Chapter 11
Endoscopic Management of Achalasia

Eric S. Hungness and Peter J. Kahrilas

Abstract Achalasia is an esophageal motility disorder characterized by impaired LES relaxation and absent peristalsis in the distal esophagus. Note, however, that absent peristalsis means that there is no progressively sequenced esophageal contraction; it does not imply the complete absence of esophageal contractions or intraluminal pressure. In fact, spastic contractions and panesophageal pressurization of the esophagus are often seen in patients with achalasia, and these criteria are now part of the Chicago classification for subtypes of achalasia (Bredenoord AJ, Fox M, Kahrilas PJ et al, Neurogastroenterol Motil:24(Suppl 1):57, 2012). The scope of endoscopic treatment for achalasia has also evolved over the past 5 years with the emergence of per-oral endoscopic myotomy.

Keywords Myotomy • Achalasia • Endoscopic • Submucosal • Manometry • Pneumatic • Dilation

Introduction

Achalasia is an esophageal motility disorder characterized by impaired LES relaxation and absent peristalsis in the distal esophagus. Note, however, that absent peristalsis means that there is no progressively sequenced esophageal contraction; it

E.S. Hungness, MD (✉)
Department of Surgery, Feinberg School of Medicine, Northwestern University,
676 St Clair St, Suite 650, Chicago, IL 60611, USA
e-mail: ehungnes@nmh.org

P.J. Kahrilas, MD
Department of Medicine, Feinberg School of Medicine, Northwestern University,
Chicago, IL 60611, USA
e-mail: p-kahrilas@northwestern.edu

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does not imply the complete absence of esophageal contractions or intraluminal pressure. In fact, spastic contractions and panesophageal pressurization of the esophagus are often seen in patients with achalasia, and these criteria are now part of the Chicago classification for subtypes of achalasia [1]. The scope of endoscopic treatment for achalasia has also evolved over the past 5 years with the emergence of per-oral endoscopic myotomy.

Pathophysiology

The loss of functional myenteric ganglion neurons in the distal esophagus and lower esophageal sphincter (LES) is the hallmark pathology of achalasia [2]. This likely occurs as an autoimmune process triggered by an indolent viral infection in a genetically susceptible host [3]. From a functional viewpoint, inhibitory myenteric plexus neurons in the LES are uniformly affected while the degree of functional impairment observed in the distal esophagus and with excitatory (cholinergic) myenteric plexus neurons is variable among cases. Dysfunction of inhibitory post-ganglionic neurons results in an imbalance between excitatory and inhibitory control causing impaired deglutitive LES relaxation and either absent or spastic contractility in the adjacent distal esophagus.

The distal esophagus adjacent to the LES has no myogenic tone making it flaccid in the absence of neuronal stimulation. Paradoxically, selective loss of inhibitory myenteric plexus neurons with preservation of excitatory (cholinergic) neurons in this region leads to a pattern of premature contraction [4] causing bolus trapping in the distal esophagus ("corkscrew" or "rosary bead" esophagus) as seen with distal esophageal spasm. The same mechanism may be involved when panesophageal pressurization is seen and that may represent an early stage of achalasia when the primary abnormality of outflow obstruction is associated with preserved esophageal shortening, UES contraction, and some preserved circular muscle contraction [5, 6]. Absent peristalsis might then represent late stage disease due to more widespread neuronal degeneration and/or long-term obstruction. If left untreated, achalasia can progress to severe esophageal dilatation and deformation (sigmoid esophagus) associated with increased morbidity and decreased treatment efficacy.

Clinical Presentation

Achalasia is rare with an annual incidence of 1 per 100,000 and a prevalence of 10 in 100,000, most presenting between the ages of 30 and 60 years [7]. The primary presenting symptom is dysphagia for both solids and liquids. The dysphagia occurs with such consistency that patients often learn to adapt to the condition, simply describing themselves as "slow eaters." The dysphagia is often accompanied by non-bilious regurgitation of undigested food and saliva minutes, hours, or even days

after the meal. Regurgitation episodes can occur when trying to sleep flat requiring patients to elevate the head of the bed or even sleep upright. Patients also sometimes experience chest pain or heartburn making the distinction between achalasia and reflux disease difficult and leading experts to recommend that esophageal manometry be a routine part of the workup prior to antireflux surgery [8, 9]. It is important to note that the etiology of chest pain in achalasia is less clear than is that of dysphagia or regurgitation and its response to therapy is less predictable.

