Treatment Modalities for Achalasia

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Abbreviations

ARM	Anti-reflux mucosectomy
EGD	Esophagogastroduodenoscopy
EGJ	Esophagogastric junction
GERD	Gastroesophageal reflux
HRM	High resolution manometry
IQR	Interquartile range
IRP	Integrated relaxation pressure
LES	Lower esophageal sphincter
LHM	Laparoscopic Heller myotomy
PD	Pneumatic dilation
PIVI	Preservation and incorporation of valuable endoscopic innovations
POEM	Peroral esophageal myotomy
PPI	Proton pump inhibitors
RCT	Randomized controlled trial

Introduction

Esophageal achalasia, is an uncommon esophageal motility disorder, with an incidence of 1/100,000 individuals per year and prevalence of 10/100,000. There is no gender or racial predilection and the peak incidence occurs between the third and the sixth decades of life. The disease may stem from an autoimmune,

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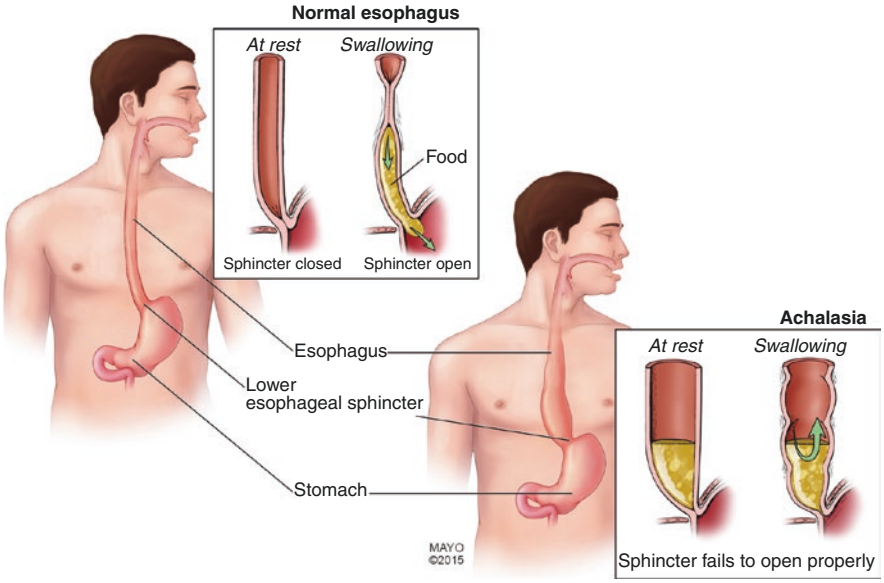

Fig. 6.1 Comparison of a normal esophagus to an esophagus with achalasia

viral or neurodegenerative process [1, 2]. Achalasia is characterized by failure of relaxation of the lower esophageal sphincter (LES) and the absence of progressive peristalsis in the distal esophagus, as shown in Fig. 6.1. In addition, intraluminal pressure in the esophagus may not be completely absent and, accordingly, patients with achalasia may have panesophageal pressurization or spastic contractions [3, 4].

Achalasia is incurable, yet a variety of treatment options are available and are capable of relieving the outflow obstruction at the esophagogastric junction (EGJ) [4]. This chapter will discuss the pathophysiology, clinical presentation, diagnosis and endoscopic evaluation and treatment of achalasia.

Pathophysiology and Clinical Presentation

Achalasia is associated with a functional loss of inhibitory postganglionic neurons of the myenteric plexus in the distal esophagus and LES [5]. It is postulated that the mechanism behind the loss is inflammatory. Nitric oxide and vasoactive intestinal peptide, normally acting as neurotransmitters, lose their inhibitory function in the setting of achalasia. The resulting imbalance leads to unopposed cholinergic stimulation, resulting in impaired relaxation of the lower esophageal sphincter and hypercontractility of the distal esophagus. There is variability in presentation of these abnormalities, though impaired relaxation of the LES is the ultimate defining feature.

Patients with esophageal achalasia classically presents with regurgitation and dysphagia to both solids and liquids. Chest pain and weight loss are common as is heartburn. Achalasia, in fact, should be considered in the differential diagnosis of patients with gastroesophageal reflux (GERD) refractory to H2 blockers and proton pump inhibitors [6]. Finally, respiratory symptoms are be frequently encountered in patients with achalasia due to the decrease clearance of contents from the esophagus secondary to the primary motor abnormality.

