautious coagulation with the electrocautery knife itself or by means of a "Coag Grasper" (Olympus, Center Valley, PA, USA) using "Soft Coag" or low wattage "Forced Coag" current. Caution should be applied in case bleeding originates from a vessel running along the mucosal surface side of the tunnel in order to

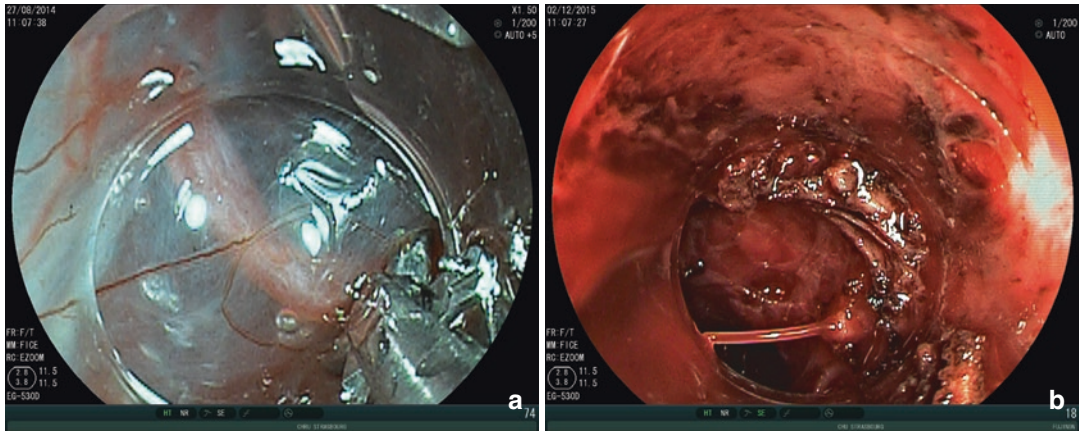

Fig. 19.3 2.5 mm arterial vessel crossing the submucosal tunnel (**a**). Secondary severe bleeding after to short sealing of the vessel ends by means of the coag-grasper (**b**)

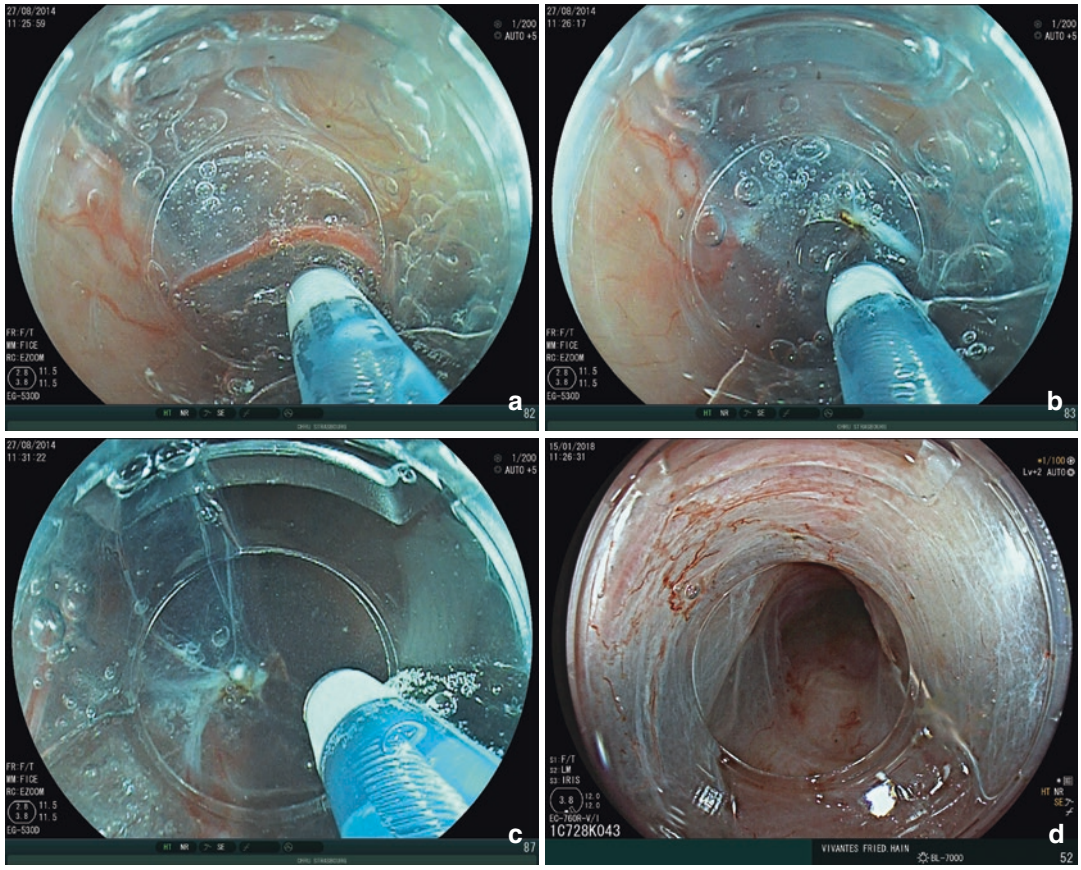

Fig. 19.4 (**a**–**d**) Coagulation of minor vessels by means of the tip of the electrosurgical knife and soft of forced coagulation current following the vessel course before transsection (**a**–**c**). Completed tunnel after dissection (**d**)

