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CLINICAL REVIEW

STATE OF THE ART REVIEW

Diagnosis and management of esophageal achalasia

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Abstract

Achalasia is a rare esophageal motility disorder that is usually idiopathic in origin. It is characterized by dysphagia, and patients often have chest pain, regurgitation, weight loss, and an abnormal barium radiograph showing esophageal dilation with narrowing at the gastroesophageal junction. Abnormal or absent esophageal peristalsis and impaired relaxation of the lower esophageal sphincter (LES) are typically seen on esophageal manometry. The advent of high resolution manometry (HRM) has allowed more precise diagnosis of achalasia, subtype designation, and differentiation from other esophageal motor disorders with an initial seminal publication in 2008 followed by further refinements of what has been termed the Chicago classification. Potential treatments include drugs, endoscopic botulinum toxin injection, balloon dilation, traditional surgery (usually laparoscopic Heller myotomy; LHM), and a novel, less invasive, natural orifice transluminal endoscopic surgery (NOTES) approach to Heller myotomy termed peroral endoscopic myotomy (POEM). The first human POEM was performed in 2008, with the first publication appearing in 2010 and evidence now rapidly accumulating showing POEM to be comparable to traditional surgery in terms of clinical success and radiologic and manometric post-therapy outcomes. This review discusses the diagnosis and management of achalasia with particular emphasis on the recent developments of HRM and POEM, which arguably represent the most important advances in the field since the advent of laparoscopic Heller myotomy in the 1990s.

Introduction

Achalasia is a primary esophageal motility disorder, characterized by the absence of esophageal peristalsis and impaired relaxation of the lower esophageal sphincter (LES). These abnormalities stem from impairment of the inhibitory innervation to the esophageal smooth muscle and the lower esophageal sphincter.[1] The cause of this disorder is unknown, but the disease may be autoimmune, secondary to viral infection, or neurodegenerative.[1] Secondary achalasia or "pseudoachalasia" refers to achalasia occurring secondary to malignancy or other entities (such as Chagas disease or bariatric surgery). Achalasia is diagnosed by a combination of radiography (barium swallow) and esophageal manometry. The disorder can be treated effectively in most patients by pneumatic dilation, Heller esophagomyotomy, and, more recently, peroral endoscopic myotomy (POEM).[2] This review will discuss the diagnosis and management of achalasia, with a particular emphasis on POEM. It is aimed at internists, gastroenterologists, and surgeons involved in the care of patients with achalasia, as well as academics and non-academic physicians to whom these patients initially present.

Sources and selection criteria

We searched PubMed from 1982 to 2015 using the keywords achalasia, pneumatic dilation, esophagomyotomy, Heller myotomy, POEM, endoscopic myotomy, botulinum toxin, and esophageal manometry. We also considered review articles from 2000 to 2015, including systematic and narrative reviews, as well as any relevant articles that they referenced. We gave priority to randomized controlled trials (RCTs), especially for comparisons of treatments, but most studies were observational. Larger prospective series were prioritized over smaller retrospective series, and case reports were given the least priority. Exclusion criteria included non-English journals without reliable translation and internet sources owing to accuracy concerns.

Epidemiology

The epidemiology of achalasia has not been extensively studied. The prevalence in Europe is about 10 cases per 100 000 population, with an incidence of about one new case per 100 000 per year.[3] Peak incidence occurs between 30 and 60 years of age, and no sex or racial differences have been identified. A Canadian study reported an annual incidence of 1.6/100 000

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from 1996 to 2007, with a steady increase in overall prevalence from 2.51/100 000 in 1996 to 10.82/100 000 in 2007.[3]

Although the incidence is low, the chronicity of achalasia affects patients' health related quality of life, work productivity, and functional status.[4] In the United States, rates of hospital admission for achalasia range from 0.25 per 100 000 for patients under 18 years to 37 per 100 000 for those over 85 years.[5-7] A few reports have described familial achalasia, but this is rare in idiopathic achalasia.[5-7]

Longitudinal population studies of patients with achalasia originally suggested that the disease does not significantly influence life expectancy. In one series, the mean age at death of patients with achalasia was 80.5 years.[1] However, the Canadian study reported that people with achalasia had a significantly shorter survival than age and sex matched population controls (20% survival difference at five years and 25% at 12 years after diagnosis; P<0.001). However, this finding is of uncertain significance as this was a population based study with data derived from a central government database in the province of Alberta that did not contain information on cause of death.[3]

Pathophysiology

The pathophysiology of achalasia involves impairment of the inhibitory innervation to the esophageal smooth muscle and LES.[5-8] An inflammatory process leads to degeneration of ganglion cells in the myenteric plexus of the esophageal body and the LES, which results primarily in the loss of the inhibitory neurotransmitters nitric oxide and vasoactive intestinal polypeptide. The inflammatory reaction is associated with infiltration of T cells, which leads to slow destruction of ganglion cells.[8] The underlying cause is unknown but may be autoimmune, secondary to viral infection, or neurodegenerative. Achalasia can also be a manifestation of Chagas disease, which is caused by infection with the parasite *Trypanosoma cruzi* and is characterized by widespread destruction of the myenteric plexus.[9] A genetic predisposition has been reported when achalasia is associated with syndromes such as Aligrove's syndrome or Down's syndrome.[10 11]

Clinical presentation

Idiopathic achalasia can occur at any age, from early childhood to the ninth decade of life. The course is indolent, and at presentation the symptoms have typically been present for six years.[1]

Dysphagia (difficulty in swallowing) is the cardinal symptom of achalasia. At the time of treatment, dysphagia is present in nearly all patients (approximately 98%).[12] Typically, dysphagia occurs for both solid food and liquids and slowly worsens with time. Ultimately, dysphagia becomes a constant problem. Dysphagia and sitophobia (fear of eating) can lead to weight loss, which is present in more than half of patients.[12]

Regurgitation of stagnant, undigested food that collects in the dilated esophagus is seen in 78% of patients.[1] It occurs most often at night because in the recumbent position there is no effect of gravity. In severe cases, food and secretions are noticed on the pillow on awakening. Regurgitation can lead to aspiration that may present clinically as nocturnal cough, aspiration pneumonia, and even lung abscess.

Chest pain can occur (around 42% of patients), but is rarely severe.[5-12] A burning discomfort localized to the epigastric area can be secondary to stasis esophagitis, drug induced ulcerations, or candida esophagitis.[6] In untreated achalasia, symptoms of regurgitation and dysphagia may prompt the diagnosis of gastroesophageal reflux disease (GERD) and prescription of proton pump inhibitors (PPIs).[5 13] True heartburn related to GERD is generally not seen in untreated achalasia but can be seen after treatment with pneumatic dilation, Heller esophagomyotomy, or POEM.[5]

Associated abnormalities

Abnormal distal esophageal acid exposure has been documented in 2-20% of untreated patients with achalasia.[13 14] In untreated patients, 24 hour pH tracings can show reflux episodes of slow clearance or prolonged episodes of acid exposure with failure to clear the acid. Possible causes include slow esophageal clearance of refluxed acid owing to an aperistaltic esophageal body or fermentation of retained food.[15 16]

Patients with achalasia can develop inflammatory changes of the distal esophagus by three mechanisms: infection, stasis, and caustic injury.[1] Infectious esophagitis can occur; stasis promotes candida infection. Poor clearance of episodes of acid reflux can also cause injury. Fermentation of residual food in the esophagus results in a pH of 3-4, which in the absence of pepsin is not thought to cause serious mucosal injury.[15]

Epiphrenic diverticula are thought to represent pulsion diverticula, which are caused by increased intraluminal esophageal pressure. These are not specific for achalasia, and two thirds of patients with epiphrenic diverticula have manometric disorders, most often diffuse esophageal spasm or achalasia.[5]

Patients with longstanding achalasia may develop a markedly dilated esophagus (megaesophagus or sigmoid esophagus) (fig 1⇓). Myotomy may be considered, but esophagectomy (open, thorascopic, minimally invasive) and interposition of colon, stomach (most preferred), or jejunum may be the best option.[17] Achalasia was the most common benign cause of esophagectomy for benign disease in one case series of 111 patients undergoing esophagectomy, and 30 day mortality was 2.1%.[18]

Cancer

Patients with longstanding achalasia are at increased risk of developing esophageal squamous carcinoma (3.5% of patients).[2] The average duration from initial onset of symptoms of achalasia to detection of cancer is 25 years.[19-21] It has been suggested that this occurs mainly in untreated achalasia and is caused by chronic esophageal stasis and inflammation.[19] There is also a marginal predilection for adenocarcinoma. In one series of 124 patients with achalasia who were followed for a mean of 5.6 years, 13 incident cases of squamous cell carcinoma and one case of adenocarcinoma were noted.[22] The presence of massive esophageal dilation, long duration of achalasia, and smoking are predisposing factors.[23] A study of 331 patients who had undergone pneumatic dilation noted 28 new cases of Barrett's esophagus and two new cases of Barrett's adenocarcinoma during a mean follow-up of 8.9 years.[24]

Gastroenterologists often carry out periodic surveillance, although no data exist to support routine endoscopy surveillance and this is left to the judgment of the physician. The American Society of Gastrointestinal Endoscopy (ASGE) does not mandate cancer surveillance in achalasia but considers it "reasonable" to check at 15 years after diagnosis.[25]

Mimics and differential diagnosis; secondary achalasia

Secondary achalasia refers to the development of clinical, radiographic, and manometric findings of achalasia as a result of an underlying disorder. Secondary achalasia can occur with cancer, Chagas disease, and intestinal pseudo-obstruction and after surgery. The development of achalasia secondary to malignant tumors has been well described. It is often referred to as secondary achalasia or pseudoachalasia and accounts for only 4% of patients with manometric findings of achalasia.[1] A variety of cancers can cause this syndrome, with adenocarcinoma of the gastric cardia accounting for 75% of reported cases.[26]

This syndrome can also be caused by non-contiguous forms of cancer, including lymphoma and primary cancers of the lung, pancreas, prostate, and liver. Because treatment is aimed at the underlying cancer, it is important to recognize this disorder. Three clinical features are thought to be suggestive of cancer as a cause of achalasia: short duration of dysphagia (<1 year), serious weight loss (>15 lb; 6.8 kg), and age over 55 years.[22-27] The presence of any of these features should raise a suspicion of cancer, even though they have a low predictive accuracy.[5 22]

The diagnosis may not be evident on routine esophagraphy and endoscopy, and further evaluation with thoracoabdominal computed tomography and endoscopic ultrasonography may be needed. Peristalsis may also be absent in the mid and distal esophagus in scleroderma, but esophageal peristalsis is often preserved in the upper striated muscle of the esophagus and the pressure of the smooth muscle LES is usually low.[7]

Achalasia can occur after surgery.[28] Severe dysphagia occurs after surgical vagotomy in some patients.[29] An achalasia-like disorder that may be indistinguishable from achalasia when conventional endoscopic, manometric, and radiologic diagnostic means are used can occur after a fundoplication that is too tight at the esophagogastric junction (EGJ).[30] In addition, the laparoscopic adjustable gastric band can cause an achalasia-like disorder if the band is too tight.[31]

Diagnosis

Diagnostic evaluation in patients with dysphagia often begins with barium esophagraphy to exclude an anatomic lesion of the esophagus such as an esophageal stricture or cancer. Achalasia can be detected in most patients by using radiology,[27] with the esophagus usually being dilated and occasionally containing excess secretions and food.[32] When esophageal dilation is severe (megaesophagus), the esophagus may assume a sigmoid configuration.

Esophageal manometry

This is the gold standard for the diagnosis of achalasia and should be used in patients in whom the diagnosis is uncertain or it is essential to achieve the correct diagnosis, often before surgery. The two classic manometric findings in the diagnosis of achalasia are aperistalsis of the esophageal body and impaired relaxation of the LES during swallowing. Classically, no peristaltic contractions are seen in the esophageal body.[5-32] Esophageal contractions that occur are usually low in amplitude and simultaneous throughout the esophagus.[32] In patients with achalasia, relaxation of the LES is absent or incomplete.[5-32] The residual pressure between the esophagus and the stomach results in functional obstruction, which leads to esophageal dilation and stasis. Basal LES pressure is raised in about two thirds of patients.[32]

Fluoroscopy

In early achalasia, fluoroscopy may detect breakdown of the normal peristaltic esophageal contraction into numerous tertiary simultaneous contractions in the body and failure of the primary wave to clear the esophagus. Classically, peristalsis is absent from the entire esophageal body.[32] The distal esophagus usually tapers to a characteristic narrowing “bird’s beak.” This represents the upper margin of the lower esophagus sphincter that fails to relax normally. Emptying of barium from the esophagus is poor (fig 2⇓). A characteristic radiograph should prompt endoscopy and manometry.