Diagnosis

The diagnosis of achalasia is contingent on demonstrating impaired LES relaxation and absent peristalsis without partial esophageal obstruction near the LES by a stricture, tumor, vascular structure, implanted device (e.g., Lapband), or infiltrating process [9]. Thus, the minimal requisite evaluation should include manometry to document the motor findings and appropriate imaging studies to rule out obstruction. With regard to esophageal manometry, a major technological evolution has occurred during the last decade with the widespread adoption of high-resolution manometry (HRM) systems. As a result of this technology, the criteria for making a diagnosis of achalasia have been tightened [1], and physiologic subtypes have been identified using the new metric of integrated relaxation pressure (IRP) to define the hallmark feature of the disease [5]. Measurement of the IRP utilizes an "electronic sleeve sensor" that compensates for potential LES movement by tracking the sphincter within a specified zone. It is calculated as the 4-s mean of maximal EGJ relaxation after swallow initiation, providing the most accurate and objective assessment of EGJ relaxation [10].

With the adoption of HRM, three distinct subtypes of achalasia have been quantitatively defined (Table 11.1) [5] with numerous subsequent publications supporting the prognostic value of this classification [11–13]. Type II patients have the best prognosis with myotomy or pneumatic dilation, while the treatment response of type I patients is less robust. Type III patients have the worst treatment outcomes, likely because the associated spasm is less likely to respond to therapies directed at the LES.

The other absolute requirement to establish a diagnosis of achalasia is inclusion of an imaging study (usually endoscopy) to rule out pseudoachalasia. Upper endoscopy can help determine the degree of esophageal dilatation, whether or not there is significant esophageal retention of food and fluid, and evaluate for Candida esophagitis. A barium esophagram is also often done and may help in instances where there are equivocal manometric findings or when the manometry catheter cannot be passed into the stomach due to severe esophageal dilatation and angulation. The esophagram can also quantify the degree of esophageal emptying if done as a "timed barium esophagram" protocol (200 ml of barium with upright images at 1, 2, and 5 min). Endoscopic ultrasound and/or CT may be necessary when suspicion of pseudoachalasia is high.

Table 11.1 HRM with pressure topography definitions of achalasia

Achalasia subtype	Manometry criteria
Type I (classic)	Impaired EGJ relaxation (IRP >10 mmHg)
	Absent peristalsis
	No significant esophageal pressurization
Type II (with compression)	Impaired EGJ relaxation (IRP >15 mmHg)
	Absent peristalsis
	≥20 % swallows with panesophageal pressurization to >30 mmHg
Type III (spastic)	Impaired EGJ relaxation (IRP >17 mmHg)
	Absent peristalsis
	≥20 % swallows with premature contractions (distal latency <4.5 s)
EGJ outflow obstruction[a]	Impaired EGJ relaxation (IRP >15 mmHg)
	Some preserved weak or normal peristalsis

[a]This group is heterogeneous but includes cases of variant achalasia

Endoscopic Management

There are three endoscopic options for achalasia that merit discussion: botulinum toxin injection, pneumatic dilation, and per-oral endoscopic myotomy. In general, medical therapy with smooth muscle relaxants is ineffective and should be reserved for patients with substantial comorbidity making them poor risks for anesthesia and/or surgery. Patients who are judged fit for general anesthesia should be counseled to pursue a definitive treatment capable of alleviating EGJ outflow obstruction such as endoscopic pneumatic dilation, endoscopic surgical myotomy, or laparoscopic Heller myotomy. Surgical myotomy will be discussed in the subsequent chapter of this text.