prevent secondary mucosal defects and perforation after coagulation. A gentle compression with the tip of the endoscope +/− cautious secondary coagulation is carried out in these cases. The placement of clips in the tunnel is usually avoided as secondary perforation of the covering mucosa should be feared.

Guidelines recommend to perform POEM without anticoagulant or antiplatelet therapy except for acetylsalicylic acid. It is recommended that all patients should have a blood type and antibody screening before starting the procedure [51, 52]. Postoperative bleeding apparently is infrequent. In a large series of Li et al. with 428 patients, delayed bleeding has been reported in 0.7% [53].

Secondary bleeding into the tunnel is infrequent (Fig. 19.5a, b). However, a massive hematoma in the tunnel can result in pressure necrosis of the mucosal flap with potentially disastrous consequences in case of wide perforation. A CT scan should be performed to discriminate a mere bleeding into the tunnel from additional mediastinal effusion. Li et al. reported on three patients (0.7%, 3/428) who experienced delayed bleeding in the submucosal tunnel after POEM. None of these patients had any predisposing factor to bleeding, such as hypertension, coagulation disorders, and antiplatelet/anticoagulant therapy before undergoing POEM. There were no special difficulties related to tunnel creation or myotomy performance in these cases. In one patient, a small hematoma was observed by CT before any clinical manifestation occurred; this patient then reported progressive serious retrosternal pain from the first day after surgery and vomited fresh blood on the third day. Two other patients suddenly vomited large amounts of fresh blood on the first and third days after the intervention, respectively; no submucosal hematoma was observed on CT scans before hematemesis occurred in these two patients. Emergency esophago-gastroscopy was performed immediately on all three patients, revealing a hematoma in the submucosal tunnel. After removing the metal clips from the mucosal entry, a large quantity of blood clots were discovered inside the submucosal tunnel and were removed. In the first patient, the bleeding source could not be identified, and a Sengstaken–Blakemore tube was directly placed into the stomach and lower esophagus to compress the bleeding sites. In the other two patients, active bleeding points were identified and coagulated with a hemostatic forceps in the forced coagulation mode. Almost all of the bleeding spots were from the cut muscular edges. A PPI, antibiotics, and hemocoagulase were administered to all three patients. Intermittent balloon deflation was performed every 24 h. The Sengstaken–Blakemore tube gastric balloon was permanently deflated on the first day after placement, and the esophageal balloon was deflated on the second day after insertion.

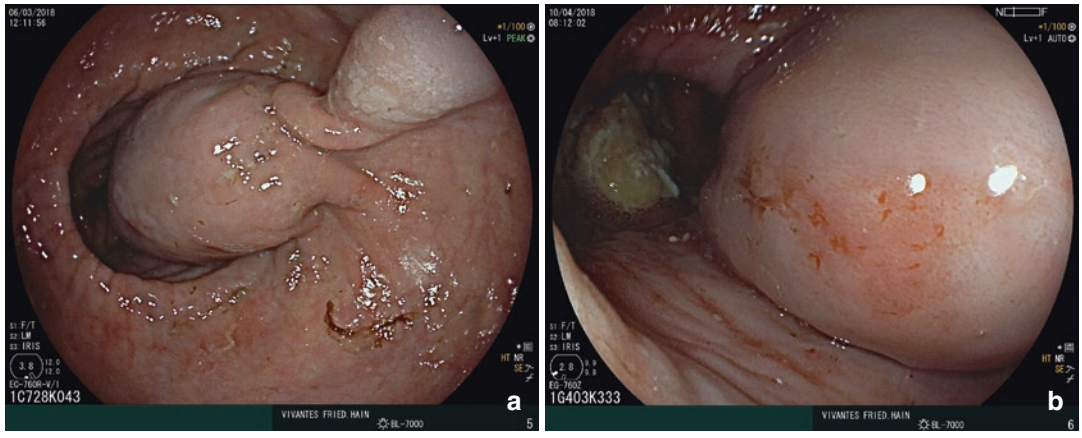

Fig. 19.5 (**a, b**) Enormous secondary hematoma at the level of the submucosal tunnel developing within the first 48 h post procedure possibly after repeat coughing