Videoesophagraphy

Studies suggest that videoesophagraphy has a good sensitivity compared with esophageal manometry for detecting esophageal dilation, narrowing of the EGJ, and lack of peristalsis fluoroscopically. The overall sensitivity of videoesophagraphy is between 58% and 95% for the aforementioned three criteria.[33-35] When achalasia is detected radiologically, the endoscopy should also include a detailed examination of the fundus and cardia to look for lesions causing secondary achalasia.[5 7] American Gastrointestinal Association (AGA) guidelines strongly recommend endoscopic assessment of the EGJ and cardia of all achalasia patients. An additional role for radiological examination is to provide objective assessment of esophageal emptying. The timed barium esophagram measures the barium column height one and five minutes after upright ingestion of a large barium bolus.[36] This helps to evaluate the severity of achalasia and also can be used to gauge treatment success (fig 3⇓; table 1⇓).[37-39]

Endoscopy

Endoscopy is used in patients with achalasia to exclude other disease entities and to diagnose complications. In idiopathic achalasia, the mucosa is normal and there is mild to moderate resistance to passage of the endoscope through the EGJ. Severe resistance may suggest the presence of infiltrating tumor at or around the EGJ.[40] Retained saliva, liquid, and indigested food particles can be seen in the esophagus and, in the absence of mucosal stricturing or tumor, may suggest achalasia.[2] As the disease progresses, luminal dilation and tortuosity make the diagnosis more obvious.

High resolution esophageal manometry

High resolution esophageal manometry (HREM) with closely spaced manometry sensors is a relatively recent advance in manometric evaluation.[41] HREM can detect esophageal shortening, presumably as a result of longitudinal muscle contractions. This esophageal shortening can result in cephalad movement of the high pressure zone (LES), which may appear as appropriate LES relaxation on traditional manometry but not on HREM.[39 41] Thus the sensitivity of detection of achalasia may be higher with HREM.[39 41] The sensitivity is reported to be 97%.[35] Furthermore, using HREM, the LES shows an EGJ outflow obstruction pattern defined by a raised integrated residual pressure (IRP) of more than 15 mm Hg in patients with achalasia, and this provides a more objective measure than the LES relaxation pressure used in traditional manometry.[41] This IRP value was chosen to help maximize the sensitivity and specificity for detecting achalasia.

Apart from improving the sensitivity of manometry in the detection of achalasia by objectively defining impaired deglutitive EGJ relaxation, HREM has also made it possible to subclassify achalasia on the basis of the pattern of contractility in the esophageal body. Three clinically relevant subtypes of achalasia have been defined on the basis of the patterns of non-peristaltic esophageal pressurization that accompanies the raised IRP (fig 4⇓).[42 43] Type I achalasia is characterized by failed contractions and no esophageal pressurization with swallows. Type II achalasia is defined by pan-esophageal pressurization with swallows and type III achalasia by the presence of spastic or premature contractions. Interestingly, several studies have shown that type II achalasia, the most common subtype, seems to have the most favorable response to treatment, whereas type III, the least common subtype, seems to have the least favorable response.[2-43] This is probably because the proximal segments of spasm associated with type III achalasia are not targeted by treatment, resulting in persistent dysphagia and chest pain (fig 5⇓).

Esophageal motility testing, upper endoscopy, and barium esophagraphy play complementary roles in the diagnosis of achalasia.[2 43] The clinical features and the combination of these modalities allow for the accurate diagnosis of achalasia or its exclusion. According to AGA guidelines, "esophageal motility testing, EGD, and barium esophagram play complementary diagnostic roles." Whereas EGD is essential to rule out pseudoachalasia, esophageal motility testing and barium esophagraphy may play confirmatory roles. In people with classic motility findings, barium esophagraphy may be redundant. Similarly, in those with classic barium esophagram findings, esophageal motility testing serves only to confirm the suspicion of achalasia. In people with equivocal motility findings, barium esophagraphy is essential to assess for retention of barium and confirm the diagnosis.

Treatment

Evidence for the various treatments is discussed in detail below. Overall, treatment with oral or sublingual smooth muscle relaxants is largely ineffective in achalasia. Several more durable therapeutic options focus on LES weakening or ablation, including endoscopic (botulinum toxin, pneumatic balloon dilation), surgical (laparoscopic, thoracoscopic, open abdominal myotomy) and most recently natural orifice transluminal endoscopic surgery (NOTES) and POEM. Endoscopic injection of botulinum toxin is safe and has good short term efficacy, but its effect wanes over months. Pneumatic balloon dilation and surgical myotomy are now considered the most effective treatments, with comparable efficacy in RCTs with follow-up of up to five years. The most appropriate treatment is determined by patient preference, practitioner recommendations, and local expertise. Important factors to consider include the patient's age and medical conditions, extent of esophageal dilation, and previous interventions for achalasia. POEM is performed through endoscopy and therefore represents a refinement of surgical myotomy.

Drug therapy

Drug therapy for achalasia has mainly been with nitrates and calcium channel blockers. These drugs reduce LES pressure and produce relief from dysphagia of variable duration. They have little or no effect on the deglutitive inhibition of the LES (that is, LES relaxation) or esophageal peristalsis.[5-45] Both are available in sublingual form, but the effect is transient and both sublingual and oral formulations have prohibitive side effects including headache and dizziness.[44] Calcium channel blockers have maximal effect 20-45 minutes after ingestion, with a duration of effect between 30 and 120 minutes, whereas nitrates have maximal effect three to 27 minutes after ingestion, with a duration of effect between 30 and 90 minutes. An observational study reported that most patients treated with nifedipine had improvement in clinical symptoms which persisted at one year follow-up. In this observational study, 20 achalasia patients were treated first with nifedipine and then with placebo and nine achalasia patients were treated first with placebo and then with nifedipine. Nifedipine decreased LES basal tone manometrically and resulted in clinical improvement in symptoms, whereas patients taking placebo had deterioration in symptoms. Seven of 20 patients in the first group and one of nine patient in the second group sought definitive treatment—that is, pneumatic dilation or Heller myotomy—owing to persistent symptoms.[45] Other drugs including loperamide, cimetropium, and sildenafil have been shown to lower LES pressure in achalasia patients but not to relieve dysphagia.[46-48]

Endoscopic botulinum toxin injection (EBTI)

Botulinum toxin (botox) is a potent inhibitor of acetylcholine release, and its injection into the LES should mitigate the unopposed cholinergic stimulation and lower LES pressure. In an initial validating series, 31 patients with achalasia received botox injections. EBTI attained efficacy, defined as decrease of the Eckardt score to 3 or less, in 70% of patients at 18 months, although 40% of patients needed more than one injection.[49] The literature is inconsistent with regard to dosage (25-100 U), technique, and scheduling. A prospective randomized trial of 118 achalasia patients receiving one of three doses (50, 100, 200 units) and one of two schedules (one injection or reinjection in 30 days) of botox injections reported that 68% of patients receiving two 100 U injections one month apart still had a response (Eckardt score ≤3) at two years.[50] A meta-analysis of nine prospective case-control and cohort studies reported a 79% treatment response (Eckardt score ≤3) at one month, with a decline in response at three, six, and 12 months (70%, 53%, 41%).[51] Older patients and those with vigorous achalasia (type III achalasia in the Chicago classification) were most likely to respond to EBTI.[52] The reduction in efficacy over time may relate to tissue fibrosis and the formation of antibodies to the toxin.[50-52] Previous botox injection diminished efficacy in one series of achalasia patients treated by laparoscopic Heller myotomy (LHM), but previous EBTI did not affect efficacy in achalasia patients treated with POEM.[53 54] The ease of EBTI and the infrequent and usually mild adverse events make this treatment appealing, but its limited duration of efficacy relegates EBTI to use in frail and elderly patients and in those unwilling to have more definitive therapy.

Pneumatic dilation

Pneumatic dilation using a high caliber air filled balloon for divulsion (disruption) of the LES is an established and well validated treatment for achalasia. Before the advent of LHM and EBTI, pneumatic dilation was often the first intervention used with the intent of avoiding an open surgery for achalasia. Dilators that were used decades ago produced good results and low complication rates—15 retrospective studies of more than 2000 patients and a mean follow-up of five years showed a symptomatic response in an average of 71% (range 34-96%) of patients and a perforation rate of 3%.[55] Most dilations are now performed with the Rigiflex balloon dilator, which consists of polyethylene polymer and comes in 30 mm, 35 mm, and 40 mm sizes (fig 6⇓). The other available dilator is the Witzel polyvinyl dilator, which comes in only a 40 mm size. Pneumatic dilation is a fluoroscopic procedure with the dilating balloon straddling the LES; Witzel balloon dilation requires endoscopic visualization at the time of dilation.

Heterogeneity of technique, different balloon sizes, and the variety of study designs make it difficult to make comparisons in the literature. Nonetheless, this technique has been shown to be inexpensive and effective, although concern exists about its durability. In a comprehensive review that used inclusion criteria of study period after 1995 (when modern balloons started being used) and availability of efficacy data that included at a minimum the efficacy of a single balloon dilation at one year, 20 studies met inclusion criteria, with 2497 patients in total. Most of the studies were case series, and only three were controlled studies. On the basis of the pooled estimates provided by this review, after a single dilation, 60%, 59%, 55%, and 25% of patients were in symptomatic remission at one, two, three, and five years, respectively.[56] However, in four studies in which patients had two or more dilations at the initial session, 92%, 84%, 78%, and 64% were in remission at these time points.[56] The perforation rate was 4% in this last group of patients compared with 2% with a single dilation. A retrospective study of 150 patients treated with pneumatic dilation between 1992 and 2004 assessed the effect of graded dilations with a larger balloon every two to three weeks until remission occurred.[57] The initial remission rate was 91%, with five and 10 year remission rates of 97% and 93% compared with 67% and 50%, respectively, if only a single dilation was performed.[57] Similar results were reported in another large retrospective analysis of 200 patients in which patients had graded dilation over one to three days until their resting LES pressure was less than 15 mm. In this study, 66% of patients needed no additional therapy at a mean follow-up of six years and 23% required repeat dilation, yielding a long term pneumatic dilation success rate of 77%.[58] A third study of similar design (graded dilation with LES pressure measurements in all patients after pneumatic dilation) found five, 10, and 15 year success rates of 78%, 61%, and 58%, respectively, although symptoms were the parameter for success and the perforation rate was 5%.[59]Table 2⇓ highlights some larger case series of pneumatic dilation.[60-64]

Predictors of relapse after pneumatic dilation include male sex, younger age (<40 years), very dilated esophagus, and poor esophageal emptying on a timed barium swallow.[52-65] Complications from this technique are rare and usually manageable. Chest pain and fever can occur transiently, and GERD is seen in up to 20-35% of patients but is usually responsive to PPIs.[16-66] Perforation occurs in about 2% of procedures and is associated with first dilation, difficulty keeping the dilating balloon in the proper position, and balloon larger than 30 mm.[67 68]

Heller myotomy

Ernest Heller performed the first successful surgical myotomy for achalasia in 1913.[69] In its various iterations (open abdominal or thoracic, thorascopic, laparsocopic, robotic, adjunctive GERD procedures), surgical myotomy is an excellent option for achalasia, and, arguably, until the development of POEM, the gold standard because of its reliability and durability. The operation is now usually performed laparoscopically (LHM), and recent emphasis has been on extending the myotomy 2-3 cm into the proximal stomach to incise the gastric sling muscles and further reduce LES pressure (optimally to <10 mm Hg) and the tendency for dysphagia.[70] The extended myotomy increases the risk of GERD, and the current consensus is to add a partial fundoplication (anterior Dor or posterior Toupet) to decrease this risk.[71]

The meta-analysis of more than 3000 patients who received LHM noted excellent relief (defined in most of these studies by the usual criterion of decrease in the Eckardt score to ≤3) in 89.3% of patients, with an average follow-up of 35 months.[51] Young men with very high LES pressures are particularly suitable candidates for LHM. The efficacy of Heller myotomy diminishes with time; in one series, the clinical response as measured by the Eckardt score decreased from 89% at six months to 57% at six years.[72] Complications of LHM include death (0.1%) and esophageal perforation (7-15%).[67] GERD is still the most common complication (10-40%) even with a Dor or Toupet fundoplication. Dor is an anterior 180° wrap, and Toupet is a posterior 270° wrap of the stomach across the gastroesophageal junction. These partial fundoplications can loosen with time, and patients often require PPIs.[73] A tighter Nissen fundoplication (360° wrap) is rarely performed in achalasia patients, as it may cause dysphagia and this might be difficult to distinguish from incomplete myotomy.