Endoscopic Injection of Botulinum Toxin

The standard protocol for endoscopic botulinum toxin (Botox) injection into the LES is to inject 100 units with a sclerotherapy needle about 1 cm proximal to the squamocolumnar junction in four radially dispersed aliquots. Using this technique, Pasricha reported improved dysphagia in 66 % of achalasia patients for 6 months [14]. Botox prevents acetylcholine release at cholinergic synapses thereby negating the effect of these nerves on the sphincter. The physiologic effect is eventually reversed by axonal regeneration and most patients who derive benefit from the procedure relapse and require retreatment within 12 months. However, there have been reports that repeated treatments result in fibrosis of the sphincter making subsequent Heller myotomy more challenging [15–17]. Recognizing these limitations, Botox injection should not be utilized as a first-line therapy for achalasia for most patients. Rather, it should be reserved for poor surgical candidates and special circumstances.

Pneumatic Dilation

An achalasia dilator is a noncompliant, cylindrical balloon that is positioned across the LES and inflated with air using a handheld manometer. The only design currently available in the USA, the Rigiflex dilator, is positioned fluoroscopically over a guidewire and is available in 30, 35, and 40 mm diameters. Bougie and standard through-the-scope balloon dilators (maximal diameter of 20 mm) have no sustained efficacy in achalasia and should not be used. A cautious approach to dilation with the Rigiflex dilators is to initially use the 30 mm dilator and follow with a 35 mm dilator 2–4 weeks later if the initial dilation was insufficient. The reported efficacy of pneumatic dilation ranges from 32 to 98 % [18]. Patients with a poor result or rapid recurrence of dysphagia are unlikely to respond to additional dilations, but subsequent response to myotomy is not influenced. The major complication of pneumatic dilation is esophageal perforation. Although the reported incidence of perforation from pneumatic dilation ranges from 0 to 16 %, a recent systematic review on the topic concluded that using modern technique, the risk was less than 1 %, comparable to the risk of unrecognized perforation during Heller myotomy [19]. Furthermore, most perforations are clinically obvious and when surgically repaired within 6–8 h have outcomes comparable to patients undergoing elective Heller myotomy.

Although there is no standardized approach to the technique of pneumatic dilation, there are some basic principles that should be followed (Table 11.2). The patient should have appropriate dietary instructions before the procedure so that there is minimal residual food in the esophagus during the procedure. The balloon dilator is completely deflated prior to both passage and prior to withdrawal using a T-piece and large syringe to minimize trauma to the oropharynx. Pneumatic dilation requires concomitant endoscopy and fluoroscopy to place and visualize the guidewire and to verify appropriate balloon position. Our practice has been to use stiff spring-tipped Savary guidewires rather than the flimsy wires provided by the manufacturer. The balloon size is chosen using a graded approach, starting with a 30 mm balloon and increasing to the 35 mm size if patients do not respond. We do not recommend using the 40 mm balloon because of reports suggesting an unacceptable perforation rate. Accurate placement of the balloon is crucial to the effectiveness of the procedure, and this must be verified fluoroscopically during the initial stages of balloon inflation (Fig. 11.1). The inflation pressure of the balloon is not stipulated; full effacement of the sphincter on fluoroscopy is the endpoint of interest, which is usually associated with distention pressures of 8–15 psi. Patients should be observed in recovery for at least 2 h with careful assessment for post-procedure pain. A gastrografin/barium swallow study should be obtained if there is any worry of perforation. Patients should be explicitly advised to seek care emergently if they develop fever, shortness of breath, severe pain (especially if pleuritic), or subcutaneous emphysema.

Studies using pneumatic dilation as the initial treatment of achalasia have reported excellent long-term symptom control. However, a third of patients will

Table 11.2 Pneumatic dilation protocol. "Recommended" should be universally applied while there is no consensus among experts on "other suggestions"

	Recommended	Other suggestions
Pre-dilation	N.P.O. ≥ 12 h	Clear liquids for 24–48 h
Anesthesia	Same as for diagnostic EGD	MAC or general
Dilator size selection	30 mm unless previously unsuccessful, either within the past month or in prior treatment series	35 mm balloon in young male patients
Positioning	Localize the EGJ using fluoroscopy over a stiff guidewire	
Balloon inflation	Slow inflation to capture the "waist" of the LES Deflate and reposition if the waist is not visible or is seen to migrate off the top of the balloon Maintain tension on the dilator during inflation to resist balloon getting "pulled" into the esophagus	Inflate balloon to at least 8 psi
Time of inflation	One inflation, slowly increasing balloon pressure until the "waist" of the LES is seen to fully efface on fluoroscopy; then fully deflate, aspirate empty with a large syringe connected by a T-piece, position the patient on their side, and remove wire and dilator in unison	Inflate balloon for 15–60 s Repeat the dilation twice
Post-procedure	Observe in recovery for at least 2 h Water-soluble contrast study prior to discharge if pain or other clinical parameters are concerning	Routine contrast study PRN pain medications 2 weeks of PPI therapy
Follow-up	Assess efficacy at 2–4 weeks, 6 months, and 12 months Repeat dilation with 35 mm dilator if treatment failure within 6 months	Repeat dilation at shorter intervals (2–4 weeks)