Diagnosis

The main diagnostic procedures used when evaluating a patient with suspected achalasia include esophageal manometry, along with two complimentary tests, esophageal radiography (esophagram) and esophagogastroduodenoscopy (EGD) [4].

It is important to note that there are diseases that may mimic achalasia in its evaluation. These include pseudoachalasia, secondary achalasia and achalasia due to Chagas disease. EGJ adenocarcinoma comprises the most common malignancies of pseudoachalasia, along with pancreas, esophagus, lung, kidney, hepatobililary, lymphoma and mesothelioma. Secondary achalasia should be considered following fundoplication surgery or gastric banding due to the development of scar tissue or an overly tight fundic wrap [7, 8].

Radiography

An esophagram will demonstrate esophageal dilation, aperistalsis, and a "bird beak" appearance due to EGJ narrowing and decreased emptying of the contrast material (Fig. 6.2). It may also reveal a tortuous or "sigmoid" esophagus which is seen in end-stage achalasia. "megaesophagus or sigmoid esophagus", which is tortuous esophagus seen in end-stage achalasia. Esophagrams are essential for posttreatment follow up [4]. Obtaining a timed barium esophagram in this instance can help identify patients who are likely to eventually fail treatment despite early improvement in their symptoms [5].

Endoscopy

Endoscopic evaluation of achalasia is important in patients who undergo EGD for the assessment of GERD. It is crucial to rule out other causes of compromised relaxation of the EGJ or abnormal contractility of the esophageal body, as in mechanical obstruction or pseudoachalasia due to infiltrating malignancy [4, 6].

Endoscopy may demonstrate normal appearing esophagus, dilated esophagus, esophagitis with ulcers secondary to stasis or candida esophagitis. The EGJ may have the appearance of a thickened muscular ring and the endoscopist may face resistance as he attempts to enter the stomach [4]. In addition, esophageal biopsies

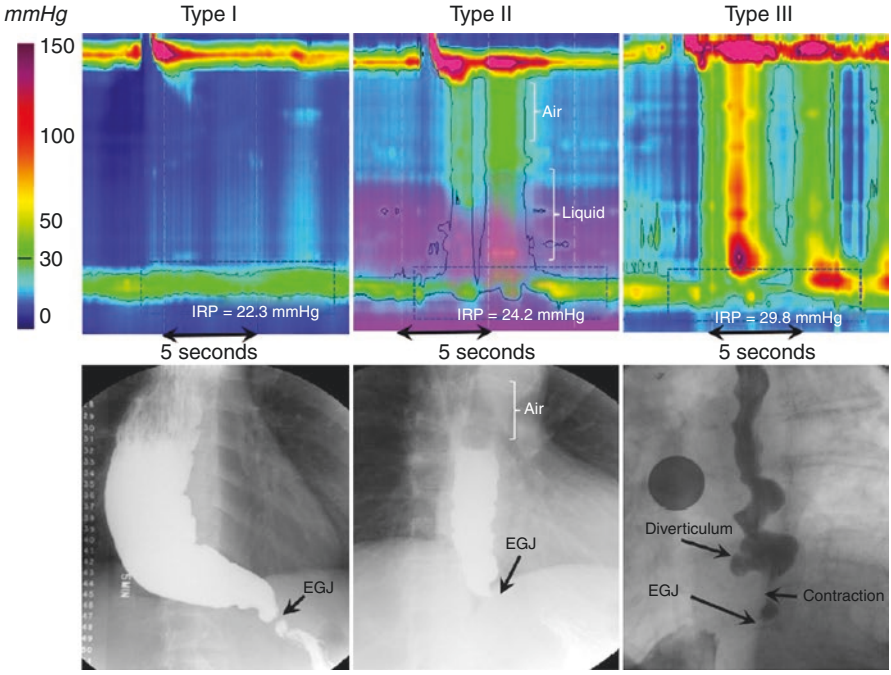

Fig. 6.2 High resolution manometry and Esophagram images comparing the three subtypes of achalasia [3]. *With permission from the Esophageal Center at Northwestern – John E. Pandolfino, MD*

in a patient with achalasia may show eosinophilia that responds to corticosteroids. This can be confused with eosinophilic esophagitis, making the presentation more complex. However, manometry along with the presenting symptoms of dysphagia can help differentiate achalasia from eosinophilic esophagitis [4, 7].