Comparative analysis

The general consensus is that pneumatic dilation is more efficacious than EBTI in patients with achalasia, especially over time (table 3⇓).[74-78] This was borne out in a meta-analysis of seven studies in 2014, which found no significant differences in post-treatment LES pressures or one month clinical scores but a marked difference at six months favoring pneumatic dilation and even a more marked difference at one year ($P<0.001$).[79] In a high quality RCT comparing LHM with EBTI (40 patients in each group), improvement of symptoms was comparable at six months, with 82% efficacy in LHM and 66% in EBTI ($P<0.05$), but a greater proportion of patients who had undergone LHM were symptom free at two years (88% *v* 34%; $P<0.05$).[80] An earlier more complex crossover study of LHM versus EBTI suggested that patients preferred EBTI but that subjective improvement was similar up to a year, only patients who had EBTI needed subsequent intervention, and only the those who had LHM had significantly reduced LES pressures.[81]

Ample literature compares pneumatic dilation and surgical myotomy, but there are only four RCTs to date (table 4⇓).[16-84] Again, as discussed, graded pneumatic dilation has been most likely to keep achalasia patients dysphagia free, but most studies have considered the need for repeat pneumatic dilation as failure. Csendes noted 65% of pneumatic dilation patients having a good clinical response at 58 months, while 95% of the LHM patients at 62 months had an excellent response.[85] An outdated (Mosher) dilating balloon was used and repeat pneumatic dilation was considered treatment failure. Kostic allowed two initial dilations within days and followed patients for up to five years.[82] At three and five years respectively, the pneumatic dilation/LHM "failures" ratio was 9/1 and 10/2. Finally, Boeckxstaens compared pneumatic dilation and LHM-Dor fundoplication patinets.[86] This study was unique in that graded dilations were allowed and primary pneumatic dilation failure was denoted only after a larger balloon was used and symptom recurrence was within two years of the second dilation; otherwise graded dilations were again allowed. In this more favorable study construct, pneumatic dilation fared much better. The rate of therapeutic success was 90% at one year and 86% at two years—not significantly different from the LHM-Dor group. In addition, at two years, no significant differences existed between the two groups in terms of LES pressure and height of a timed barium study. Of note, the pneumatic dilation group had significant complications, with four of the first 13 pneumatic dilation patients sustaining perforation with the 35 mm balloon, so the protocol was changed to start with the 30 mm balloon.[86] This group recently published their five year follow-up data from the initial RCT cohort, which showed that five year efficacy remained comparable (84% LHM *v* 82% pneumatic dilation; P=0.92). There were no significant differences in terms of LES pressure and height of a timed barium study. Repeat dilation was performed in 25% of pneumatic dilation patients.[84]

A meta-analysis published in 2013, which included the two earliest randomized studies in table 4⇓, evaluated 161 studies and found only three RCTs with newly diagnosed untreated achalasia patients who were randomized into two groups—graded or non-graded pneumatic dilation versus LHM. It found that the one year cumulative response rate was significantly higher for LHM than for pneumatic dilation (86% *v* 76%).[66] A 4.8% rate of esophageal perforation was noted in the pneumatic dilation group. An earlier meta-analysis of 36 studies had a similar conclusion, with a clinical remission rate at five and 10 years of 80% and 62%, respectively, for LHM and 76% and 48% for pneumatic dilation.[87] Perforation occurred in 2.4% of patients who underwent pneumatic dilation. Table 5⇓ summarizes additional meta-analyses.[88 89] A large comparative (pneumatic dilation *v* LHM) single center study found similar response rates at six months but a significantly better response at six years for those who had undergone LHM (57% *v* 44%).[72]

People with achalasia often receive multiple treatments in their lifetimes, and "rescue" treatments are not uncommon. LHM is usually performed if pneumatic dilation is unsuccessful, and pneumatic dilation has been performed after LHM.[83 90] Transthoracic myotomy may be necessary after pneumatic dilation perforations, although results are similar to those seen with elective surgery.[67] Pneumatic dilation and EBTI are less costly than LHM, but such analysis does not consider the costs of retreatment.[67]

Miscellaneous treatments

Treatments for achalasia that have not gained widespread acceptance include transcutaneous electrical nerve stimulation, covered metal stents (20 mm, 25 mm, or 30 mm), and ethanolamine (sclerosant) injection into the LES.[91-93] Self expanding metal stents, such as nitinol coils, Ultraflex stents, or the specially designed Z-stent, have been used as a temporary treatment measure.[92-95] Their use has been limited to three to 30 days, probably because of the high risk of complications, such as stent migration, chest pain, stent occlusion, inflammatory stricture, and aortoenteric fistula. Their effectiveness is related to the stent diameter: 87% for 30 mm, 73% for 25 mm, and 43% for 20 mm.[96] Single center experiences of the use of endoscopic sclerotherapy with ethanolamine oleate showed a trend towards longer symptom-free time to recurrence in the sclerotherapy group than in the pneumatic dilation group but similar durability in the sclerotherapy and botox groups.[93 97] Long term data are lacking, and reports are from single center studies only.

POEM

POEM is a serendipitous offshoot of research into a submucosal tunnel technique to allow transluminal "scarless" endoscopic access to the mediastinum through the wall of the esophagus when performing procedures traditionally performed through skin incisions (such as mediastinoscopy and lymph node biopsy).[98 99] An attempt in 1980 at direct peroral endoscopic myotomy using an electrosurgical knife without the use of a submucosal tunnel was not developed further, probably because of the high risk of esophageal perforation and leak.[100]

Haruhiro Inoue performed the first modern human myotomy in Japan in 2008 using the submucosal tunnel technique.[101] He also coined the acronym POEM for the procedure. The first human POEM procedure to be performed outside Japan took place in the US in 2009,[102] and this was followed by rapid growth across the globe. The Natural Orifice Surgery Consortium for Advancement and Research (NOSCAR), which includes the two main US endoscopic societies (ASGE and Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)) sponsored an international survey of pioneering POEM centers in early 2012. Twenty centers were performing POEM worldwide at that point. Sixteen of these centers, including all high volume centers (>30 POEMs)—seven from North America, five from Asia, and four from Europe, with an aggregate volume of 841 POEMs—participated in a detailed survey. This survey covered all aspects of POEM, including operator discipline (surgeon or gastroenterologist), experience and previous training, selection of patients, setting (operating room versus endoscopy unit), technique preferences and variations, results, adverse events, regulatory requirements, and perspectives on the future of the technique.

These survey results were published as the international POEM survey in 2013, and they provided a global snapshot of POEM in its first four years of existence.[103] On the basis of the excellent results reported by these pioneering centers, POEM continued to grow rapidly across the globe, with publications on about 2000 POEM procedures and more than 40 centers performing POEM in the US alone. As further testament to the popularity and rapid adoption of this technique, just two years after the initial peer reviewed publications in 2010 the major endoscopic societies in the US convened international expert panels to provide comprehensive assessments of POEM. These efforts culminated in publication over the past year of the NOSCAR POEM white paper and the ASGE POEM PIVI (preservation and incorporation of valuable endoscopic innovations).[104 105]

Technique

The flexible endoscope is inserted through the mouth into the esophagus. A small electrosurgical knife inserted through the instrument channel of the endoscope is used to create a small mucosal incision at the mid-esophagus, enabling the endoscope to be inserted into the submucosal space between the mucosa and muscularis propria, which consists of loose connective tissue.[101] The submucosal space (normally only 1-2 mm thick) is expanded to about 15 mm by repeated saline injections to accommodate the endoscope, which is about 10 mm in diameter. With gradual advancement of the endoscope and submucosal dissection with the electrosurgical knife, a tunnel is created in the submucosa that extends from the mid-esophagus to the gastric cardia. Care is taken to preserve an intact mucosa as the "roof" of this tunnel. Then, with the endoscope located in this tunnel and starting a few centimeters distal to the mucosal incision, the electrosurgical knife is used to incise the muscle of the esophagus and perform a Heller myotomy using an endoscopic "scarless" approach through a natural orifice (the mouth). This contrasts with the traditional transcutaneous laparoscopic approach, which requires five surgical incisions and extensive abdominal dissection to reach and mobilize the esophagus. With this ingenious tunneling technique, simply closing the 15-20 mm mucosal incision that forms the entry site to the submucosal tunnel with a few endoscopic clips or sutures completely seals the tunnel and isolates the myotomy from the lumen of the esophagus, thus preventing risk of leakage of esophageal contents (fig 7⇓; fig 8⇓). Any minor translocation of bacteria during this process as a result of operating through a non-sterile field (mouth, esophagus) has proved clinically irrelevant if the usual NOTES precautions are followed (meticulous cleaning of the esophagus with antibiotic solution before the procedure, periprocedural prophylactic antibiotics, and secure closure of the tunnel).

Efficacy

The NOSCAR POEM white paper provided a comprehensive review and tabulation of efficacy outcomes for series published up to early 2014.[104] These 14 early series generally had median follow-up of one year or less, and many of them had small numbers of patients (15-30).[101-118] All were single center prospective series, except for one, which was a multicenter study mainly from northern Europe with five centers contributing 70 patients.[117] All series measured efficacy by using the parameter used by most studies over the past two decades—a decrease in the Eckardt score to 3 or less (table 5⇓).[119] Efficacy was uniformly excellent (90-100% at 3-12 months), except in the multicenter European series, where efficacy was 82% in patients who completed one year of follow-up (the maximum follow-up available).[117] This may have been the result of a learning curve effect because this trial pooled the first five to 20 patients of each of the five contributing centers.[120]

Studies have shown that centers need to perform a minimum of 20-40 POEM procedures to achieve competence,[120 121] and about 60 to achieve mastery of this technically challenging procedure.[121] A small number of studies also assessed efficacy by timed barium esophagraphy,[114-124] an objective quantitative assessment of esophageal emptying.[39 125] Reassuringly, these objective measurements confirmed the high efficacy shown by the more subjective Eckardt score assessment (table 6⇓).

Over the past two years, single center publications with longer follow-up of approximately one year or longer have appeared. Four Western series from pioneering centers in Portland (USA), Chicago (USA), Mineola (USA), and Rome (Italy) with 100, 41, 93, and 100 patients, respectively, reported clinical success rates of 92%, 93%, 96%, 94% at mean follow-up of 21.5, 12, 22, and 11 months (table 7⇓).[121-124]

Two publications with longer follow-up in the two to three year range have appeared over the past year. The Portland and Rome groups also combined their data with a third center (Hamburg, Germany) in a recent publication,[126] which aimed to provide early mid-term outcomes from patients who had completed at least two years of follow-up. This study probably included patients from Hamburg who had also been included in the five center northern European series reviewed above, and it showed similar modest efficacy, with an initial high clinical success of 94% at three to six months, which decreased to 88% at 12-18 months and 78% at two years or more (mean 29 months, range 24-41) in the 79 patients contributed by the three centers.[117] As was the case with the European multicenter controlled trial reviewed above, these more modest results were attributed by the authors to a learning curve effect because half of the failures occurred in the first 10 patients from each of the three contributing centers. In the largest POEM series to date, Inoue et al reported outcomes in 500 patients, with 105 patients at more than three years after POEM.[127] The procedure was technically successful in all patients. Moderate adverse events occurred in 3.2% and included pneumothorax, bleeding, mucosal injuries, postoperative hematomas, pleural effusion, and inflammation of the lesser omentum. Most were managed conservatively. There were no severe adverse events. Two month outcomes showed significant reductions in Eckardt scores and LES pressures. Clinical success (improvement of the Eckardt score) was achieved in 91.7%. On endoscopy, 65% had signs of reflux esophagitis, but only 17% of patients complained of GERD symptoms. At three years, the overall success remained high at 88.5%, with symptomatic GERD in 21% and signs of reflux esophagitis in 56%. All reflux symptoms were effectively managed with proton pump inhibitors.[127]

As we have previously noted,[128] there are several limitations. Firstly, significant differences exist between Asian and Western series. For example, comparing the Inoue et al series with our series from Winthrop (the largest single operator series in the US with 248 POEMs as of November 2015),[129] the patient population was significantly younger by more than a decade in the Inoue series (mean age of 43 in the Inoue series versus 54 in our series). Furthermore, there were significantly less challenging patients such as those previously treated with botox or Heller (1% and 2% respectively in the Inoue series versus 21% previous botox and 16% previous Heller in our series) and severe esophageal dilation to greater than 6 cm esophageal diameter (4% in the Inoue series versus 27% in our series). Secondly, an unusual efficacy definition was used in the Inoue series (post-POEM Eckardt <2 or decrease of the Eckardt score by ≥4 points) that differs from the definition used by all other published POEM series and most LHM series (that is, decrease of the Eckardt score to ≤3). This makes comparison with efficacy in other series less straightforward. Thirdly, there was a significant amount of missing follow-up data—for example, even though 105 patients were at more than three years from their POEM, Eckardt score data were available in only 61 (58%) and follow-up endoscopy in only 16 (15%).