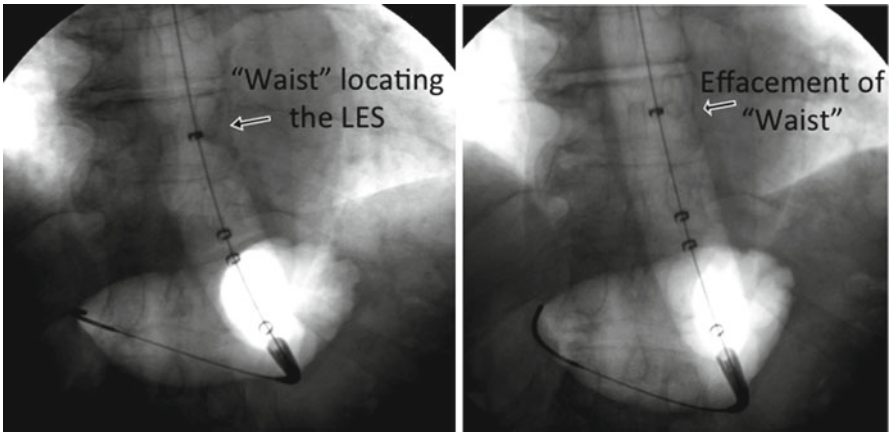

Fig. 11.1 Fluoroscopic images taken during pneumatic dilation showing proper localization of the LES on the expanding balloon (*left*) and complete effacement of the sphincter (*right*)

relapse in 4–6 years and may require repeat dilation. Response to therapy may be related to preprocedural clinical parameters, such as age (favorable if age > 45), gender (female > male) [20], esophageal diameter (inversely related to response), and achalasia type (type II better than I and III) [5, 13]. Although surgical myotomy has a greater response rate than a single pneumatic dilation, it appears that a strategy utilizing a series of dilations with the potential for repeat is comparable to surgery and a reasonable alternative to surgery. A recent randomized controlled trial compared this type of graded strategy to surgical myotomy and found it to be non-inferior in efficacy [21].

Per-oral Endoscopic Myotomy (POEM)

Although laparoscopic Heller myotomy and pneumatic dilation are effective treatments for achalasia, some drawbacks exist with each. Consequently, there has been interest in developing a hybrid technique incorporating an endoscopic approach, but applying principles of a surgical myotomy. This technique termed per-oral endoscopic myotomy, or POEM, was initially described by Pashricha et al. [22] and subsequently developed by Inoue et al. in Japan (Fig. 11.2) [23].

The procedure should be done in the operating room under general anesthesia (positive pressure ventilation) with CO_2 endoscopic insufflation (Table 11.3). After preoperative intravenous antibiotics are given, diagnostic endoscopy should be done to rule out retained food or Candida esophagitis, as the presence of either should postpone the procedure. We also suggest tight blood pressure control (SBP ~ 100 mmHg) to help reduce submucosal bleeding. It is critical to turn off the air insufflation to avoid tension pneumomediastinum and subcutaneous emphysema.