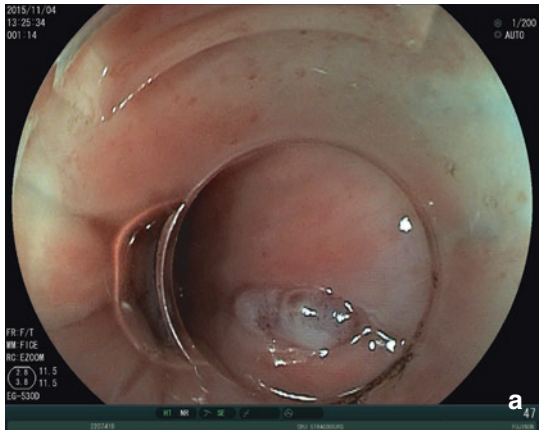

Fig. 19.6 (**a, b**) Mucosotomy, definded as defect or injury of the mucosal tunnel wall during electrosurgical preparation happening especially during coagulation of bleeding vessels on the side of the covering mucosa (**a**) Adaptation of the mucosa left and right of the coagulation defect by means of three short arm clips (Hemoclip green; Olympus Tokyo, Japan)

Benech et al. from Lyon, France, reported on successful conservative management [54]. The patient had experienced massive epigastric pain shortly after the procedure and showed a drop in hemoglobin from 14.2 to 11.2 g/dl. We had a similar case, managed conservatively (Fig. 19.5a, b).

Perforation

After dissection of the muscular layer, even a small mucosal defect can become potentially dangerous. In case such a mucosotomy is detected during submucosal tunneling, closure should be performed immediately as otherwise a significant increase of the defect may occur (Fig. 19.6a, b) [38]. Preoperative edema of the mucosa is suggested a risk factor for mucosal injury during intervention. Mucosal edema makes closure difficult and promotes perforation. Edema has been seen in 8% of patients in a retrospective study of over 1600 patients [38]. The endoscopic tunnel should be created very close to the muscular layers to avoid injury to the mucosal flap and because of a lower vascularity adjacent to the muscle [55]. Most perforations happen at the level of the lower esophageal sphincter due to a narrowing at the cardia. If a mucosotomy is identified, it should be closed immediately with endoscopic clips. Larger mucosotomies have been closed using a flexible endoscopic suturing device (OverStitch; Apollo Endosurgery, Austin, TX, United States) [56, 57]. Other salvage techniques used included fibrin glue and over-the-scope clips (OTSCs; Ovesco, Tuebingen, Germany) [58, 59]. In case of multiple ruptures which cannot be clipped, a covered retrievable stent may be used as rescue technique [60, 61].

Postprocedural Chest Pain

The most common periprocedural side effect is substernal chest pain. Data suggest an average mild to moderate chest pain after the procedure and during the following 3 days (4.6/10 immediately after POEM, 3.2–3.3/10 the following 2 days) [40]. As in tubular esophageal ESD, the application of a fentanyl patch, adapted to patients weight, age, and general condition, e.g., 25 mcg/g (12.5–50 mcg/h), applied at the beginning of the procedure, has been very valuable in our own experience over the last 5 years.

Infections and Pneumonia

In general index gastroscopy should be performed one to several days before the POEM procedure. In case signs of *Candida* esophagitis, a

systemic antifungal treatment should be initiated immediately. Remaining material in the lower esophagus should be removed, and the patient is set on a strictly liquid diet 24–48 h before treatment. Single-shot antibiosis of, e.g., ceftriaxone plus metronidazole, is usually sufficient in a non-immunocompromised patient.

Sterility is still under debate as the endoscope is penetrating into a space in direct contact with the mediastinum and abdominal cavity. On the other hand, infectious complications have been reported less frequent as feared in the initial era of procedure [46, 47]. As a routine, we remove the endoscope with sterile gloves from the washing machine after reprocessing it shortly before the procedure. The same is done if a drying cabinet is used for storage. It is then placed into a tray with a sterile cloth inside and covered which a second sterile cloth until its use for the procedure. The use of a sterile coat and sterile gloves is recommended for the procedure [46, 47]. However, this practice varies from center to center and many units perform POEM with the endoscope processed and handled as for any other upper endoscopy. Single centers ask the patients to flush the mouth with chlorhexidine solution before the intervention [62].

Pleural Effusion

Pleural effusion is noticed in 5–40% of POEM patients. Depending on the size of effusion, laboratory findings plus clinical signs of infection (fever, etc.), antibiotics and early pleural drainage or just waiting for spontaneous absorption is indicated [42].