Some recent publications have focused on outcomes of POEM in certain groups of patients in whom POEM may be preferable to LHM. Firstly, patients with Chicago classification type III "spastic" achalasia require a long myotomy in the esophageal body that cannot be performed with a laparoscopic approach but can easily be performed through the peroral approach. A recent multicenter study showed excellent outcomes after POEM in patients with spastic esophageal disorders, with clinical improvement in 93% of patients during a mean follow-up of 234 days.[130] Secondly, children present distinct surgical challenges. Six recent small case series showed excellent outcomes after POEM in children similar to POEM in adults and similar to laparoscopic Heller myotomy outcomes in children but obviously with much lower invasiveness compared with LHM.[131-137] Thirdly, patients with end stage achalasia often require esophagectomy, so LHM has traditionally been avoided in these patients because it would be unlikely to prevent the need for esophagectomy and would cause scarring and adhesions around the hiatus that might make subsequent esophagectomy more challenging. Because no tissues deep to the muscle of the esophagus are dissected during POEM, there is no periesophageal scarring or adhesions with this technique. A trial of myotomy using POEM is therefore a reasonable approach to try to forestall the need for esophagectomy in patients with a very dilated or sigmoid "end stage" esophagus. In a recent single center prospective study of 32 end stage achalasia patients who had POEM, 96% of cases were clinically successful at mean 30 month follow-up when treatment success was measured by symptom score reduction (mean Eckardt score decrease from 7.8 to 1.4; P<0.001).[138] Fourthly, patients who have previously been treated with Heller myotomy, botox, or balloon dilation are candidates for POEM. Generally, all of these treatments cause submucosal scarring with areas of fusion of the mucosa and muscularis that would be expected to make LHM and POEM more difficult. Patients in whom LHM has been unsuccessful have adhesions and scarring around the esophagus and proximal stomach that would make a "redo" LHM challenging. However, POEM has been shown to be effective in patients who have previously undergone endoscopic treatments[139] and LHM.[140-142]

Adverse events

The incidence of serious adverse events after POEM is low, and no deaths have been reported. The recent ASGE PIVI and NOSCAR white paper reviewed adverse events in published series in detail.[104 105] Interestingly, the international POEM survey yielded a higher incidence of serious adverse events,[103] although it was still better than for LHM and even pneumatic dilation. This may be because the international POEM survey method ensured centers' anonymity or because of the higher rate of adverse events in the early days of POEM covered by the survey (2008 to mid-2012). Minor intraprocedural technical errors or "incidents" using the terminology of the ASGE lexicon (events that are clinically inconsequential)[143] include:

- Small accidental cautery injuries to the mucosa overlying the submucosal tunnel easily closed with endoscopic clips during the procedure
- Limited asymptomatic pneumomediastinum, pneumothorax, pneumoperitoneum, or intraprocedural tense pneumoperitoneum easily vented intraprocedurally by use of an angiocath or Veress needle
- Intraprocedural bleeding that is controlled through endoscopic hemostasis.

Such incidents occur in 10-25% of cases in most series,[103-105] and their incidence decreases with experience.[121]

Intraprocedural and periprocedural adverse events of moderate severity (graded according to the ASGE lexicon),[143] include aspiration of luminal contents (usually during intubation) and symptomatic pneumothorax requiring drain placement.[144] Delayed adverse events generally occur within the immediate postoperative period (24-48 hours) and rarely up to seven to 10 days after surgery. Such delayed events include events of moderate severity such as bleeding that requires repeat endoscopy for hemostasis,[122-145] and, rarely, in severe cases, surgical intervention or Blakemore balloon tamponade.[146] Other delayed events are tunnel closure dehiscence requiring repeat endoscopy for endoscopic closure[122] and cardiopulmonary events such as pneumonia[147] or atrial fibrillation.[148] Severe events such as mediastinal leaks requiring surgical drainage and prolonged hospital stay are rare.[123-150]

No deaths have been reported, and all published series have reported low rates of adverse events (<2-3%), except for an early series from a Chinese center that reported adverse events in more than 50% of patients, mainly insufflation related events including a high number of patients requiring chest tubes for pneumothorax.[144] The authors attributed this to their early use of air rather than the recommended carbon dioxide. Air is the traditional insufflation gas for endoscopy but not for surgery, in which carbon dioxide is used as it is absorbed about 170 times faster than air from body cavities such as the mediastinum, thorax, and abdomen. After this Chinese center, which has currently performed the highest number of POEMs in the world (>1700), switched to carbon dioxide, the adverse event rate decreased to the low rate reported by other centers. Currently, POEM seems to be extremely safe in the experienced hands of highly skilled pioneers and early adopters.

GERD after POEM

The problem of GERD after POEM is of intense interest because POEM is rapidly displacing LHM as the first line therapy for achalasia in most patients. Early series reported little or no GERD after POEM (≤10%),[101-107] probably because of dependence mostly on symptom scores or unstructured clinical interviews. Once systematic objective assessment was undertaken with endoscopy to assess reflux esophagitis and pH studies to measure acid exposure, it was evident that the rate of GERD after POEM was substantially higher than previously thought. To date, only four series have presented substantial data on GERD assessment in their patients using all three methods (systematic symptom assessment, endoscopic evaluation, and ambulatory pH study; table 8⇓).[115-151]

These studies found that 27-59% of patients had endoscopic signs of GERD after POEM (mainly mild Los Angeles class A or B esophagitis), 29-38% had abnormally elevated acid exposure on pH studies, and 15-23% had frequent symptoms of GERD. These patients have been effectively treated with PPIs. As previously mentioned, achalasia patients may have false positive pH studies owing to stasis (poor clearance of acid in the absence of peristalsis) and fermentation of retained food causing a decrease in pH due to lactic acid.[15 16] Therefore, expert assessment of the overall clinical picture is needed to diagnose GERD. For example, the Rome group considered an abnormal pH study as indicative of "clinically relevant GERD" only if accompanied by symptoms of GERD and/or presence of erosive esophagitis on endoscopy. Using this definition, even though they found abnormal acid exposure in 50.5% of patients, clinically relevant GERD was present in only 29%.[151] Encouragingly, patients with GERD after POEM have uniformly been effectively treated with PPIs. In the Portland, Rome, and Hamburg multicenter study that focused on data from patients who had completed two year follow-up, 37% had erosive esophagitis and 37% were on PPIs at two years or more of follow-up (mean 29 months, range 24-41).[126] No pH data were provided. Interestingly, in that study the strongest predictor of relief from dysphagia seemed to be the presence of GERD (odds ratio 6.7), which lends support to the widely held belief that the more effective the disruption of the LES, the more effective the relief of dysphagia, but at the cost of a higher risk of GERD.

Because of this perceived "trade-off" between dysphagia relief and reflux, most authorities believe that during POEM or LHM, the efficacy of the myotomy should not be compromised in an effort to decrease the incidence of GERD. This is because GERD can be easily detected and treated, whereas persistent dysphagia and impaired esophageal emptying after LHM or POEM present a much more difficult diagnostic and therapeutic problem. It is important to emphasize, however, that GERD may be asymptomatic in 40-50% of cases.[122 151] Diligent follow-up is therefore needed after POEM, with at least one pH study postoperatively and endoscopic surveillance at one to two yearly intervals to detect patients with GERD so that they can be treated and longstanding reflux complications, such as Barrett's esophagus and peptic strictures, can be forestalled. Such reflux related complications were the most common cause of late failure after LHM with Dor fundoplication.[152] It is hoped that POEM operators will avoid relearning this lesson by vigilant detection of GERD, which is easily treated with PPIs.

However, even if a Dor or Toupet fundoplication is needed for some reason, POEM does not interfere with such an approach. Specifically, POEM does not disturb the anatomy of the hiatus or cause any periesophageal scarring or adhesions, as was confirmed, for example, when Heller myotomy was performed as salvage therapy in patients with persistent dysphagia after POEM.[123] It should be noted that the Dor or Toupet "loose" fundoplications performed in conjunction with a LHM in patients with achalasia have only modest efficacy. High quality studies from expert LHM centers have shown that 18-42% of patients have abnormal acid exposure after LHM with fundoplication,[153-155] rates that are not dissimilar to those after POEM. Furthermore, these pH data were collected only six to 12 months postoperatively and may be even less favorable at long term follow-up. It is unclear why the rate of GERD after POEM is not substantially greater than that after LHM combined with fundoplication. It may be because of the lack of hiatal dissection during POEM compared with extensive dissection of the hiatus during a standard LHM. This extensive dissection disrupts important "suspensory ligaments" of the esophagus, notably the phrenoesophageal membrane, which is thought to contribute to the maintenance of the angle of His and to have an important anti-reflux function separate from the esophageal "sphincter" itself. Two recent studies lend support to this hypothesis by showing that a modified LHM with as limited dissection of the hiatus as possible results in much lower rates of GERD even without a fundoplication (9% and 31%).[156 157]

POEM compared with conventional therapies

The recent ASGE PIVI reviewed outcomes of conventional therapies and those of POEM in detail and proposed the following efficacy and safety thresholds for the adoption of POEM:

- At least 80% efficacy at 12 months (defined as an Eckardt score ≤3 with a dysphagia component of ≤2)
- A rate of serious adverse events of 6% or lower
- A 30 day mortality rate of 0.1% or lower.[105]

On the basis of the published data so far, POEM outcomes exceed these thresholds. Currently there are no randomized trials of POEM versus conventional therapies.

Two European multicenter randomized trials comparing POEM with pneumatic dilation and LHM are still only about halfway through their enrollment targets after two years. Furthermore, patient enrollment may be decelerating as an increasing number of patients are unwilling to consider LHM or pneumatic dilation, with the rapidly accumulating prospective data showing that POEM combines the minimal invasiveness of endoscopic therapies such as pneumatic dilation with the efficacy and durability of LHM.

Three retrospective cohort studies from the US have compared LHM and POEM.[109-158] The first compared 18 POEM procedures with 55 LHMs and found that POEM was faster (113 *v* 125 min; P<0.05) with less blood loss (10 *v* 55 mL; P<0.001), but that adverse events (one perforation requiring surgery and prolonged hospital stay in each group) and hospital stay (median one day) were similar for both techniques. The second study compared 18 POEMs with 21 LHMs and found similar adverse events (one leak that required surgery and prolonged hospital stay in each group), but less postoperative pain (P=0.02) and faster return to activities of daily living after POEM (2.2 *v* 6.4 days; P=0.03). The third study compared 37 POEMs with 64 LHMs and found similar adverse events (one severe event in each group). However, POEM had a shorter procedure duration (120 *v* 160 min; P<0.001), shorter hospital stay (1.1 *v* 2.5 days; P<0.001), better (lower) Eckardt score at one month (0.8 *v* 1.8; P<0.001) and six months (1.2 *v* 1.7; P=0.1), and significantly less dysphagia in response to solids at six months (0% *v* 29% of patients with dysphagia to solids at least weekly; P<0.001). The study also obtained pH data for 23 POEMs and 31 LHMs and found similar rates of GERD (POEM 39% *v* LHM 32%; not significant).

Overall, these studies found that POEM was equivalent or superior to LHM in all areas assessed. These findings are even more robust considering the fact that these POEM operators were surgeons, whose main training and experience, unlike gastroenterologist POEM operators, is with rigid laparoscopic instruments rather than the flexible endoscope used in POEM. In addition, their first attempts at performing POEM, early in their learning curve, were compared with their mature LHM experience.

On the basis of these comparative data and the excellent POEM outcomes from more than 20 published prospective series, and taking into account the greater invasiveness of LHM, it is unlikely that any attempt at a randomized trial between LHM and POEM in the US would recruit an adequate number of patients. A more clinically relevant and potentially feasible avenue of investigation would be to compare POEM with pneumatic dilation, which offers the advantages of a simpler, low cost ambulatory procedure albeit at the cost of shorter durability and the need for more interventions over time.

Guidelines

Achalasia guidelines from major gastrointestinal societies are three to four years old and do not acknowledge more recent advances in treatment. Guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons in 2012[159] and American College of Gastroenterology in 2013[40] recommend that achalasia should be suspected in patients with dysphagia to solids and liquids who have regurgitation that does not respond to PPIs. Patients require endoscopy to exclude mechanical obstruction and pseudoachalasia, barium esophagraphy to assess emptying, and manometry testing to confirm the diagnosis. Treatment should be guided by age, sex, patient's preference, and institutional expertise. Generally, definitive treatment (pneumatic dilation or myotomy) is recommended, with EBTI being reserved for patients who are not good candidates for definitive treatment. Follow-up using the Eckardt score (subjective score) and esophagraphy (objective test) is recommended after treatment.

There are no clear recommendations regarding surveillance endoscopy for esophageal cancer and disease progression. However, some experts recommend endoscopic or radiologic surveillance in patients who have had achalasia for more than 10-15 years at an interval of every three years.

Conclusions

Achalasia is a rare esophageal motility disorder, manifested mainly by dysphagia, for which there has recently been a paradigm shift in its diagnosis and treatment. High resolution manometry has enabled accurate diagnosis of achalasia, differentiation from other similar disorders, and classification of achalasia into clinically relevant subtypes. Medical therapy is ineffective for achalasia, and before 2008 treatment was limited to pneumatic dilation, botulinum toxin injection, or LHM. Over the past six years, however, prospective trials with short term and early intermediate term outcomes have shown that POEM has excellent efficacy and safety. POEM represents a major advance in the treatment of achalasia because it combines the superior efficacy of LHM with the relative ease and non-invasiveness of endoscopy. POEM has been successful in all subtypes of achalasia and in patients who had previously undergone Heller esophagomyotomy, pneumatic dilation, and EBTI. Patients treated with LHM or POEM should have close follow-up with pH testing because GERD is the most common adverse event after both procedures and patients often need

PPIs. Upper endoscopy should be performed periodically because of the increased risk of cancer associated with GERD and achalasia. Studies comparing the long term results of POEM with the well established record of LHM are awaited. Clinicatrials.gov reports ongoing studies in Brazil, Europe, and the US, but these results are not yet available. Pneumatic dilation for achalasia is not likely to become obsolete, but it may be displaced as a primary therapy. Technological advances in diagnosis and the addition of POEM into the therapeutic armamentarium should benefit people with achalasia.