Esophageal Manometry

Esophageal manometry is essential in the diagnosis of achalasia. Esophageal manometry confirms the absence of peristalsis and incomplete relaxation of LES while excluding mechanical obstruction. Other findings that support the diagnosis include: elevated baseline pressures of the LES or the esophageal body or absence of simultaneous propagating contractile activity. This can be presented using the conventional manometry line tracing format or using esophageal pressure topography (high resolution manometry) [2].

In 2009, the Chicago Classification was first published to categorize esophageal motility disorders in high resolution manometry (HRM) using color pressure topography plots [8]. This classification was updated in 2011 and 2014 by the International HRM Working Group, to formulate version 3.0 of the Chicago Classification of esophageal motility disorders. It describes three subtypes of achalasia.

HRM tracings and esophagrams comparing the three subtypes of achalasia are shown in Fig. 6.2. Comparison is based on non-peristaltic contractility of the esophageal body and pressurization along with elevated integrated relaxation pressure (IRP) [3, 9]:

1. Type I achalasia (classic achalasia): Characterized by 100% absent peristalsis and no apparent esophageal contractility with elevated IRP > 10 mmHg. IRP is less than type II and III as there is no panpressurization of the esophagus.
   Esophagram shows dilated esophagus.
2. Type II achalasia (with esophageal compression): Abnormal relaxation of the EGJ with panesophageal pressurization that occurs with at least 20% of swallows (IRP > 30 mmHg).
   Esophagram findings correlate with manometry; air filling the proximal esophagus and liquid filling the distal esophagus.
3. Type III achalasia (spastic): Impaired EGJ relaxation and spastic contractions. To establish the diagnosis at least two swallows should be associated with a contraction that has distal latency <4.5 s. In addition, panesophageal pressurization, absent peristalsis or rapid contractions can be seen.
   Esophagram shows esophageal spasm with corkscrew pattern.

The Chicago Classification subtypes of achalasia help predict treatment response. Recent studies showed that type II achalasia patients experience the best treatment response (up to 96%). The lowest response rates were seen in type III achalasia (29–70%) [10]. Opioid use is associated with significantly higher IRP and esophageal manometric patterns consistent with type III achalasia. Therefore caution should be taken during interpretation of these patterns in opioid users [11].

Of note, abnormal EGJ relaxation pressure maybe associated with normal or weak peristalsis that does not meet the criteria for diagnosis of any of the achalasia subtypes. This is suggestive of EGJ outflow obstruction, which can be a manifestation of eosinophilic esophagitis, strictures, LES hypertrophy, paraesophageal hernia, pseudoachalasia or a variant of achalasia [1].

Treatment

While there is no cure for achalasia, current therapies are directed towards reduction of the LES's elevated pressure and improvement of patient's symptoms [4]. Because of their overall ineffectiveness, few studies support oral pharmacologic therapy, e.g. sublingual isosorbide dinitrate or sublingual nifedipine.

Botulinum Toxin Treatment

Botulinum toxin treatment is a safe and easy approach that is capable of LES baseline pressure reduction by about 50% [12]. It disrupts the neurogenic but not the myogenic component of the LES. The standard treatment is injection of 100 units

of the toxin in at least four quadrants just above the squamocolumnar junction [4]. Figure 6.3a illustrates this treatment.

While the response rate in the first month can reach up to 75%, the success rate at 1 year is only ~40% requiring repeat injection. It is uncommon to have serious adverse events secondary to this intervention, however up to 25% develop chest pain and on rare occasions mediastinitis occur with inflammatory or allergic reactions. For these reasons use of botulinum toxin treatment should be restricted to patients that are not candidates for endoscopic or surgical therapies.

Endoscopic Pneumatic Dilation

Pneumatic dilation is an effective endoscopic procedure in the management of achalasia. The goal of the procedure is to disrupt the myogenic component of the LES,