Reflux After POEM and LHM

The most common long-term adverse event with POEM seems to be gastroesophageal reflux (GER). As the premise behind the POEM procedure, similar to Heller myotomy, is to decrease lower esophageal sphincter pressure, it is not surprising that post-POEM GER is encountered [63]. Early studies were focused on technical feasibility and safety, with a short duration of follow-up. Furthermore, a large proportion of the early literature came from Asia, where GER is less prevalent. Finally, the consequences of asymptomatic or proton pump inhibitor (PPI)-responsive GER after POEM had not been clear at the time.

When objective data are reviewed, such as erosive esophagitis in EGD and/or an abnormal acid exposure on a pH study, the prevalence of GER after POEM appears to be in recent studies high and varies between 20% and 46% after POEM [51, 63–65]. Barrett's metaplasia has been reported in first few cases as found earlier after Heller myotomy [66, 67].

In patients with a hiatal hernia, the risk for erosive esophagitis and GERD post-POEM seems increased [68]. If the rates can be compared to those seen with Heller myotomy plus partial fundoplication had been long time contradictory [69–71]. Kumbhari et al. note that when Heller myotomy was first introduced, it was not combined with an anti-reflux procedure and initially not deemed necessary [72]. Subsequently a high rate of GERD became evident, and a partial fundoplication became standard practice [70, 73, 74].

Kumbhari et al. analyzed results from seven tertiary academic centers (one Asian, two US, four European). POEM had been carried out in 467 patients during the 5-year study period. A total of 282 patients were included in the analysis. One hundred eighty-five patients were excluded because no pH study was performed at ≥3 months after POEM. A post-procedure DeMeester score of ≥14.72 was seen in 57.8% of patients. Multivariable analysis revealed female sex to be the only independent association (odds ratio 1.69, 95% confidence interval 1.04–2.74) with post-POEM GER. No intraprocedural variables were associated with GER. Upper GI endoscopy was available in 233 patients, 54 (23.2%) of whom were noted to have reflux esophagitis (majority Los Angeles grade A or B). GER was asymptomatic in 60.1%. The authors concluded that post-POEM GER was seen in the majority of patients. No intraprocedural variables could be identified to allow for potential alteration in procedural technique.

Repici et al. published a meta-analysis on gastroesophageal reflux disease after POEM as compared with laparoscopic Heller's myotomy plus fundoplication published until February 2017 [65]. They identified 17 and 28 prospective studies, including 1542 and 2581 subjects who underwent POEM and LHM, respectively. Pooled rate of post-procedure reflux symptoms was 19.0% (95% CI, 15.7–22.8%) after POEM and 8.8% (95% CI, 5.3–14.1%) after LHM, respectively. Pooled rate estimate of abnormal acid exposure at pH monitoring was 39.0% (95% CI, 24.5–55.8%) after POEM and 16.8% (95% CI, 10.2–26.4%) after LHM, respectively. Rate of post-POEM esophagitis was 29.4% (95% CI, 18.5–43.3%) after POEM and 7.6% (95% CI, 4.1–13.7%) after LHM. At meta-regression, heterogeneity was partly explained by POEM approach and study population. They concluded that the incidence of reflux-disease appears to be significantly more frequent after POEM than after LHM with fundoplication. pH monitoring and appropriate treatment after POEM should be considered in order to prevent long-term reflux-related adverse events [65].

However, long-term results after LHM indicate that the antireflux effect of the fundoplication might only be of temporary nature. In their editorial, Rosch et al. asked the question "Will Reflux Kill POEM?" [66]. Rosch discusses that only one small randomized controlled trial ($n = 43$) has been published showing reflux rates of 9.1% versus 47.6% in the groups of Heller myotomy with and without Dor fundoplication, respectively [73]. Kummerow Broman et al. published the long-term symptomatic follow-up results on part of this group in 2018 [75]. They collected patient-reported measures of dysphagia and gastroesophageal reflux using the Dysphagia Score and the Gastroesophageal Reflux Disease-Health-Related Quality of Life (GERD-HRQL) instrument. Patient-reported re-interventions for dysphagia were verified by obtaining longitudinal medical records. Among living participants, 27/41 (66%) all completed the follow-up study at a mean of 11.8 years postoperatively. Median Dysphagia Scores and GERD-HRQL scores were slightly worse for Heller than Heller plus Dor but were not statistically different (6 vs 3, $p = 0.08$ for dysphagia; 15 vs 13, $p = 0.25$ for reflux). Five patients in the Heller group and six in Heller plus Dor underwent re-intervention for dysphagia with most occurring more than 5 years postoperatively. One patient in each group underwent redo Heller myotomy and subsequent esophagectomy. Nearly all patients (96%) stated that they would undergo operation again. The authors concluded that long-term patient-reported outcomes after Heller alone and Heller plus Dor for achalasia were comparable, providing support for either procedure [75].