The initial step of the POEM procedure is a submucosal saline injection (usually with indigocarmine and 1:10,000 dilution of epinephrine) approximately 12 cm proximal to the squamocolumnar junction. A 2 cm longitudinal mucosal incision is created using a triangle-tipped knife with monopolar electrocautery. A high-resolution forward-viewing endoscope is then navigated into the submucosal space utilizing an obliquely angled dissecting cap (long bevel edge down), and a submucosal tunnel is created along the anterior esophagus all the way to the gastric cardia, as areolar submucosal fibers between the circular muscle and mucosa are spray coagulated after being held in tension by the dissection cap (Fig. 11.3a). Correct orientation of the tunnel is periodically checked by dripping saline. Careful attention is made to avoid mucosal injury, particularly at the esophagogastric junction, where the submucosal space is much tighter. Additional saline injections facilitate safe dissection by increasing the distance between the mucosa and circular muscle (Fig. 11.3b). The injections also give the mucosa a bluish (from the dye), white (epinephrine effect) appearance when viewed endoscopically from the true lumen of the esophagus (Fig. 11.3c).

Extension of the tunnel onto the gastric cardia is critical to the procedure's success, and several anatomic cues help make this determination. First, the submucosal

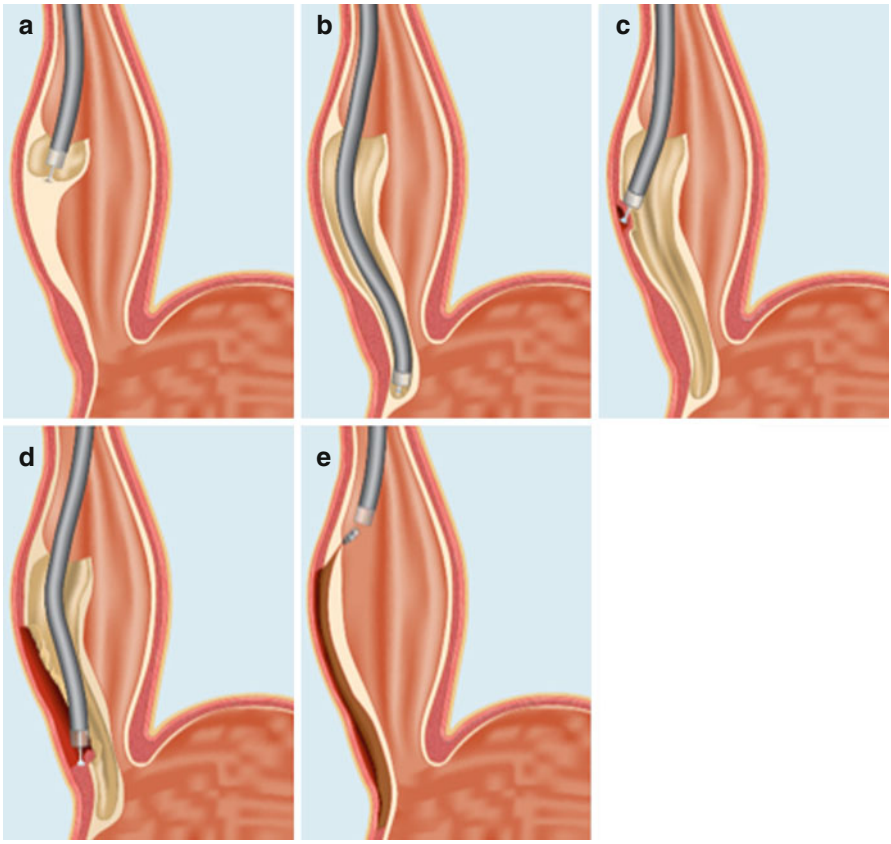

Fig. 11.2 Schematic of the POEM procedure (see text): (**a**) entry into the submucosal space, (**b**) submucosal tunnel to the gastric cardi, (**c**) beginning the myotomy, (**d**) completion of the myotomy, and (**e**) closing the mucosotomy with endoclips (Inoue et al. [23])

space narrows considerably in the distal esophagus at the level of the EGJ, but then dramatically increases in the stomach. Second, palisading blood vessels are encountered on the gastric side. Lastly, the circular muscle fibers become much more disorganized as more oblique sling fibers are visualized.