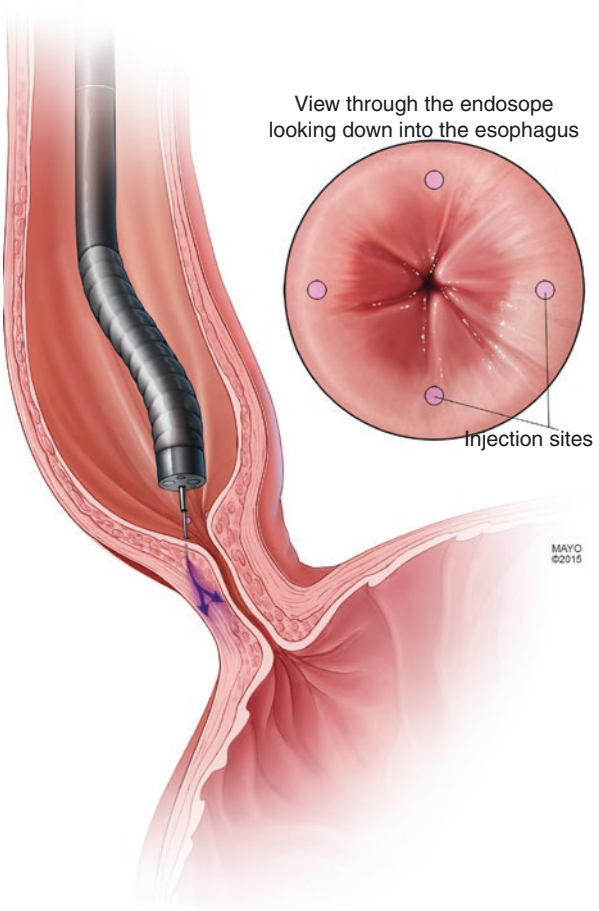

Fig. 6.3 (**a**) Example of botox injection into lower esophageal sphincter. (**b**) Example of pneumatic balloon dilation. (**c**) Example of the Heller myotomy and Toupet and Dor fundoplication

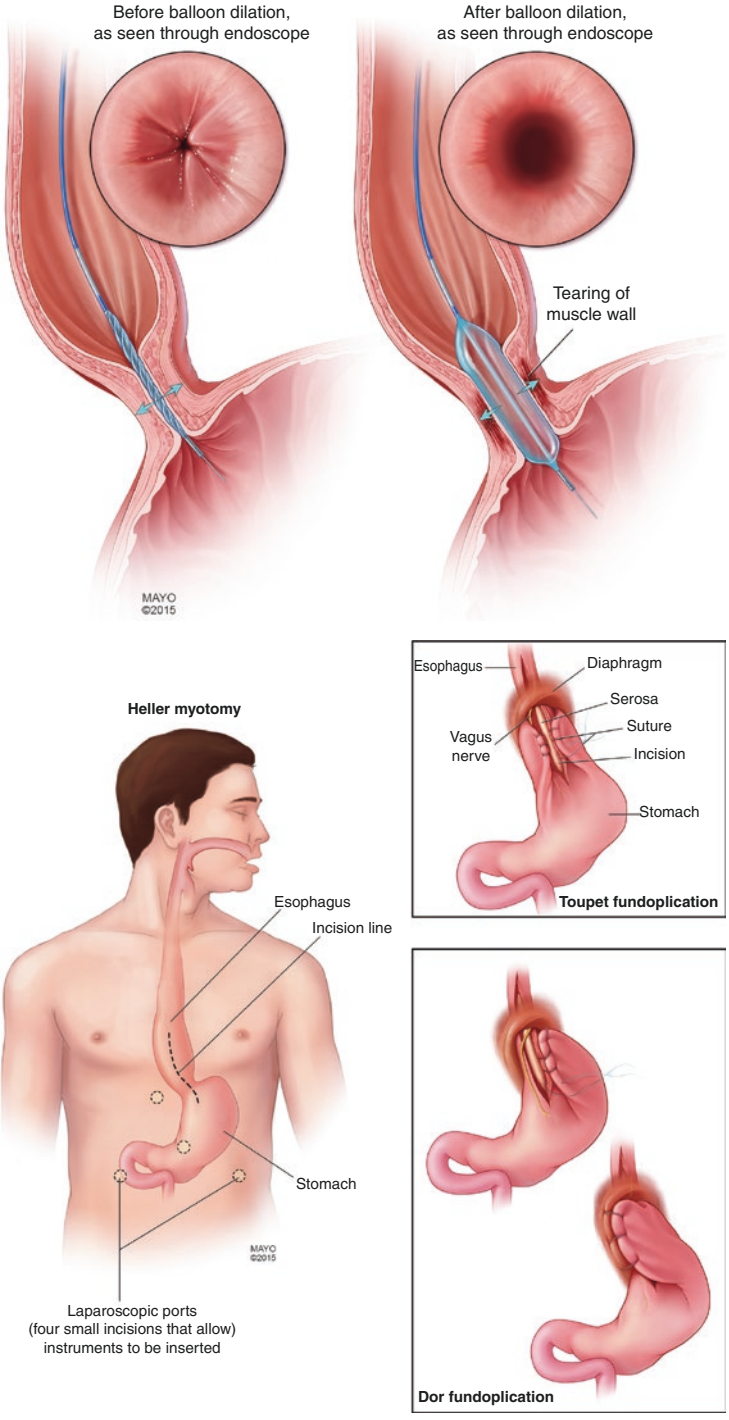

Fig. 6.3 (continued)