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1 Reynolds JC, Parkman HP. Achalasia. *Gastroenterol Clin North Am* 1989;18:223-55.pmid:2668168.
2 Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol* 2013;108:1238-49, quiz 1250. doi:10.1038/ajg.2013.196pmid:23877351.
3 Sadowski DC, Ackah F, Jiang B, Svenson LW. Achalasia: incidence, prevalence and survival. A population-based study. *Neurogastroenterol Motil* 2010;22:e256-61. doi:10.1111/j.1365-2982.2010.01511.xpmid:20465592.
4 Nenshi R, Takata J, Stegienko S, et al. The cost of achalasia: quantifying the effect of symptomatic disease on patient cost burden, treatment time, and work productivity. *Surg Innov* 2010;17:291-4. doi:10.1177/1553350610376392pmid:20647236.
5 O'Neill OM, Johnston BT, Coleman HG. Achalasia: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2013;19:5806-12. doi:10.3748/wjg.v19.i35.5806pmid:24124325.
6 Enestvedt BK, Williams JL, Sonnenberg A. Epidemiology and practice patterns of achalasia in a large multi-centre database. *Aliment Pharmacol Ther* 2011;33:1209-14. doi:10.1111/j.1365-2036.2011.04655.xpmid:21480936.
7 Pandolfino JE, Gawron AJ. Achalasia: a systematic review. *JAMA* 2015;313:1841-52. doi:10.1001/jama.2015.2996pmid:25965233.
8 Park W, Vaezi MF. Etiology and pathogenesis of achalasia: the current understanding. *Am J Gastroenterol* 2005;100:1404-14. doi:10.1111/j.1572-0241.2005.41775.xpmid:15929777.
9 de Oliveira RB, Rezende Filho J, Dantas RO, Iazigi N. The spectrum of esophageal motor disorders in Chagas' disease. *Am J Gastroenterol* 1995;90:1119-24.pmid:7611209.
10 Zárate N, Mearin F, Gil-Vernet JM, Camarasa F, Malagelada JR. Achalasia and Down's syndrome: coincidental association or something else?*Am J Gastroenterol* 1999;94:1674-7. doi:10.1111/j.1572-0241.1999.01161.xpmid:10364043.
11 Sarathi V, Shah NS. Triple-A syndrome. *Adv Exp Med Biol* 2010;685:1-8. doi:10.1007/978-1-4419-6448-9_1pmid:20687490.
12 Tsuboi K, Hoshino M, Srinivasan A, et al. Insights gained from symptom evaluation of esophageal motility disorders: a review of 4,215 patients. *Digestion* 2012;85:236-42. doi:10.1159/000336072pmid:22472689.
13 Shoenut JP, Micflikier AB, Yaffe CS, Den Boer B, Teskey JM. Reflux in untreated achalasia patients. *J Clin Gastroenterol* 1995;20:6-11. doi:10.1097/00004836-199501000-00004pmid:7884182.
14 Patti MG, Arcerito M, Tong J, et al. De Pinto M de Bellis M. Importance of preoperative and postoperative pH monitoring in patients with esophageal achalasia. *J Gastrointest Surg* 1997;1:505-10. doi:10.1016/S1091-255X(97)80065-0pmid:9834385.
15 Crookes PF, Corkill S, DeMeester TR. Gastroesophageal reflux in achalasia. When is reflux really reflux?*Dig Dis Sci* 1997;42:1354-61. doi:10.1023/A:1018873501205pmid:9246028.
16 Novais PA, Lemme EM. 24-h pH monitoring patterns and clinical response after achalasia treatment with pneumatic dilation or laparoscopic Heller myotomy. *Aliment Pharmacol Ther* 2010;32:1257-65. doi:10.1111/j.1365-2036.2010.04461.xpmid:20955445.
17 Glatz SM, Richardson JD. Esophagectomy for end stage achalasia. *J Gastrointest Surg* 2007;11:1134-7. doi:10.1007/s11605-007-0226-8pmid:17623258.
18 Madenci AL, Reames BN, Chang AC, Lin J, Orringer MB, Reddy RM. Factors associated with rapid progression to esophagectomy for benign disease. *J Am Coll Surg* 2013;217:889-95. doi:10.1016/j.jamcollsurg.2013.07.384pmid:24035659.
19 Minami H, Yamaguchi N, Matsushima K, et al. Improvement of endocytoscopic findings after per oral endoscopic myotomy (POEM) in esophageal achalasia; does POEM reduce the risk of developing esophageal carcinoma? Per oral endoscopic myotomy, endocytoscopy and carcinogenesis. *BMC Gastroenterol* 2013;13:22. doi:10.1186/1471-230X-13-22pmid:23363448.
20 Leeuwenburgh I, Scholten P, Alderliesten J, et al. Long-term esophageal cancer risk in patients with primary achalasia: a prospective study. *Am J Gastroenterol* 2010;105:2144-9. doi:10.1038/ajg.2010.263pmid:20588263.
21 Eckardt AJ, Eckardt VF. Editorial: Cancer surveillance in achalasia: better late than never?*Am J Gastroenterol* 2010;105:2150-2. doi:10.1038/ajg.2010.257pmid:20927062.
22 Brücher BL, Stein HJ, Bartels H, Feussner H, Siewert JR. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. *World J Surg* 2001;25:745-9. doi:10.1007/s00268-001-0026-3pmid:11376410.
23 Dunaway PM, Wong RK. Risk and surveillance intervals for squamous cell carcinoma in achalasia. *Gastrointest Endosc Clin N Am* 2001;11:425-34, ix.pmid:11319071.
24 Leeuwenburgh I, Scholten P, Caljé TJ, et al. Barrett's esophagus and esophageal adenocarcinoma are common after treatment for achalasia. *Dig Dis Sci* 2013;58:244-52. doi:10.1007/s10620-012-2157-9pmid:23179142.
25 Hirota WK, Zuckerman MJ, Adler DG, et al. Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006;63:570-80. doi:10.1016/j.gie.2006.02.004pmid:16564854.
26 Parkman HP, Cohen S. Malignancy-induced secondary achalasia. *Dysphagia* 1993;8:292-6. doi:10.1007/BF01354553pmid:8359052.
27 Tucker HJ, Snape WJ Jr, , Cohen S. Achalasia secondary to carcinoma: manometric and clinical features. *Ann Intern Med* 1978;89:315-8. doi:10.7326/0003-4819-89-3-315pmid:686541.
28 Ellingson TL, Kozarek RA, Gelfand MD, Botoman AV, Patterson DJ. Iatrogenic achalasia. A case series. *J Clin Gastroenterol* 1995;20:96-9. doi:10.1097/00004836-199503000-00004pmid:7769210.
29 Duntemann TJ, Dresner DM. Achalasia-like syndrome presenting after highly selective vagotomy. *Dig Dis Sci* 1995;40:2081-3. doi:10.1007/BF02208682pmid:7555468.
30 Stylopoulos N, Bunker CJ, Rattner DW. Development of achalasia secondary to laparoscopic Nissen fundoplication. *J Gastrointest Surg* 2002;6:368-76, discussion 377-8. doi:10.1016/S1091-255X(02)00019-7pmid:12022989.
31 Kia L, Kahrilas PJ. An unusual complication after laparoscopic gastric lap band placement. *Gastroenterology* 2014;147:e9-10. doi:10.1053/j.gastro.2014.07.043pmid:25450091.
32 Parkman HP, Maurer AH, Caroline DF, Miller DL, Krevsky B, Fisher RS. Optimal evaluation of patients with nonobstructive esophageal dysphagia. Manometry, scintigraphy, or videoesophagography?*Dig Dis Sci* 1996;41:1355-68. doi:10.1007/BF02088560pmid:8689912.
33 El-Takli I, O'Brien P, Paterson WG. Clinical diagnosis of achalasia: how reliable is the barium x-ray?*Can J Gastroenterol* 2006;20:335-7. doi:10.1155/2006/193823pmid:16691299.
34 Ott DJ, Richter JE, Chen YM, Wu WC, Gelfand DW, Castell DO. Esophageal radiography and manometry: correlation in 172 patients with dysphagia. *AJR Am J Roentgenol* 1987;149:307-11. doi:10.2214/ajr.149.2.307pmid:3496755.
35 Richter JE. High-resolution manometry in diagnosis and treatment of achalasia: help or hype. *Curr Gastroenterol Rep* 2014;16:420. doi:10.1007/s11894-014-0420-2pmid:25543338.
36 de Oliveira JM, Birgisson S, Doinoff C, et al. Timed barium swallow: a simple technique for evaluating esophageal emptying in patients with achalasia. *AJR Am J Roentgenol* 1997;169:473-9. doi:10.2214/ajr.169.2.9242756pmid:9242756.
37 Pechlivanides G, Chrysos E, Athanasakis E, Tsiaoussis J, Vassilakis JS, Xynos E. Laparoscopic Heller cardiomyotomy and Dor fundoplication for esophageal achalasia: possible factors predicting outcome. *Arch Surg* 2001;136:1240-3. doi:10.1001/archsurg.136.11.1240pmid:11695966.
38 Vaezi MF, Baker ME, Richter JE. Assessment of esophageal emptying post-pneumatic dilation: use of the timed barium esophagram. *Am J Gastroenterol* 1999;94:1802-7. doi:10.1111/j.1572-0241.1999.01209.xpmid:10406238.
39 Rohof WO, Lei A, Boeckxstaens GE. Esophageal stasis on a timed barium esophagogram predicts recurrent symptoms in patients with long-standing achalasia. *Am J Gastroenterol* 2013;108:49-55. doi:10.1038/ajg.2012.318pmid:23007004.
40 Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol* 2013;108:1238-49, quiz 1250. doi:10.1038/ajg.2013.196pmid:23877351.
41 Kahrilas PJ. Esophageal motor disorders in terms of high-resolution esophageal pressure topography: what has changed?*Am J Gastroenterol* 2010;105:981-7. doi:10.1038/ajg.2010.43pmid:20179690.
42 Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008;135:1526-33. doi:10.1053/j.gastro.2008.07.022pmid:18722376.
43 Kahrilas PJ, Bredenoord AJ, Fox M, et al. International High Resolution Manometry Working Group. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil* 2015;27:160-74. doi:10.1111/nmo.12477pmid:25469569.
44 Hoogerwerf WA, Pasricha PJ. Pharmacologic therapy in treating achalasia. *Gastrointest Endosc Clin N Am* 2001;11:311-24, vii.pmid:11319064.
45 Bortolotti M, Labò G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. *Gastroenterology* 1981;80:39-44.pmid:7450409.
46 Penagini , Bartesaghi B, Negri G, Bianchi PA. Effect of loperamide on lower oesophageal sphincter pressure in idiopathic achalasia. *Scand J Gastroenterol* 1994;29:1057-60. doi:10.3109/00365529409094887pmid:7886391.
47 Marzio L, Grossi L, DeLaurentiis MF, Cennamo L, Lapenna D, Cuccurullo F. Effect of cimetropium bromide on esophageal motility and transit in patients affected by primary achalasia. *Dig Dis Sci* 1994;39:1389-94. doi:10.1007/BF02088038pmid:8026247.
48 Bortolotti M, Mari C, Lopilato C, Porrazzo G, Miglioli M. Effects of sildenafil on esophageal motility of patients with idiopathic achalasia. *Gastroenterology* 2000;118:253-7. doi:10.1016/S0016-5085(00)70206-Xpmid:10648452.
49 Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. *Gastroenterology* 1996;110:1410-5. doi:10.1053/gast.1996.v110.pm8613045pmid:8613045.
50 Annese V, Bassotti G, Coccia G, et al. GISMAD Achalasia Study Group. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut* 2000;46:597-600. doi:10.1136/gut.46.5.597pmid:10764700.
51 Campos GM, Vittinghoff E, Rabl C, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 2009;249:45-57. doi:10.1097/SLA.0b013e31818e43abpmid:19106675.
52 Fishman VM, Parkman HP, Schiano TD, et al. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. *Am J Gastroenterol* 1996;91:1724-30.pmid:8792688.
53 Portale G, Costantini M, Rizzetto C, et al. Long-term outcome of laparoscopic Heller-Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. *J Gastrointest Surg* 2005;9:1332-9. doi:10.1016/j.gassur.2005.10.001pmid:16332491.
54 Orenstein SB, Raigani S, Wu YV, et al. Peroral endoscopic myotomy (POEM) leads to similar results in patients with and without prior endoscopic or surgical therapy. *Surg Endosc* 2015;29:1064-70. doi:10.1007/s00464-014-3782-5pmid:25249143.
55 Kadakia SC, Wong RK. Pneumatic balloon dilation for esophageal achalasia. *Gastrointest Endosc Clin N Am* 2001;11:325-46, vii.pmid:11319065.
56 Katzka DA, Castell DO. Review article: an analysis of the efficacy, perforation rates and methods used in pneumatic dilation for achalasia. *Aliment Pharmacol Ther* 2011;34:832-9. doi:10.1111/j.1365-2036.2011.04816.xpmid:21848630.
57 Zerbib F, Thétiot V, Richy F, Benajah DA, Message L, Lamouliatte H. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. *Am J Gastroenterol* 2006;101:692-7. doi:10.1111/j.1572-0241.2006.00385.xpmid:16635216.