Once the tunnel is complete, the endoscope is removed and its adequacy assessed by luminal inspection of the EGJ and proximal stomach (Fig. 11.3d). The tunnel is then reentered and a selective myotomy of the circular muscle accomplished with electrocautery tools for a minimum length of 6 cm up the esophagus and 3 cm distal to the SCJ onto the gastric cardia (Fig. 11.4a). Portions of the longitudinal muscle often "split" during this portion of the procedure, but this is of no clinical consequence. At our institution, we also assess the adequacy of the myotomy by using intraoperative functional lumen image planimetry (FLIP), which usually demonstrates at least a fourfold increase in EGJ distensibility (unpublished results). The endoscope is then withdrawn after infusion of antibiotic containing irrigant,

Table 11.3 Per-oral endoscopic myotomy protocol. "Recommendations" should be universally applied

	Recommendations	Other suggestions
Pre-procedure	N.P.O. ≥ 12 h	Nystatin S/S for 5 days
	Clear liquids for 48 h	
	Intravenous antibiotics	
Anesthesia	General	
Endoscopic equipment	High-definition endoscope	Overtube
	CO_2 insufflation	
	Triangle-tipped needle knife	
	Obliquely cut dissection cap	
Submucosal tunnel creation	Submucosal injection with 0.9 % saline, indigocarmine (0.2 mg/ml), epinephrine (5 mcg/ml) 12 cm above squamocolumnar junction	Mark distal target of tunnel with indigocarmine
	2 cm longitudinal mucosotomy	
	Tunnel along anterior aspect of esophagus	
	Extend 3 cm onto the stomach	
Myotomy	Start 3 cm caudal to mucosotomy	Confirm adequacy of myotomy (increased distensibility) with functional lumen image probe (FLIP)
	Selectively divide circular muscle	
	Extend myotomy to the end of the tunnel	
Mucosal closure	Infuse tunnel with antibiotic solution	Use endoscopic suturing device
	Use standard endoscopic clips	
Post-procedure	Admit for 23-h observation	
	Scheduled antiemetics	
	Water-soluble contrast on morning of POD 1 before advancing to clear liquids	
	Full liquid diet for 1 week, then soft food for 2 additional weeks	
	PPI treatment for 6 months	
Follow-up	2–3-week post-op check	Repeat FLIP study
	6–9-month F/U with symptom scoring, endoscopy, pH study off PPIs	

collapsing the tunnel. Commercially available hemostatic clips are used to reapproximate the mucosa. The first clip is place at the distal aspect to create mucosal ridge (Fig. 11.4a), facilitating sequential application of the usual 7–9 additional clips (Fig. 11.4b).

Initial reports of success rates of the POEM procedure in prospective cohorts of achalasia patients have been greater than 90 %, comparable to those of laparoscopic Heller myotomy [24–27]. To date, no randomized prospective trials comparing POEM with either laparoscopic myotomy or pneumatic dilation have been reported. Hence, although POEM is clearly a very promising technique, its relative efficacy compared to the well-studied alternatives of pneumatic dilation or laparoscopic Heller myotomy in terms of long-term dysphagia control, progression of esophageal dilation, and post-procedure reflux remains to be established.