There is no consensus on how to manage patients with symptomatic gastroesophageal reflux disease, but a primary attempt with low-dose PPIs seems to work well for most patients [8, 10, 32, 38–45]. In case of the necessity of a secondary fundoplication only a partial or "floppy" fundoplication is recommended in order to not impair esophageal emptying with secondary dysphagia again [8, 10, 32, 38–45]. Kumta et al. even reported one case of endoscopic fundoplication in an patient with gastroesophageal reflux symptoms refractory to proton pump inhibitors [76].

Training in POEM

Requirements to Perform POEM

The first step for a "POEM learner" is an excellent knowledge of the specific thoracic and abdominal anatomy and the different steps of the procedure [77]. The second step is usually an "ex vivo" and "in vivo" training in the porcine model similar to ESD training [78]. The first clinical POEM cases in patients should be accompanied by an expert endoscopist from an external POEM referral center [79].

The NOSCAR (Natural Orifice Surgery Consortium for Assessment and Research) has proposed the following prerequisites for an endoscopic team planning to perform POEM in the future [46]:

1. A multidisciplinary team encompassing endoscopists and surgeons.
2. "Ex vivo" experience with animal or cadaver models before planning to perform first POEMs in humans.

3. A local institutional review board approval.
4. All cases should be registered in an outcome registry maintained by the concerned scientific societies.

Clinical Training in POEM

In general, it is recommended to start with POEM after reaching the top level of the endoscopic learning pyramid [80]. However, until today there are no valid data if an endoscopist experienced, e.g., in endoscopic submucosal dissection (ESD) acquires competence in POEM faster than an endoscopist without this qualification. Mittal et al. state that most advanced endoscopy training programs in the United States do not provide formal training in submucosal endoscopy or POEM [7]. In Europe, POEM procedures have been limited to a few centers so far and have been performed by experienced endoscopists only. As the procedure is carried out in the thoracic cavity close to the mediastinum in case of complications such as infection, bleeding or perforation consequences may be severe. It seemed logic that an extensive experience in interventional endoscopy, especially in hemostasis and perforation closure, seems necessary as well as the need for a specialized surgical team in case of severe complications. Furthermore the number of patients concerned is limited.

The ASGE recommends that competence acquisition in a "major skill" like POEM should be performed at teaching institutions with appropriate numbers using a preceptorship model. A quorum of procedures required to assess POEM has not been defined so far. In centers familiar with POEM, clinical training is mostly started by an advanced fellow or experienced consultant [7].

Before starting POEM, an intensive study of the literature, watching videos, attending live demonstrations, and a hands-on training course are usually recommended. Early training steps of POEM include a progressive approach to the technique in "ex vivo" pig esophagi. Training in live pigs is a common next step to train the technique in an environment with natural GI motility and vascularization. However, the discrepancy of the tender muscle layer in pigs and the potentially hypertrophic muscle layer in humans has to be noted as significant difference and limitation (Fig. 19.7a, b). After having attended a systematic course with practical exposure to the technique, a visit to an expert center is recommended to observe and assist the performance of several procedures. A close student–teacher relationship and sufficient phases of watching the procedure seem important

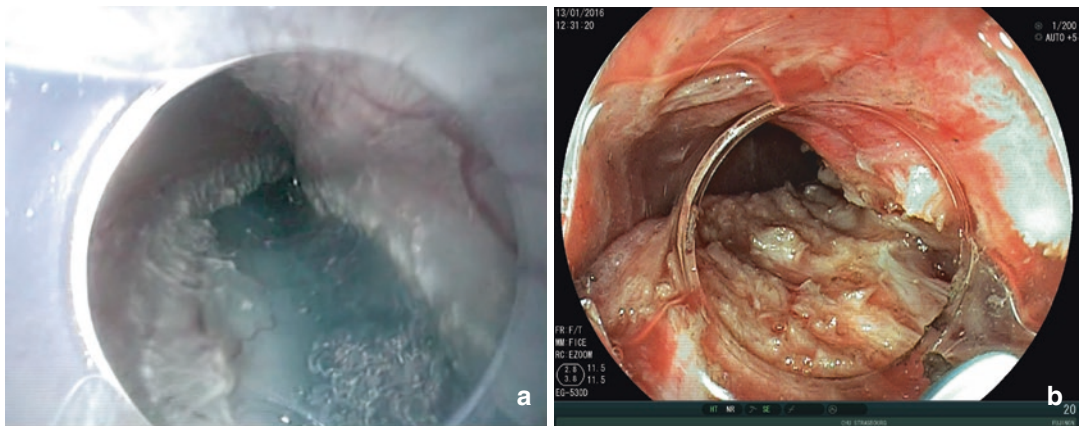

Fig. 19.7 Training for POEM in the animal model and situation in 'the real world': discrepancy in thickness of the tender muscular layer in the pig (**a**) and in a patient with achalasia Type III and enormous hypertrophy of the muscular layer (**b**)