Glossary of abbreviations

AGA—American Gastrointestinal Association
ASGE—American Society of Gastrointestinal Endoscopy
EBTI—endoscopic botulinum toxin injection
EGJ—esophagogastric junction
GERD—gastroesophageal reflux disease
HREM—high resolution esophageal manometry
IRP—integrated residual pressure
LES—lower esophageal sphincter
LHM—laparoscopic Heller myotomy
NOSCAR—Natural Orifice Surgery Consortium for Advancement and Research
NOTES—natural orifice transluminal endoscopic surgery
PIVI—preservation and incorporation of valuable endoscopic innovations
POEM—peroral endoscopic myotomy
PPI—proton pump inhibitor
RCT—randomized controlled trial
SAGES—Society of American Gastrointestinal and Endoscopic Surgeons

58 Hulselmans M, Vanuytsel T, Degreef T, et al. Long-term outcome of pneumatic dilation in the treatment of achalasia. *Clin Gastroenterol Hepatol* 2010;8:30-5. doi:10.1016/j.cgh.2009.09.020pmid:19782766.
59 Katsinelos P, Kountouras J, Paroutoglou G, et al. Long-term results of pneumatic dilation for achalasia: a 15 years' experience. *World J Gastroenterol* 2005;11:5701-5. doi:10.3748/wjg.v11.i36.5587pmid:16237769.
60 Abid S, Champion G, Richter JE, McElvein R, Slaughter RL, Koehler RE. Treatment of achalasia: the best of both worlds. *Am J Gastroenterol* 1994;89:979-85.pmid:8017394.
61 Wehrmann T, Jacobi V, Jung M, Lembcke B, Caspary WF. Pneumatic dilation in achalasia with a low-compliance balloon: results of a 5-year prospective evaluation. *Gastrointest Endosc* 1995;42:31-6. doi:10.1016/S0016-5107(95)70239-3pmid:7557173.
62 Guardino JM, Vela MF, Connor JT, Richter JE. Pneumatic dilation for the treatment of achalasia in untreated patients and patients with failed Heller myotomy. *J Clin Gastroenterol* 2004;38:855-60. doi:10.1097/00004836-200411000-00004pmid:15492600.
63 Dobrucali A, Erzin Y, Tuncer M, Dirican A. Long-term results of graded pneumatic dilatation under endoscopic guidance in patients with primary esophageal achalasia. *World J Gastroenterol* 2004;10:3322-7. doi:10.3748/wjg.v10.i22.3322pmid:15484309.
64 Chan KC, Wong SK, Lee DW, et al. Short-term and long-term results of endoscopic balloon dilation for achalasia: 12 years' experience. *Endoscopy* 2004;36:690-4. doi:10.1055/s-2004-825659pmid:15280973.
65 Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. *Gastroenterology* 1992;103:1732-8. doi:10.1016/0016-5085(92)91428-7pmid:1451966.
66 Yaghoobi M, Mayrand S, Martel M, Roshan-Afshar I, Bijarchi R, Barkun A. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2013;78:468-75. doi:10.1016/j.gie.2013.03.1335pmid:23684149.
67 Richter JE. Update on the management of achalasia: balloons, surgery and drugs. *Expert Rev Gastroenterol Hepatol* 2008;2:435-45. doi:10.1586/17474124.2.3.435pmid:19072391.
68 Metman EH, Lagasse JP, d'Alteroche L, Picon L, Scotto B, Barbieux JP. Risk factors for immediate complications after progressive pneumatic dilation for achalasia. *Am J Gastroenterol* 1999;94:1179-85. doi:10.1111/j.1572-0241.1999.01062.xpmid:10235189.
69 Heller E. Extramukoese cardinplastik bein chronischen cardiopsasmus mit dilation des oesophagus. *Mitt Grenzgeb Med Chir* 1914;27:141-5.
70 Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. *Arch Surg* 2003;138:490-5, discussion 495-7. doi:10.1001/archsurg.138.5.490pmid:12742951.
71 Richards WO, Torquati A, Holzman MD, et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. *Ann Surg* 2004;240:405-12, discussion 412-5. doi:10.1097/01.sla.0000136940.32255.51pmid:15319712.
72 Vela MF, Richter JE, Khandwala F, et al. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. *Clin Gastroenterol Hepatol* 2006;4:580-7. doi:10.1016/S1542-3565(05)00986-9pmid:16630776.
73 Bonatti H, Hinder RA, Klocker J, et al. Long-term results of laparoscopic Heller myotomy with partial fundoplication for the treatment of achalasia. *Am J Surg* 2005;190:874-8. doi:10.1016/j.amjsurg.2005.08.012pmid:16307937.
74 Vaezi MF, Richter JE, Wilcox CM, et al. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. *Gut* 1999;44:231-9. doi:10.1136/gut.44.2.231pmid:9895383.
75 Ghoshal UC, Chaudhuri S, Pal BB, Dhar K, Ray G, Banerjee PK. Randomized controlled trial of intrasphincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. *Dis Esophagus* 2001;14:227-31. doi:10.1046/j.1442-2050.2001.00189.xpmid:11869325.
76 Bansal R, Nostrant TT, Scheiman JM, et al. Intrasphincteric botulinum toxin versus pneumatic balloon dilation for treatment of primary achalasia. *J Clin Gastroenterol* 2003;36:209-14. doi:10.1097/00004836-200303000-00005pmid:12590230.
77 Mikaeli J, Farrokhi F, Bishehsari F, Mahdavinia M, Malekzadeh R. Gender effect on clinical features of achalasia: a prospective study. *BMC Gastroenterol* 2006;6:12. doi:10.1186/1471-230X-6-12pmid:16579859.
78 Bakhshipour A, Rabbani R, Shirani S, Soleimani HA, Mikaeli J. Comparison of pneumatic dilation with pneumatic dilation plus botulinum toxin for treatment of achalasia. *Acta Med Iran* 2010;48:107-10.pmid:21133003.
79 Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *Cochrane Database Syst Rev* 2014;12:CD005046.pmid:25485740.
80 Zaninotto G, Annese V, Costantini M, et al. Randomized controlled trial of botulinum toxin versus laparoscopic heller myotomy for esophageal achalasia. *Ann Surg* 2004;239:364-70. doi:10.1097/01.sla.0000114217.52941.c5pmid:15075653.
81 Andrews CN, Anvari M, Dobranowski J. Laparoscopic Heller's myotomy or botulinum toxin injection for management of esophageal achalasia. Patient choice and treatment outcomes. *Surg Endosc* 1999;13:742-6. doi:10.1007/s004649901090pmid:10430676.
82 Kostic S, Kjellin A, Ruth M, et al. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. *World J Surg* 2007;31:470-8. doi:10.1007/s00268-006-0600-9pmid:17308851.
83 Persson J, Johnsson E, Kostic S, Lundell L, Smedh U. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: long-term results of a prospective, randomized study. *World J Surg* 2015;39:713-20. doi:10.1007/s00268-014-2869-4pmid:25409838.
84 Moonen A, Annese V, Belmans A, et al. Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy. *Gut* 2016;65:732-9. doi:10.1136/gutjnl-2015-310602pmid:26614104.
85 Csendes A, Braghetto I, Henríquez A, Cortés C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. *Gut* 1989;30:299-304. doi:10.1136/gut.30.3.299pmid:2651226.
86 Boeckxstaens GE, Annese V, des Varannes SB, et al. European Achalasia Trial Investigators. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011;364:1807-16. doi:10.1056/NEJMoa1010502pmid:21561346.
87 Weber CE, Davis CS, Kramer HJ, Gibbs JT, Robles L, Fisichella PM. Medium and long-term outcomes after pneumatic dilation or laparoscopic Heller myotomy for achalasia: a meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2012;22:289-96. doi:10.1097/SLE.0b013e31825a2478pmid:22874676.
88 Wang L, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. *Dig Dis Sci* 2009;54:2303-11. doi:10.1007/s10620-008-0637-8pmid:19107596.
89 Schoenberg MB, Marx S, Kersten JF, et al. Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Ann Surg* 2013;258:943-52. doi:10.1097/SLA.0000000000000212pmid:24220600.
90 Ferguson MK, Reeder LB, Olak J. Results of myotomy and partial fundoplication after pneumatic dilation for achalasia. *Ann Thorac Surg* 1996;62:327-30. doi:10.1016/0003-4975(96)00176-2pmid:8694585.
91 Guelrud M, Rossiter A, Souney PF, Sulbaran M. Transcutaneous electrical nerve stimulation decreases lower esophageal sphincter pressure in patients with achalasia. *Dig Dis Sci* 1991;36:1029-33. doi:10.1007/BF01297442pmid:1864193.
92 Zeng Y, Dai YM, Wan XJ. Clinical remission following endoscopic placement of retrievable, fully covered metal stents in patients with esophageal achalasia. *Dis Esophagus* 2014;27:103-8. doi:10.1111/dote.12083pmid:23796127.
93 Mikaeli J, Veisari AK, Fazlollahi N, et al. Ethanolamine oleate versus botulinum toxin in the treatment of idiopathic achalasia. *Ann Gastroenterol* 2015;28:229-35.pmid:25830939.
94 Coppola F, Gaia S, Rolle E, Recchia S. Temporary endoscopic metallic stent for idiopathic esophageal achalasia. *Surg Innov* 2014;21:11-4. doi:10.1177/1553350613492024pmid:23793575.
95 Zhao JG, Li YD, Cheng YS, et al. Long-term safety and outcome of a temporary self-expanding metallic stent for achalasia: a prospective study with a 13-year single-center experience. *Eur Radiol* 2009;19:1973-80. doi:10.1007/s00330-009-1373-ypmid:19296113.
96 Cheng YS, Ma F, Li YD, et al. Temporary self-expanding metallic stents for achalasia: a prospective study with a long-term follow-up. *World J Gastroenterol* 2010;16:5111-7. doi:10.3748/wjg.v16.i40.5111pmid:20976849.
97 Moretó M, Ojembarrena E, Barturen A, Casado I. Treatment of achalasia by injection of sclerosant substances: a long-term report. *Dig Dis Sci* 2013;58:788-96. doi:10.1007/s10620-012-2476-xpmid:23179151.
98 Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Knipschield MA. Transesophageal mediastinoscopy by submucosal endoscopy with mucosal flap safety valve technique. *Gastrointest Endosc* 2007;65:679-83. doi:10.1016/j.gie.2006.10.017pmid:17383463.
99 Pasricha PJ, Hawari R, Ahmed I, et al. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007;39:761-4. doi:10.1055/s-2007-966764pmid:17703382.
100 Ortega JA, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980;26:8-10. doi:10.1016/S0016-5107(80)73249-2pmid:7358270.
101 Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010;42:265-71. doi:10.1055/s-0029-1244080pmid:20354937.