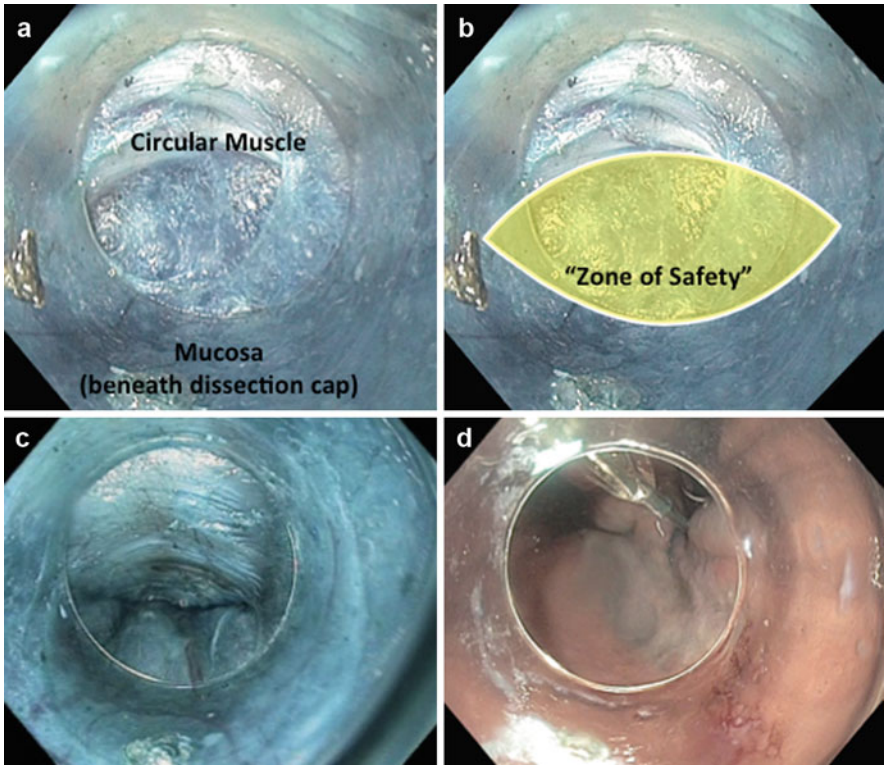

Fig. 11.3 Images of the submucosal dissection (see text): (**a**) after the submucosal space is entered, the circular muscle is positioned at the top of the image to maintain orientation as the flimsy areolar tissue is tensed with the use of the dissection cap and divided with a triangle-tipped needle knife using spray coagulation; (**b**) care is taken to stay within the "zone of safety" (*shaded area*), between the circular muscle (*top*) and mucosa (*bottom*); (**c**) after the submucosal tunnel is extended 3 cm onto the gastric cardia, the tunnel is inspected and the scope is returned to the true lumen; and (**d**) on inspection from the stomach, the mucosa in the region of the EGJ will appear bluish white due to the combination effect of dilute indigocarmine and epinephrine confirming the extension of the dissection on the gastric cardia

Posttreatment Follow-Up

Patients should have a post-procedure evaluation of effectiveness of achalasia treatment within the first few weeks and then at 6 months after the intervention to assess adequacy of symptom response. In the case of pneumatic dilation, this early assessment may mandate a repeat dilation with the larger diameter (35 mm) dilator. At the 6-month follow-up, subjective findings of symptom reduction and objective findings evaluating esophageal retention and continued EGJ outflow obstruction should be assessed as highlighted in work published by Vaezi et al. assessing long-term outcome in patients after pneumatic dilation [28]. The authors showed that concordance of symptom improvement and minimal bolus retention on timed barium

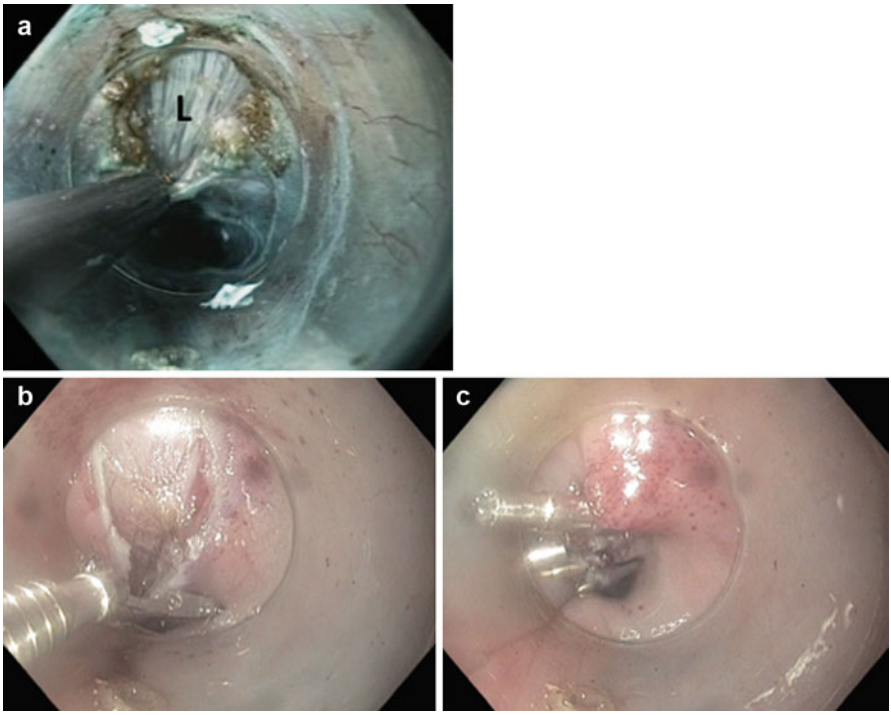

Fig. 11.4 (**a**) A selective myotomy of the circular muscle is made by hooking and coagulating the fibers with a triangle-tipped needle knife. The longitudinal muscle layer (*L*) is seen beyond and is preserved. (**b**) Mucosal closure is achieved with hemostatic endoscopic clip placement beginning at the distal aspect. (**c**) Sequential clips are placed proximally to completely reapproximate the mucosa