Table 19.2 POEM training steps and protocol according to Dacha et al. [35]

Steps	Assessment parameters
Step 1: Dissection, establishing a submucosal tunnel	1. Able to identify the orientation of the submucosal tunnel, including the location of the mucosal layer and the location of the muscular layer 2. Able to judge need for more submucosal injection while performing submucosal dissection to prevent inadvertent complications 3. Able to secure hemostasis with a knife or a coagulation forceps 4. Able to perform all of the above without instructions and assistance from the mentor
Step 2: Myotomy inside the submucosal tunnel	1. Continue all above listed in step 1 2. Able to identify gastroesophageal junction 3. Able to identify circular muscular layer 4. Able to identify longitudinal muscular layer 5. Able to perform myotomy either on circular muscular layer or full-thickness myotomy 6. Able to perform all above without instructions or assistance from the mentor
Step 3: Creating a submucosal tunnel orifice	1. Continue all above listed in step 1 and step 2 2. Ability to raise a mucosal bleb with submucosal injection prior to performing mucosotomy incision 3. Able to enter submucosal tunnel efficiently after performing mucosotomy incision (2 and 3 should take no longer than 15 min) 4. Able to perform all of the above without instruction and assistance from the mentor
Other trainings	1. Ability to safely close mucosotomy incision with endoclips 2. Able to safely use a Veress needle to decompress symptomatic capnoperitoneum (even if it is not encountered) 3. Able to perform all the above without instruction and assistance from the mentor

before a student goes to unsupervised clinical procedure. A short course or workshop seems not to be a good platform to gather sufficient knowledge (see also below) [81]. Didactic training and hands-on fundamentals seminars are available, e.g., from the American Society for Gastrointestinal Endoscopy (ASGE) [82].

Mittal et al. suggest the following areas to be covered during training for POEM [7]:

1. Interpretation of high-resolution manometry and barium esophagram
2. Diagnostic endoscopic evaluation of the esophagus, gastroesophageal junction, and stomach
3. Appropriate site selection for mucosal entry
4. Identification of esophageal wall layers during submucosal dissection
5. Identification of dissection planes and orientation of mucosa and muscle layer during submucosal tunneling
6. Identification of the anatomical changes and structures at the gastroesophageal junction and cardia
7. Identification of circular and longitudinal muscle planes
8. Performance of selective circular vs full-thickness myotomy
9. Management of bleeding
10. Management of mucosal injury or perforation
11. Mucosotomy closure

A similar "checklist" for the single clinical training steps in POEM has been described by Dacha et al. [35] (Table 19.2).

Training in Porcine Models

For training purposes, first steps are usually performed in the pig model even though the pig is not optimal due to its thin muscular layer compared to a patient with spastic esophageal motor disorder (Fig. 19.7a, b). Training may include "ex vivo" porcine specimens with an esophagus left in its total length as well as training on live pigs under general anesthesia in the acute animal experiment. Table 19.3 shows advantages and disadvantages of both models.

Ren et al. as well as Chiu et al. described the learning curve for POEM in the early days of POEM including "ex vivo" and live porcine

Table 19.3 Advantages (+ to +++) and disadvantages (− to −−−) of the "ex vivo" and "in vivo" porcine model for the training of the POEM procedure

Model	Costs	Ethical concerns	Assessment of trainee performance	Reality of environment Training of complication management (bleeding/perforation, etc.)
Ex vivo porcine model	++	++	++	−−
Live pig model	−−	−−	++	++

models. Ren et al. trained the procedure in a total of five ex vivo porcine specimen before starting with the first patient (see below). Chiu et al. trained in two acute and seven survival pig models. Perforations occurred in 3/5 "ex vivo" specimen and in 1/7 survival animal models with acute fatal pneumomediastinum in one animal. The latter was attributed to the use of room air instead of CO_2 during the experiments. Both groups rated a training in "ex vivo" specimen and live pigs as very valuable [83, 84]. With the clinical experience in POEM of today, tutored experimental experience and clinical proctoring would have been strongly recommended.