i.e. the circular muscle fibers. Air pressure is used to dilate the LES by way of a nonradiopaque polyethylene balloon with fluoroscopy guidance. "Rigiflex dilators" are available in three diameters, 3.0, 3.5 and 4.0 cm. Application of this technique requires expertise in the precise positioning across the LES, as shown in Fig. 6.3b. Distension of the balloon to the maximum diameter is important for effective dilation. The air pressure range is 8–15 psi and is applied between 15 and 60 s [4].

Larger diameter dilations of the LES correlates with increased symptomatic response, such that the greater the size of the dilator (3.0, 3.5 and 4.0 cm) the better symptom relief the patients experience (74, 86 and 90%) over at least the first 1.5 years following dilation [13]. However it has been also shown that more conservative dilations of smaller size (3.0 cm) over a shorter duration (15 s) are equivalent to longer and larger dilations [14]. Serial dilations are superior to single pneumatic dilations [15].

Patient response to treatment with pneumatic dilation is substantial, especially among type II achalasia patients [16]. However about 30% of the patients develop symptom recurrence over the following 5 years. In general, female patients, patients older than 45 years, or those who have a narrow esophagus prior to pneumatic dilation and or an LES pressure < 10 mmHg following dilation are likely to have better treatment response and symptomatic relief. Having type II achalasia on HRM is also predictive of better response to pneumatic dilation. However, male patients younger than 45 years may have suboptimal response to serial dilations. This is likely due to a thicker LES. These patients may benefit from balloons larger than 3.5 cm or may require myomectomy [4, 17].

While pneumatic dilation is a safe outpatient procedure, it may be complicated by esophageal perforation (median rate 1.9%). Therefore radiographic evaluation with gastrografin should be initiated in the setting of chest pain, vomiting or fever following pneumatic dilation. Small perforation can be managed conservatively with antibiotics, parenteral nutrition and stenting while larger defects may require surgical intervention including thoracotomy. Therefore, patients undergoing pneumatic dilation should be candidates for surgical intervention in case perforation occurs. Lower rates of perforation are seen among those who undergo serial balloon dilations. A more common adverse event of pneumatic dilation is GERD which occur in up to 35% of patients. This may lead to dysphagia secondary to esophageal stricture formation and PPI therapy should be instituted in this setting [4, 15].

Heller Myotomy

Heller myotomy is the standard surgical approach for the treatment of achalasia, which was first described by Ernest Heller in 1913 [18]. It involves division of the circular muscle fibers of the LES, and is successful in up to 94% of patients on long term follow up for up to 36 years. Over the years, minimally invasive laparoscopic myotomy has been developed, providing short term recovery and has lower morbidity rates [4]. Combination of myotomy with fundoplication, also known as modified

Heller myotomy is a more recent excellent surgical strategy with symptomatic relief being achieved in up to 97% of patients [19, 20]. Figure 6.3c illustrates this surgical intervention.

Different myotomy approaches have variable efficacies in terms of symptom improvement. Laparoscopic myotomy (LHM) has the highest efficacy (89%, range 77–100%), followed by the open transabdominal myotomy (85%, range 48–100%) and the thoracoscopic myotomy (78%, range 31–94%) [13]. Long term efficacy of LHM at 6 month and 6 year were 89 and 57%, respectively [4, 15]. Higher response rates are detected among type II achalasia (based on the Chicago Classification v3.0) patients compared to type I and III achalasia. In addition, type III achalasia can be well treated by LHM [16].

Heller myotomy is complicated by GERD in about one third of the cases regardless of the surgical modality, without fundoplication. However combining myotomy with fundoplication decreases the rate of developing GERD to 8–14% [13]. A randomized double-blind controlled trial compared the results on pH studies among those who underwent myotomy with or without fundoplication. It showed that abnormal acid exposure was found in 47% of patients without a fundoplication compared to only 9% among those who had Dor fundoplication performed following myotomy [21]. In addition, this combined technique is more cost effective than myotomy alone given the decreased need for GERD treatment [22]. There is a risk of developing dysphagia among patients undergoing myotomy which is independent from combining it with a fundoplication or not. Nonetheless, PPI therapy is needed for those who complain of heartburn and reflux symptoms after this procedure [4, 13].