102 Stavropoulos SN, Harris MD, Hida S, Brathwaite C, Demetriou C, Grendell J. Endoscopic submucosal myotomy for the treatment of achalasia (with video). *Gastrointest Endosc* 2010;72:1309-11. doi:10.1016/j.gie.2010.04.016pmid:21111876.
103 Stavropoulos SN, Modayil RJ, Friedel D, Savides T. The international per oral endoscopic myotomy survey (IPOEMS): a snapshot of the global POEM experience. *Surg Endosc* 2013;27:3322-38. doi:10.1007/s00464-013-2913-8pmid:23549760.
104 Stavropoulos SN, Desilets DJ, Fuchs KH, et al. NOSCAR POEM White Paper Committee. Per-oral endoscopic myotomy white paper summary. *Gastrointest Endosc* 2014;80:1-15. doi:10.1016/j.gie.2014.04.014pmid:24950639.
105 Chandrasekhara V, Desilets D, Falk GW, et al. American Society for Gastrointestinal Endoscopy PIVI Committee. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on peroral endoscopic myotomy. *Gastrointest Endosc* 2015;81:1087-100.e1. doi:10.1016/j.gie.2014.12.007pmid: 25799295.
106 von Renteln D, Inoue H, Minami H, et al. Peroral endoscopic myotomy for the treatment of achalasia: a prospective single center study. *Am J Gastroenterol* 2012;107:411-7. doi: 10.1038/ajg.2011.388pmid:22068665.
107 Costamagna G, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis* 2012;44:827-32. doi:10.1016/j.dld.2012.04.003pmid:22609465.
108 Swanstrom LL, Kurian A, Dunst CM, Sharata A, Bhayani N, Rieder E. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. *Ann Surg* 2012;256:659-67. doi:10.1097/SLA.0b013e31826b5212pmid:22982946.
109 Hungness ES, Teitelbaum EN, Santos BF, et al. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *J Gastrointest Surg* 2013;17:228-35. doi:10.1007/s11605-012-2030-3pmid:23054897.
110 Inoue H, Ikeda H, Onimaru M, et al. Clinical results in 300 cases of POEM for esophageal achalasia a single institute registered prospective study. *Gastrointest Endosc* 2013;77(5S):AB121-2doi:10.1016/j.gie.2013.04.007.
111 Chiu PW, Wu JC, Teoh AY, et al. Peroral endoscopic myotomy for treatment of achalasia: from bench to bedside (with video). *Gastrointest Endosc* 2013;77:29-38. doi:10.1016/j.gie.2012.08.018pmid:23043852.
112 Lee BH, Shim KY, Hong SJ, et al. Peroral endoscopic myotomy for treatment of achalasia: initial results of a korean study. *Clin Endosc* 2013;46:161-7. doi:10.5946/ce.2013.46.2.161pmid:23614126.
113 Minami H, Isomoto H, Yamaguchi N, et al. Peroral endoscopic myotomy for esophageal achalasia: clinical impact of 28 cases. *Dig Endosc* 2014;26:43-51. doi:10.1111/den.12086pmid:23581563.
114 Verlaan T, Rohof WO, Bredenoord AJ, Eberl S, Rösch T, Fockens P. Effect of peroral endoscopic myotomy on esophagogastric junction physiology in patients with achalasia. *Gastrointest Endosc* 2013;78:39-44. doi:10.1016/j.gie.2013.01.006pmid:23453184.
115 Stavropoulos SN, Modayil RJ, Brathwaite CE, et al. Outcomes of a 5-year, large prospective series of per oral endoscopic myotomy (POEM). Emphasis on objective assessment for GERD and luminal patency. *Gastrointest Endosc* 2015;81(5S):AB118-9doi: 10.1016/j.gie.2015.03.018.
116 Zhou P, Yao L, Zhang YQ, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia: 205 case reports. *Gastrointest Endosc* 2012;75:AB132-3doi:10.1016/j.gie.2012.04.042.
117 Von Renteln D, Fuchs KH, Fockens P, et al. Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology* 2013;145:309-11.e1-3. doi:10.1053/j.gastro.2013.04.057pmid:23665071.
118 Charton JP, Schumacher B, Toermer T, et al. Per oral endscopic myotomy (POEM) for achalasia: pilot case series of a Western referral center. *Gastrointest Endosc* 2013;77(5S):AB351doi:10.1016/j.gie.2013.03.1163.
119 Eckardt AJ, Eckardt VF. Treatment and surveillance strategies in achalasia: an update. *Nat Rev Gastroenterol Hepatol* 2011;8:311-9. doi:10.1038/nrgastro.2011.68pmid:21522116.
120 Kurian AA, Dunst CM, Sharata A, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic esophageal myotomy: defining the learning curve. *Gastrointest Endosc* 2013;77:719-25. doi:10.1016/j.gie.2012.12.006pmid:23394838.
121 Patel KS, Calixte R, Modayil RJ, Friedel D, Brathwaite CE, Stavropoulos SN. The light at the end of the tunnel: a single-operator learning curve analysis for per oral endoscopic myotomy. *Gastrointest Endosc* 2015;81:1181-7. doi:10.1016/j.gie.2014.10.002pmid: 25597422.
122 Sharata AM, Dunst CM, Pescarus R, et al. Peroral endoscopic myotomy (POEM) for esophageal primary motility disorders: analysis of 100 consecutive patients. *J Gastrointest Surg* 2015;19:161-70, discussion 170. doi:10.1007/s11605-014-2610-5pmid:25183406.
123 Teitelbaum EN, Soper NJ, Santos BF, et al. Symptomatic and physiologic outcomes one year after peroral esophageal myotomy (POEM) for treatment of achalasia. *Surg Endosc* 2014;28:3359-65. doi:10.1007/s00464-014-3628-1pmid:24939164.
124 Familiari P, Gigante G, Marchese M, et al. Peroral endoscopic myotomy for esophageal achalasia: outcomes of the first 100 patients with short-term follow-up. *Ann Surg* 2016;263:82-7. doi:10.1097/SLA.0000000000000992pmid:25361224.
125 Vaezi MF, Baker ME, Achkar E, Richter JE. Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. *Gut* 2002;50:765-70. doi:10.1136/gut.50.6.765pmid:12010876.
126 Werner YB, Costamagna G, Swanström LL, et al. Clinical response to peroral endoscopic myotomy in patients with idiopathic achalasia at a minimum follow-up of 2 years. *Gut* 2016;65:899-906. doi:10.1136/gutjnl-2014-308649pmid:25934759.
127 Inoue H, Sato H, Ikeda H, et al. Per-oral endoscopic myotomy: a series of 500 patients. *J Am Coll Surg* 2015;221:256-64. doi:10.1016/j.jamcollsurg.2015.03.057pmid:26206634.
128 Modayil R, Stavropoulos SN. A Western perspective on "new NOTES" from POEM to full-thickness resection and beyond. *Gastrointest Endosc Clin N Am* 2016;26:413-32. doi: 10.1016/j.giec.2015.12.014pmid:27036906.
129 Stavropoulos SN, Modayil R, Braithwaite C, et al. Outcomes of a large prospective series on per oral endoscopic myotomy (POEM) for achalasia: an effective and durable treatment modality than can safely be performed in the endoscopy suite. *Gastrointest Endosc* 2016;83(5S):AB479-80.
130 Khashab MA, Messallam AA, Onimaru M, et al. International multicenter experience with peroral endoscopic myotomy for the treatment of spastic esophageal disorders refractory to medical therapy (with video). *Gastrointest Endosc* 2015;81:1170-7. doi:10.1016/j.gie.2014.10.011pmid:25634487.
131 Familiari P, Marchese M, Gigante G, et al. Peroral endoscopic myotomy for the treatment of achalasia in children. *J Pediatr Gastroenterol Nutr* 2013;57:794-7. doi:10.1097/MPG.0b013e3182a803f7pmid:23941997.
132 Li C, Tan Y, Wang X, Liu D. Peroral endoscopic myotomy for treatment of achalasia in children and adolescents. *J Pediatr Surg* 2015;50:201-5. doi:10.1016/j.jpedsurg.2014.10.017pmid:25598123.
133 Chen WF, Li QL, Zhou PH, et al. Long-term outcomes of peroral endoscopic myotomy for achalasia in pediatric patients: a prospective, single-center study. *Gastrointest Endosc* 2015;81:91-100. doi:10.1016/j.gie.2014.06.035pmid:25088923.
134 Caldaro T, Familiari P, Romeo EF, et al. Treatment of esophageal achalasia in children: Today and tomorrow. *J Pediatr Surg* 2015;50:726-30. doi:10.1016/j.jpedsurg.2015.02.047pmid:25783358.
135 Tang X, Gong W, Deng Z, et al. Usefulness of peroral endoscopic myotomy for treating achalasia in children: experience from a single center. *Pediatr Surg Int* 2015;31:633-8. doi:10.1007/s00383-015-3717-9pmid:25957132.
136 Nabi Z, Ramchandani M, Reddy DN, et al. Per-oral endoscopic myotomy in children with achalasia cardia. *J Neurogastroenterol Motil* 2016. doi:10.5056/jnm15172pmid:27048658.
137 Petrosyan M, Khalafallah AM, Guzzetta PC, Sandler AD, Darbari A, Kane TD. Surgical management of esophageal achalasia: Evolution of an institutional approach to minimally invasive repair. *J Pediatr Surg* 2016;S0022-3468(16)30096-3.pmid:27292598.
138 Hu JW, Li QL, Zhou PH, et al. Peroral endoscopic myotomy for advanced achalasia with sigmoid-shaped esophagus: long-term outcomes from a prospective, single-center study. *Surg Endosc* 2015;29:2841-50. doi:10.1007/s00464-014-4013-9pmid:25492452.
139 Sharata A, Kurian AA, Dunst CM, Bhayani NH, Reavis KM, Swanström LL. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. *J Gastrointest Surg* 2013;17:1188-92. doi:10.1007/s11605-013-2193-6pmid: 23609138.
140 Vigneswaran Y, Yetasook AK, Zhao JC, Denham W, Linn JG, Ujiki MB. Peroral endoscopic myotomy (POEM): feasible as reoperation following Heller myotomy. *J Gastrointest Surg* 2014;18:1071-6. doi:10.1007/s11605-014-2496-2pmid:24658904.
141 Onimaru M, Inoue H, Ikeda H, et al. Peroral endoscopic myotomy is a viable option for failed surgical esophagocardiomyotomy instead of redo surgical Heller myotomy: a single center prospective study. *J Am Coll Surg* 2013;217:598-605. doi:10.1016/j.jamcollsurg.2013.05.025pmid:23891071.
142 Zhou PH, Li QL, Yao LQ, et al. Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center study. *Endoscopy* 2013;45:161-6. doi:10.1055/s-0032-1326203pmid:23389963.
143 Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010;71:446-54. doi:10.1016/j.gie.2009.10.027pmid:20189503.
144 Ren Z, Zhong Y, Zhou P, et al. Perioperative management and treatment for complications during and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA) (data from 119 cases). *Surg Endosc* 2012;26:3267-72. doi:10.1007/s00464-012-2336-ypmid:22609984.
145 Orenstein SB, Raigani S, Wu YV, et al. Peroral endoscopic myotomy (POEM) leads to similar results in patients with and without prior endoscopic or surgical therapy. *Surg Endosc* 2015;29:1064-70. doi:10.1007/s00464-014-3782-5pmid:25249143.
146 Li QL, Zhou PH, Yao LQ, et al. Early diagnosis and management of delayed bleeding in the submucosal tunnel after peroral endoscopic myotomy for achalasia (with video). *Gastrointest Endosc* 2013;78:370-4. doi:10.1016/j.gie.2013.04.172pmid:23680177.
147 Li QL, Chen WF, Zhou PH, et al. Peroral endoscopic myotomy for the treatment of achalasia: a clinical comparative study of endoscopic full-thickness and circular muscle myotomy. *J Am Coll Surg* 2013;217:442-51. doi:10.1016/j.jamcollsurg.2013.04.033pmid: 23891074.
148 Saleem AM, Hennessey H, von Renteln D, Vassiliou MC. Atrial fibrillation as an unexpected complication after peroral endoscopic myotomy (POEM): a case report. *Surg Laparosc Endosc Percutan Tech* 2014;24:e196-9. doi:10.1097/SLE.0000000000000094pmid: 25222714.
149 Ujiki MB, Yetasook AK, Zapf M, Linn JG, Carbray JM, Denham W. Peroral endoscopic myotomy: A short-term comparison with the standard laparoscopic approach. *Surgery* 2013;154:893-7, discussion 897-900. doi:10.1016/j.surg.2013.04.042pmid:24074429.
150 Pannu D, Yang D, Abbitt PL, Draganov PV. Prospective evaluation of CT esophagram findings after peroral endoscopic myotomy. *Gastrointest Endosc* 2016;84:408-15. doi:10.1016/j.gie.2016.02.022pmid:26907745.
151 Familiari P, Greco S, Gigante G, et al. Gastroesophageal reflux disease after peroral endoscopic myotomy: Analysis of clinical, procedural and functional factors, associated with gastroesophageal reflux disease and esophagitis. *Dig Endosc* 2016;28:33-41. doi: 10.1111/den.12511pmid:26173511.
152 Csendes A, Braghetto I, Burdiles P, Korn O, Csendes P, Henríquez A. Very late results of esophagomyotomy for patients with achalasia: clinical, endoscopic, histologic, manometric, and acid reflux studies in 67 patients for a mean follow-up of 190 months. *Ann Surg* 2006;243:196-203. doi:10.1097/01.sla.0000197469.12632.e0pmid:16432352.
153 Kumagai K, Kjellin A, Tsai JA, et al. Toupet versus Dor as a procedure to prevent reflux after cardiomyotomy for achalasia: results of a randomised clinical trial. *Int J Surg* 2014;12:673-80. doi:10.1016/j.ijsu.2014.05.077pmid:24892729.
154 Khajanchee YS, Kanneganti S, Leatherwood AE, Hansen PD, Swanström LL. Laparoscopic Heller myotomy with Toupet fundoplication: outcomes predictors in 121 consecutive patients. *Arch Surg* 2005;140:827-33, discussion 833-4. doi:10.1001/archsurg.140.9.827pmid:16172290.
155 Rawlings A, Soper NJ, Oelschlager B, et al. Laparoscopic Dor versus Toupet fundoplication following Heller myotomy for achalasia: results of a multicenter, prospective, randomized-controlled trial. *Surg Endosc* 2012;26:18-26. doi:10.1007/s00464-011-1822-ypmid:21789646.
156 Simić AP, Radovanović NS, Skrobić OM, Raznatović ZJ, Pesko PM. Significance of limited hiatal dissection in surgery for achalasia. *J Gastrointest Surg* 2010;14:587-93. doi:10.1007/s11605-009-1135-9pmid:20033338.
157 Zurita Macías Valadez LC, Pescarus R, Hsieh T, et al. Laparoscopic limited Heller myotomy without anti-reflux procedure does not induce significant long-term gastroesophageal reflux. *Surg Endosc* 2015;29:1462-8. doi:10.1007/s00464-014-3824-zpmid:25159656.
158 Bhayani NH, Kurian AA, Dunst CM, Sharata AM, Rieder E, Swanstrom LL. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. *Ann Surg* 2014;259:1098-103. doi:10.1097/SLA.0000000000000268pmid:24169175.
159 Stefanidis D, Richardson W, Farrell TM, Kohn GP, Augenstein V, Fanelli RD. Society of American Gastrointestinal and Endoscopic Surgeons. SAGES guidelines for the surgical treatment of esophageal achalasia. *Surg Endosc* 2012;26:296-311. doi:10.1007/s00464-011-2017-2pmid:22044977.