Hernandez Mondragon described his personal preclinical learning curve for POEM in 50 procedures performed in the animal lab [85]. He started with 30 procedures using a mannequin containing an "en bloc" organ package of the esophagus, stomach, and duodenum from the pig cleaned, prepared, frozen, and then thawed 1 h before the procedure in 25 °C warm saline. In a second learning section, POEM was carried out in 20 pigs with a weight of 40–50 kg which were followed for 30 days. The learning process was defined as ability to perform the five steps of POEM, while mastery of the technique was considered a complication-free procedure. Mucosotomies (mucosal injuries with communication between the submucosal space and esophageal or gastric lumen) or free perforation by the endoscope were documented endoscopically and on the specimen. Additionally, the animal group included the incidence of hemorrhage or procedure-related death. Subcutaneous emphysema, pneumomediastinum, pneumoperitoneum, or bleeding during the procedure were considered as Adverse Event only if they could not be controlled by endoscopic measures or medical maneuvers. The study seems to have been carried out meticulously but is hampered by its design with the same endoscopist performing procedures first "in vitro" and then "in vivo" with comparison of two sequential learning curves. The authors concluded that 16 "ex vivo" procedures and 10 in live pigs were necessary to perform the procedure without complications. After those numbers, the trainee gradually improved speed without scarifying safety [85]. The numbers given seem comparable to those recommended for the training in endoscopic submucosal dissection (ESD) where at least 25 preclinical resections "ex vivo" and "in vivo" are recommended [78, 86] (Fig. 19.3).

Clinical Learning Curve After Training

The role of prior experience of the trainee in tunneling techniques (ESD, etc.) and in the management of complications such as perforation and severe bleeding seems not completely clear so far. Werner et al. reported 24-month follow-up data of 80 patients who underwent POEM in a MC trial. More than half of the failures were reported during the first 10 procedures [39]. The authors concluded that there was a significant learning curve for POEM even for experienced interventional endoscopists. Kurian et al. analyzed their first 40 consecutive patients undergoing POEM. The learning curve plateau was at about 20 cases for an experienced endoscopist with no significant further increase in myotomy speed and length of procedure (LOP) thereafter. Patel et al. presented a paper about the personal learning curve of one of the first endoscopists performing POEM in the western world,

Stavros N. Stavropoulos from Mineola NY, USA. He described the grade of efficiency and mastery of POEM for 93 sequential procedures. The "efficiency" was reached when the procedure time started decreasing, and "mastery" was defined as plateau in procedure time (Fig. 19.8) [87]. In this analysis using penalized basis spline regression and CUSUM analysis, 40 procedures were required to gain "efficiency" and 60 procedures for "mastery" (Fig. 19.9). When the authors used adjusted regression analysis, only case number (operator experience) significantly affected procedure time (p <0.0001). The "trainee" had had prior experience in more than 60 upper and lower GI ESDs and a long experience in the management of complications such as severe bleeding or perforation [87].

Currently the optimal curriculum for POEM training is not clear. In every case, clinical proctoring at a high-volume institution seems an important step for successful clinical implementation of this technique [47]. Dacha et al. recently reported on the successful clinical integration of advanced fellows after their third year fellowship and experience in hundreds of gastroscopies and colonoscopies and at least 100 ERCPs and 100 EUS procedures. All of them had participated actively in at least five upper or lower ESD cases. The authors did split the procedure in different training steps the trainees had to successfully complete (Table 19.3). All four trainees successfully completed step 1 after an average of 4.25 patients (range 3–6), step 2 with an average of 4.0 patients (range 3–5), and step 3 with an average of 5.0 patients (range 3–6). Three of the four trainees did in the following start performing POEM independently. For each step in POEM, such as dissection, hemostasis, and myotomy, trainees needed 3–6 patients to acquire the adequate skill and to complete the step without instructions from the mentor. Finally, each of the "learners" performed two cases of an entire POEM with the mentor but without instructions from the mentor. The authors therefore considered the total