esophagram had good long-term improvement, while patients with discordance of improved symptoms but poor bolus emptying on timed barium esophagram had a worse long-term prognosis and were more prone to return with symptoms.

Timed Barium Esophagram

Improving esophageal emptying, thereby reducing regurgitation, aspiration risk, and progressive esophageal dilatation, is an important aspect of treating achalasia. Thus, a timed barium esophagram should be incorporated into the posttreatment assessment. This study is done by having the patient drink 200 ml of thin barium and obtaining single images to assess bolus retention at 1, 2, and 5 min [29]. Studies have shown that post-procedure timed barium esophagram predicts treatment success and the requirement for future intervention. Vaezi et al. reported a significant association between the result of the timed barium esophagram and symptom resolution [29] and that timed barium esophagram was predictive of treatment failure at 1 year irrespective of reported symptoms [28].

Manometry

Since abnormal EGJ relaxation is the cornerstone of the diagnosis of achalasia, incorporating an assessment of EGJ function in the posttreatment follow-up is inherently reasonable. Supportive of this, a prospective study assessing 54 patients found that patients were much more likely to be in remission (100 % versus 23 %) at 10 years if their post-procedure basal EGJ pressure was less than 10 mmHg [30]. Recent data obtained using HRM and IRP measurement also supports this concept. Nicodeme et al. recently showed that a posttreatment IRP < 15 mmHg after pneumatic dilation or myotomy was associated with lower Eckardt scores and less esophageal retention on timed barium esophagram [31]. The authors also observed that the manometric finding of weak peristalsis after intervention was predictive of a good outcome.

Posttreatment GERD

Pneumatic dilation or POEM may result in esophagitis or new reflux symptoms. Our standard practice is to put all patients on 6 months of once daily omeprazole, after which time the medication is stopped for pH testing. Endoscopy may also be helpful in detecting esophagitis as a potential cause of poor treatment response, especially in those patients that do not respond to proton pump inhibitors.

Conclusion

Although achalasia is a well-defined esophageal motility disorder, the presenting symptoms and esophageal contractile patterns vary. Once a diagnosis of achalasia is made, early definitive therapy aimed at relieving EGJ outflow obstruction should be offered, assuming the patient is a good surgical candidate. Among the endoscopic therapies (botulinum toxin injection, pneumatic dilation, and per-oral endoscopic myotomy (POEM)), this is achieved only with the latter two. The importance of relieving EGJ outflow obstruction is that this should halt the progressive esophageal dilatation that ultimately leads to end-stage achalasia, a condition with substantial morbidity and relatively poor therapeutic options. Consequently, although botulinum toxin injection may provide symptomatic relief to some patients, it should be reserved for very limited circumstances: essentially, when patients are poor surgical risks. Pneumatic dilation is a well-established treatment that can be durable for many years and compares favorably with laparoscopic Heller myotomy in controlled trials. The major risk of pneumatic dilation is inadvertent perforation. However, when the procedure is done in a cautious and methodical fashion, that risk is less than 1 %, comparable to the risk of an unrecognized perforation with Heller

myotomy. POEM is a promising technique that potentially achieves the effectiveness of a surgical myotomy with the morbidity of an endoscopic approach. Clinical trials comparing POEM to either pneumatic dilation or Heller myotomy are not yet available, but uncontrolled series have reported very promising results. Regardless of which endoscopic technique is utilized, short-term follow-up should assess for both the symptomatic outcome and the therapeutic efficacy in alleviating EGJ outflow obstruction to prevent disease progression. The latter is best achieved with timed barium esophagram and high-resolution manometry.

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