Peroral Endoscopic Myotomy

Per-oral endoscopic myotomy (POEM) is an endoscopic approach for the treatment of achalasia. This natural orifice transluminal endoscopic surgery was first described experimentally in 2007 and was first performed in humans in 2008. The initial report showed a significant change in the LES pressure among the pigs who underwent this procedure with a drop from 16.4 to 6.7 mmHg [23, 24]. POEM is safe with excellent efficacy in parallel to surgical myotomy, and is indicated in the treatment of the three achalasia subtypes of Chicago Classification version 3.0 [10, 24, 25].

POEM commonly consists of four endoscopic steps, as shown in Fig. 6.4. Figure 6.4a–f show the procedure in details. Around 2 days prior to POEM, EGD is performed to assess the mucosa and look for food retention. Prophylactic antibiotics are given, commonly a third generation cephalosporin. The initial step in POEM includes a mucosal incision, and then submucosal tunneling followed by myotomy before closure of the mucosal flap. A study of 500 patients who underwent POEM reported a median procedure time of 90 min (interquartile range [IQR] 71–120 min), median myotomy length of 14 cm (IQR 12–16 cm), and median length of hospital stay of 4 days (IQR 4–5 days). The full overview of POEM procedure and its

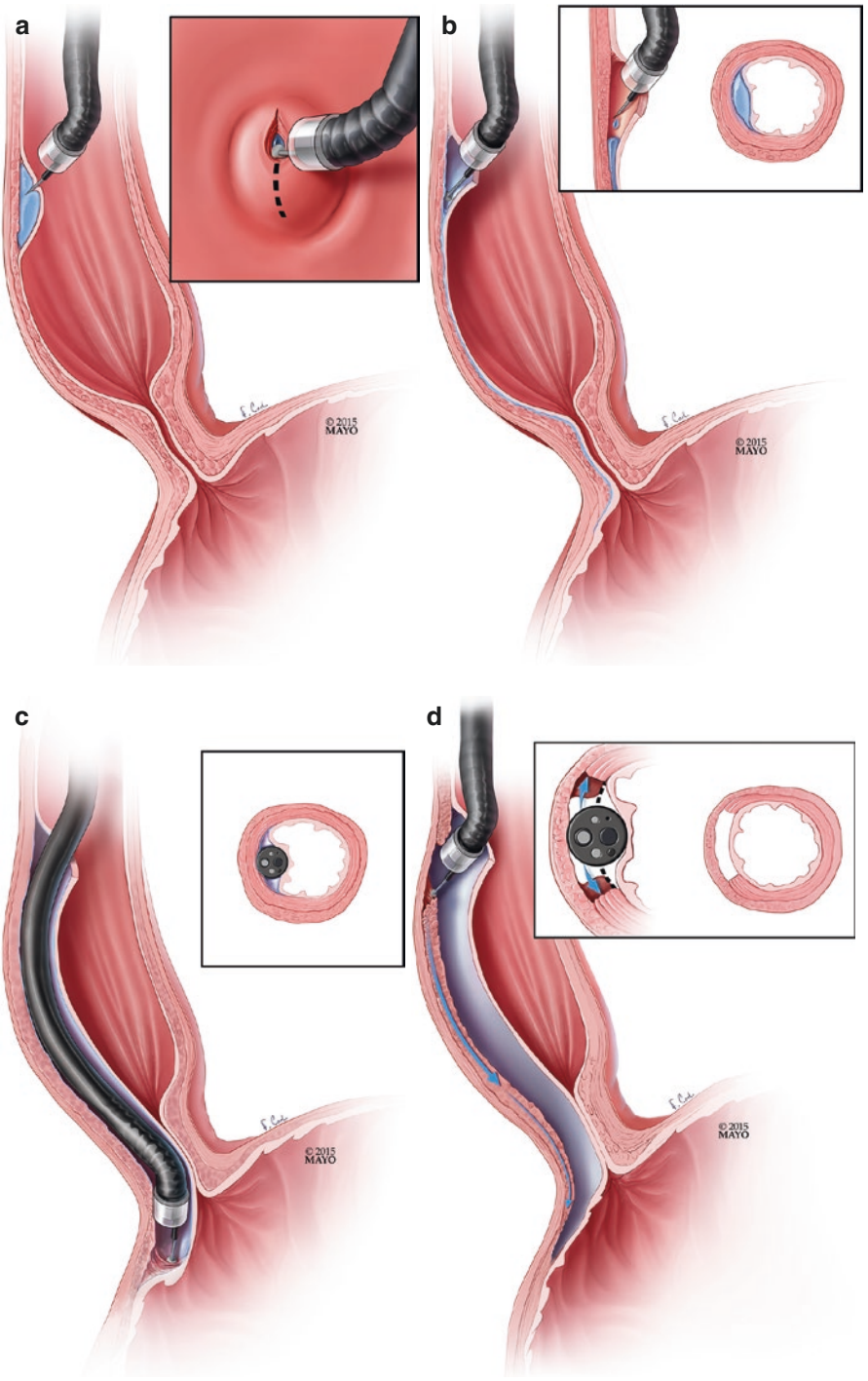

Fig. 6.4 POEM procedure. Figures (**a**)–(**f**) show the procedure in details

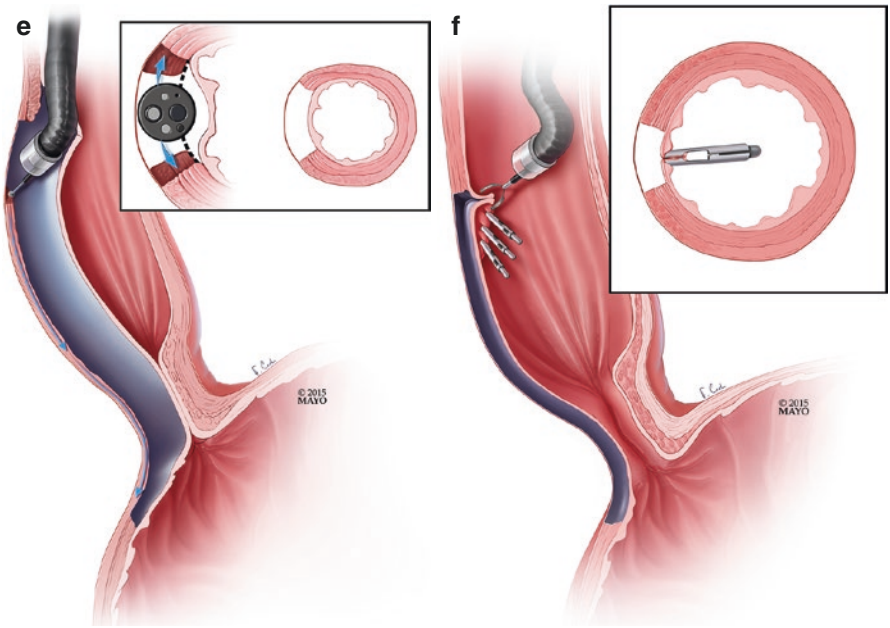

Fig. 6.4 (continued)