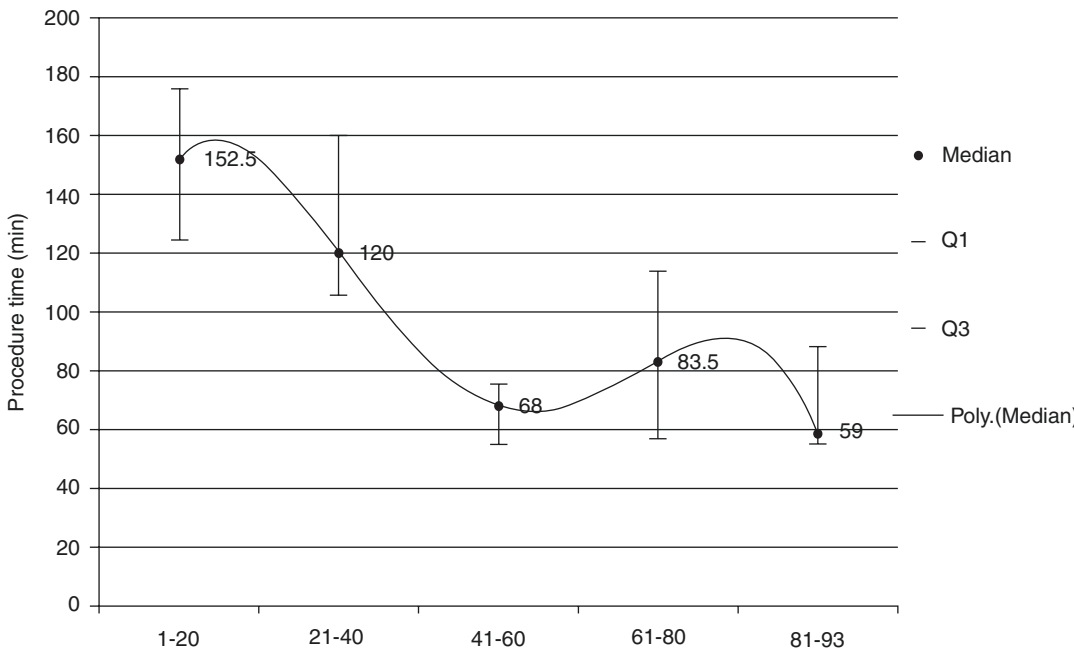

Fig. 19.8 Decrease of procedure time for POEM with increasing experience of a single endoscopist during his first 93 procedures. Sequential grouping of procedure time with median procedure time (interquartile range) in minutes. Adapted from Patel KS, Stavropoulos S. et al. [87]

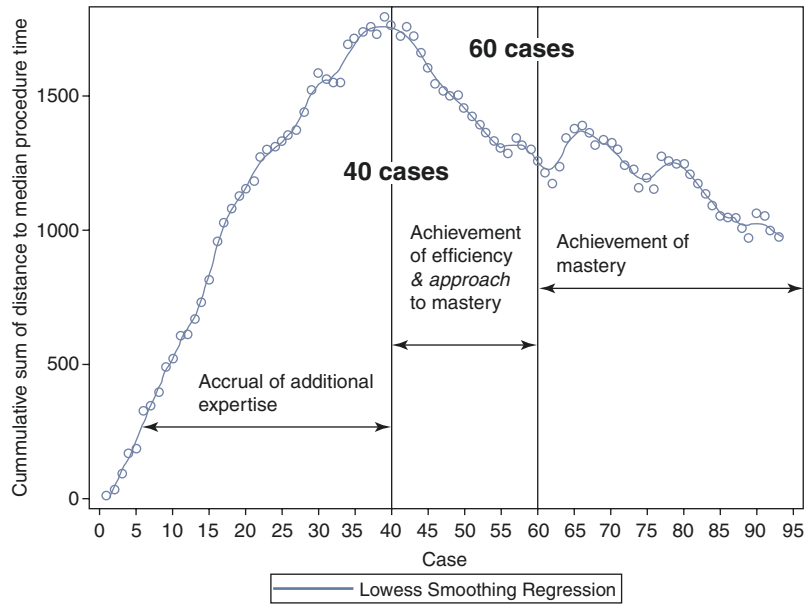

Fig. 19.9 Cumulative sum of distance to median procedure time presented as CUSUM plot for a single operator during his first 93 POEM procedures. The graph shows efficiency after 40 procedures and mastery after 60 procedures. From Patel KS, Stavros S et al. [87]

threshold number to be able to perform POEM independently about 20 cases per trainee [35].

POEM Training for All?

A study by Kishiki et al., published recently, reported on the learning progress of 65 participants in dedicated 1-day POEM training workshops at two US institutions [88]. Participants were mainly visceral surgeons in practice. Participants with more than 100 upper GI endoscopies were considered "experts," with less than 100 gastroscopies "novices." The authors called their project "into the fire." The 1-day training course included a hands-on pre−/posttest and a short quiz designed to assess participants' comprehension at the beginning and at the end of the course. Participants took part in lectures on patient selection, technique, troubleshooting, and discussion. Hands-on POEM training and competence assessment were evaluated on both "ex vivo" and "in vivo" porcine models using a new metrics for POEM performance. The participants were stimulated to start thereafter the procedure at their home institution.

This approach seems risky in case the procedure is carried out without adequate proctoring and sufficient competence in the endoscopic management of complications [47]. Unfortunately, an additional qualification of the participants has not been reported but would be desirable. One hundred diagnostic gastroscopies correspond to the level of a first- to second-year GI-fellow who would by far not qualify for the procedure. A surgical resolution of endoscopically manageable problems cannot be considered adequate for an endoscopic procedure. Clinical education and proctorship in interventional endoscopy including the early recognition and management of complications, such as severe bleedings or perforations and the handling of patients under critical clinical situations, take a long learning curve and are impossible to be replaced by pure training on pig models and lectures [89].

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