technical details can be reviewed at the American Society of Gastrointestinal Endoscopy website (*www.giejournal.org*) (video of the procedure is also available) [24, 25].

Success of the procedure can be assessed using a timed barium esophagram and measuring a change in LES pressure and IRP as well as the GEJ distensibility index. Clinically the Eckardt score can assess for symptom improvement, with a score of <3 suggesting a successful outcome. Inoue et al. showed a decrease in the Eckardt score from 6 (range 5–8) before POEM to 1 (range 1–2) at 3 years ($p < 0.01$). In the same study, the decrease in the median LES pressure was from 25 mm Hg (range 18–35 mm Hg) to 12 (range 10–15 mm Hg) at 3 years. Such findings were supported by international prospective multicenter studies and meta-analyses. In addition, the quality of life of patients with achalasia who underwent POEM improved significantly. This was assessed using the short form SF-36 [24, 25].

Efficacy of POEM has been evaluated by the American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations). The threshold efficacy was set at 80% at least 12 months after the procedure. This was defined as Eckardt score ≤3 (dysphagia component of ≤2) and a ≤6% serious adverse event rate. The 30-day mortality rate was ≤0.1% [26]. While efficacy of other treatment approaches (LHM and PD) is low in type III achalasia, POEM is effective in type III achalasia of Chicago Classification with symptom relief in 91% of patients at 24-month follow up [10, 27]. In octogenarians POEM is also safe and efficacious with up to 91% success rate on median follow up of 8–9 months [28].

Some studies reported persistence of GERD symptoms in less than one third of the patients. Adverse events has been reported with variable rates and include: endoscopic evidence of esophageal erosions, pneumo−/capnoperitoneum, pneumo−/capnomediastinum, pneumo−/capnothorax, aspiration pneumonia, subcutaneous emphysema, mucosal flap injury, accidental full-thickness muscle perforation, peritonitis, mucosal ulceration, submucosal hematoma, pleural effusions and atelectasis, leaks and perforations, esophageal strictures, dehiscence at tunnel entry, submucosal fistula, seizures and atrial fibrillation [26]. In octogenarians, a study of 76 patients with mean age of 84 years showed that in patients with achalasia (type I-III) who underwent POEM procedure, adverse events were slightly higher than in previous reports. Six capnoperitoneum/mediastinum were symptomatic and there were two esophageal leaks [28].

Certain comorbidities including cirrhosis with portal hypertension and prior radiotherapy of the thorax or abdomen may be contraindications to POEM. It may also be contraindicated in patients with prior endoscopic interventions of the esophagus including mucosal ablation, mucosal resection or submucosal dissection [24].

Controversies in Management

Achalasia subtypes of the Chicago Classification help predict treatment response. Type II achalasia patients experience the best treatment response (up to 96%), however type III achalasia is associated with the lowest response rates (29–70%) [10]. Type I & II achalasia respond to either endoscopic or surgical therapies (LHM, Pneumatic dilation, and POEM). Achalasia type III responds best to POEM [20, 27, 29]. Botulinum toxin treatment should be reserved for patients who are poor candidates for endoscopic or surgical therapies. Except for select patients where PD is a potential treatment option, POEM and LHM with fundoplication remains the main treatment modality for achalasia. Standard myotomy of the LES should be adequate in classic achalasia (achalasia types I and II), while extensive myotomy is preferred in type III achalasia to achieve a better clinical response. Extensive myotomy can be achieved with POEM [30].

POEM has favorable outcomes when compared with other treatment modalities. A randomized controlled multicenter trial (RCT) in 133 treatment naïve patients with achalasia showed that POEM had higher success rates compared to PD, 92 vs. 70% respectively. One esophageal perforation was reported as a major adverse event in the PD group. No major adverse events were reported among patients who underwent POEM. GERD was reported following POEM among 49% of patients based on pH monitoring compared to 39% of patients who underwent PD and 9% who underwent LHM with fundoplication [13, 26]. POEM was associated with higher clinical success rates compared to LHM with fundoplication for achalasia type III. The reported response rates were 98% in the POEM group compared to 80% in the LHM with fundoplication group. This is due to POEM's ability to perform an extensive myotomy (16 vs. 8 cm). Comparison of both groups showed that POEM was associated with shorter procedure time and lower rates of adverse events (6 vs. 27%). However, patients who underwent POEM had a shorter follow up period (8.6 vs. 21.5 months) [30].

In experienced centers, POEM was associated with 0–1% major adverse events and 92–100% success rates despite having a short term follow up. Post POEM GERD occurred at a rate of 22–53%, and 0–3% required additional anti-reflux surgery. The endoscopic modality of POEM does not allow performance of anti-reflux surgery. However anti-reflux surgery may not be necessary in all patients undergoing POEM. Similarly fundoplication is not absolutely necessary following LHM. With limited hiatal dissection, LHM with or without Dor fundoplication was associated with similar rates of GERD at 3 year followup [31]. Recently, endoscopic anti reflux mucosectomy (ARM) procedure was described for post POEM GERD. Surgical fundoplication is an option if ARM fail, especially if the patient has a significant hiatal hernia [32].

The POEM procedure has gained acceptance worldwide in less than a decade. It changed the treatment paradigm of achalasia. However, further research studies are needed to further evaluate the technical aspect of this procedure and its' outcomes. This include full thickness versus circular muscle myotomy, anterior versus posterior approach of POEM, endoscopist positioning, type of knife, injectant for the tunnel, fluoroscopy-assisted determination of the GE junction and endoscopic closure methods (clipping vs. suturing). The learning curve of POEM is a limitation [24].

POEM is a safe and effective treatment modality for achalasia. In experienced centers, it is not limited by age, esophageal anatomy (even in sigmoid esophagus), or history of prior treatment for achalasia. Adverse event rates are low and are rarely clinically significant. If POEM procedure fails, repeat POEM has been successful in most cases. Esophagectomy may be considered if LHM has failed. Treatment for achalasia should be tailored based on patient characteristics, patient preference and local expertise until prospective randomized controlled trials with long term follow up are available.

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