Tables

Table 1| Radiologic grading (staging) system of achalasia37

Achalasia stage	Maximum esophageal diameter
Stage I	≤3 cm
Stage II	3 cm to <6 cm
Stage III	6-8 cm
Stage IV	>8 cm or severe sigmoidization*

*Defined as portion of esophagus being horizontal or "ascending" (as assessed on barium esophagraphy or computed tomography; on computed tomography, this is evident by at least one transverse section showing an elongated horizontal esophageal lumen or two esophageal lumens)

Table 2| **Larger case series (>30 patients) of pneumatic dilation in achalasia**

Study	No of patients	Study design	Follow-up	Results
Abid (1994)[60]	36	Telephone interview: 25 point symptom score; 3.5 or 4.0 cm Rigiflex balloon	27 months (mean)	88% response rate at 27 months; 14% required repeat dilation; 7% perforation rate
Wehrmann (1995)[61]	40	Stark symptom score: 14 point scale; ≥3 decrement for response; 3.0 cm or 3.5 cm balloons initially	4-6 weeks	88% response rate; 5% had clinically relevant GERD; 2% perforation rate
Guardino (2004)[62]	108	Success defined as symptom score for dysphagia and regurgitation ≤3 on 5 point scale; graded increase in balloon size (3.0, 3.5, 40 cm) depending on response	7 months (mean)	86% response rate in untreated achalasia patients; response rate only 50% in 12 post-Heller myotomy patients; 2% perforation rate; high baseline LES pressure and older age associated with success
Dobrucali (2004)[63]	43	3.0 cm balloon initially; 3.5 cm if no response	5 years	"Remission" rates at 1 and 5 years 79% and 54%, respectively; 78% success with 35 mm balloon and 54% success with 30 mm balloon; 1 perforation (2%)
Chan (2004)[64]	66	Operator choice of initial balloon (3.0, 3.5, 4.0 cm); size increased if no response	19 years	86% symptom relief at 12 weeks; 74% at 5 years; 62% at 10 years; 5% perforation rate

GERD=gastroesophageal reflux disease; LES=lower esophageal sphincter.

Table 3| **Randomized studies comparing or combining pneumatic dilation and endoscopic botulinum toxin injection for achalasia**

Study	No of patients	Study design	Findings
Vaezi (1999)[74]	48	Newly diagnosed achalasia; EBTI or 30 mm balloon PD; 5 mm balloon or repeat EBTI if no response at 1 month; 1 month and 1 year follow-up	Similar remission rate (70%) at 1 month for both groups but significantly better rate for PD than EBTI at 1 year (70% *v* 32%); 1 perforation (4%); PD significantly better in terms of barium study esophageal emptying
Goshal (2001)[75]	17	Patients with achalasia and no previous treatment; mean follow-up 35 weeks	Patients had similar 1 week response rates (>80%) and similarly reduced response at follow-up
Bansal (2003)[76]	31	Patients with achalasia and no previous treatment; 80 U EBTI *v* Witzel 4 cm balloon; initial and 1 year follow-up	At a mean follow-up of about 1 year, 38% of EBTI group and 89% of Witzel balloon group were in remission; no perforations
Mikaeli (2006)[77]	54	Patients with newly diagnosed achalasia and no previous treatment; EBTI 1 month before PD *v* PD only	At 1 year, EBTI+PD 77% remission *v* 62% PD alone (not statistically significant)
Bakhshipour (2010)[78]	34	Achalasia patients who had not responded to EBTI or PD (30 or 35 mm balloon); patients given PD+EBTI or PD alone	No significant difference in symptoms at 1, 6, or 12 months; at 1 year, remission rate 88% for combined treatment *v* 56% for PD alone

EBTI=endoscopic botulinum toxin injection; PD=pneumatic dilation.

Table 4| **Randomized controlled trials comparing pneumatic dilation with surgical myotomy in the treatment of achalasia**

Study	No of patients	Inclusion criteria	Study design	Conclusion
Kostic (2007)[82]	51	New diagnosis of achalasia and no previous treatment	PD *v* LHM with Toupet fundoplication	At 1 year, 6 treatment failures in PD group *v* 1 in LHM group; P=0.4
Novais (2010)[16]	94	New diagnosis of achalasia	PD *v* LHM	At 3 months, no difference in manometry between groups; clinical response 73% in PD group *v* 88% in LHM group (P=0.08); GERD by pH monitor 31% in PD group *v* 5% in LHM group
Moonen (2016)[84]	201	New diagnosis of achalasia	PD *v* LHM with Dor fundoplication	Clinical response at 5 years was 91% for PD and 82% for LHM; esophageal emptying, LES pressure, and QoL scores comparable in both groups; 5% perforation in PD group, 11% mucosal tear in LHM group
Persson (2015)[83]	53	New diagnosis of achalasia	PD *v* LHM with posterior fundoplication	At 3 years: failure was 4% in LHM group *v* 32% in PD group; at 5 years: failure was 8% in LHM group *v* 36% in PD group

LHM=laparoscopic Heller myotomy; PD=pneumatic dilation; QoL=quality of life.

Table 5| **Meta-analysis and Cochrane review of achalasia therapy (since 2009 and excluding POEM)**

Study	Size	Comparison	Results
Wang (2009)[88]	17 studies; 761 patients	BTI *v* PD *v* HM	PD had a better remission rate than BTI (RR 2.2); surgical myotomy had a better remission rate than PD (1.9); no difference in complication rate
Weber (2012)[87]	36 studies; 3211 patients	PD *v* HM	5 and 10 year remission rates: 62% and 48% for PD and 76% and 80% for HM; perforation rate was twice as high for HM as for PD (4.8% *v* 2.4%)
Yaghoobi (2013)[66]	3 studies; 346 patients	PD *v* LHM	At 1 year, the cumulative response rate was significantly higher with LHM (86% *v* 76%; odds ratio 1.98, 95 CI 1.14 to 3.45); PD perforation rate was 4.8%, significantly higher than the mucosal perforation (0.6%) rate for LHM; rate of GERD was similar in both groups
Schoenberg (2013)[89]	16 studies; 590 patients	PD *v* LHM	LHM showed better remission rates at all compared intervals; odds ratio was 2.20 at 12 months (95% CI 1.18 to 4.09; P=0.01), 5.06 at 24 months (2.61 to 9.80; P<0.001), and 29.83 at 60 months (3.96 to 224.68; P=0.001); repeat dilation (up to 3) increased effect by 12%; similar complication rates in both groups.
Leyden (2014)[69 79]	7 studies; 178 patients (3 studies had 6 month data; 4 studies had 1 year data)	PD *v* BTI	Similar remissions rates at 4 weeks; at 6 months, remission rates for PD and BTI were 81% and 52%, respectively (RR 1.57, 1.19 to 2.08); at 12 months, remission rates for PD and BTI were 73% and 38%, respectively (1.88, 1.35 to 2.61); PD perforation rate was 4%

BTI=botulinum toxin injection; GERD=gastroesophageal reflux disease; HM=Heller myotomy; LHM=laparoscopic Heller myotomy; PD= pneumatic dilation; POEM=peroral endoscopic myotomy; RR=relative risk.

Table 6| **Eckardt score**

	Symptoms			
Score	**Weight loss (kg)**	**Dysphagia**	**Chest pain**	**Regurgitation**
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5-10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

Table 7| **POEM efficacy data**

Location	Year	No of patients	Mean age (years)	Mean follow-up (months)	Eckardt score*	LES pressure* (mm Hg)	Post-POEM timed barium esophagram	Efficacy (%)
Europe MCT[117]	2013	70	45	12	6.9/1	27.6/8.9	–	82.4
Chicago, USA[123]	2014	41	45	12	7/1	22/9	Mean height in 16 patients: 1 min, 6 (SD 4) cm; 2 min, 6 (4) cm; 5 min, 5 (3) cm (P<0.001)	93
Portland, USA[122]	2015	100	58 (18-83)	21.5	6/1	44.3/19.6	55/100 patients had esophagram; median barium column emptying at 1 min: 51/55 patients, 100% emptying; 4/55 patients, 80% emptying	92
Mineola, USA[121]	2015	93	52 (18-93)	22	7.8/0.44	43/18	–	96
Rome, Italy[124]	2016	100	48 (6-77)	11	8.1/1.1	41.4/19	–	94.5

LES=lower esophageal sphincter; MCT=multicenter study; POEM=peroral endoscopic myotomy.

*Values are before and after POEM

Table 8| Subjective and objective data on GERD after POEM. Values are numbers (percentages)

Study location	GERD symptoms	Erosive esophagitis	Positive pH study
Portland, USA[122]	12/100 (15)	20/73 (27)	26/68 (38)
Chicago, USA[123]	15/41(15)	13/22(59)	4/13 (31)
Rome, Italy[151]	19/103 (18)	21/103 (20)	30/103 (29)
Mineola,USA[115]	40/174 (23)	29/86 (34)	29/84 (36)

GERD=gastroesophageal reflux disease; POEM=peroral endoscopic myotomy.

Figures

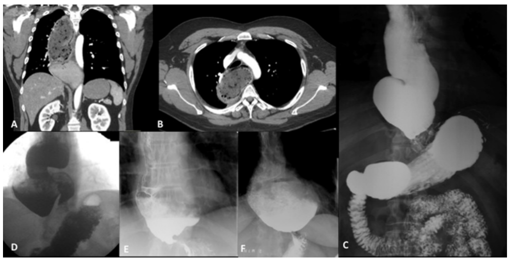

Fig 1 Imaging from patients with end stage achalasia. A: Coronal computed tomogram of 39 year old man with advanced achalasia, showing esophagus with mild sigmoidization and marked dilation (megaesophagus) filled with retained food. B: Axial computed tomogram of 39 year old man who underwent pneumatic dilation six years earlier but is now presenting with dysphagia, showing megaesophagus filled with retained food. C: Esophagram of 64 year old man who received botulinum toxin injections two years earlier but is now presenting with dysphagia and regurgitation, showing severe sigmoidization. D: Esophagram of 48 year old man who underwent Heller myotomy five years earlier but is now presenting with recurrent dysphagia and regurgitation, showing severe sigmoidization. E: Esophagram of 54 year old man who underwent pneumatic dilation eight years earlier, showing megaesophagus. F: Esophagram of 63 year old woman who underwent open Heller myotomy, pneumatic dilation, and botulinum toxin injections 30 years earlier, showing end stage achalasia

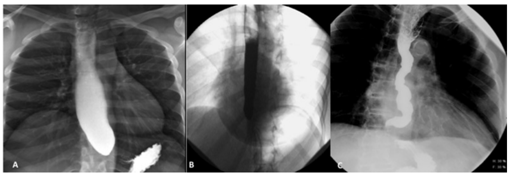

Fig 2 Esophagrams illustrating type I achalasia (A), type II achalasia (B), and type III achalasia (C)

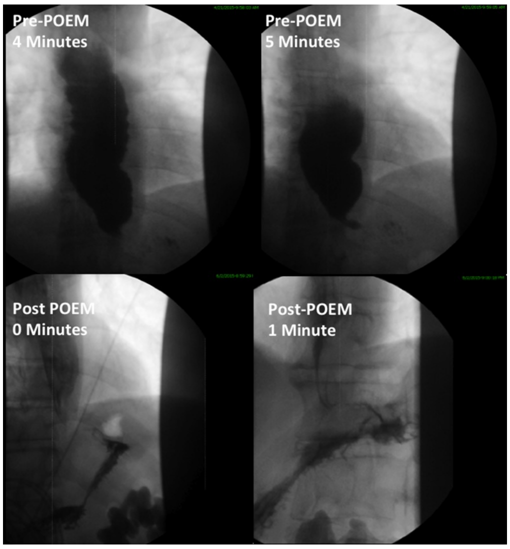

Fig 3 Timed barium esophagram in a 46 year old man with type 2 stage 2 achalasia. Images taken at four and five minutes before peroral endoscopic myotomy (POEM) show retention of most of the barium ingested. Post-POEM images show rapid emptying of the esophagus, with no notable amount of barium retained even at zero and one minute after ingestion

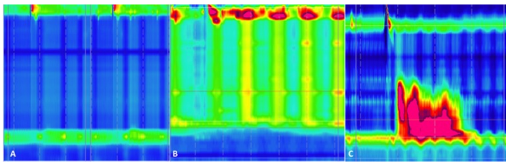

Fig 4 High resolution esophageal manometry of three different subtypes of achalasia. A: Achalasia type I showing impaired relaxation of lower esophageal sphincter and no esophagal pressurization during swallows. B: Achalasia type II showing esophageal pressurization during swallows. C: Achalasia type III showing simultaneous high amplitude repetitive contraction

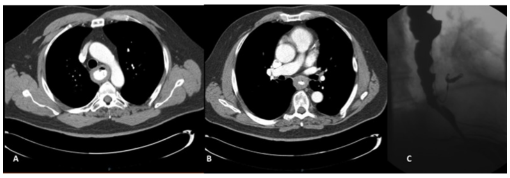

Fig 5 Computed tomography in spastic achalasia (A, B) showing markedly thickened esophageal wall and sphincter in patient with longstanding type III achalasia. C: Typical barium esophagram in patient with type III spastic achalasia showing narrow distal esophagus with scalloped appearance transitioning to smoother dilated esophagus in proximal third of esophagus

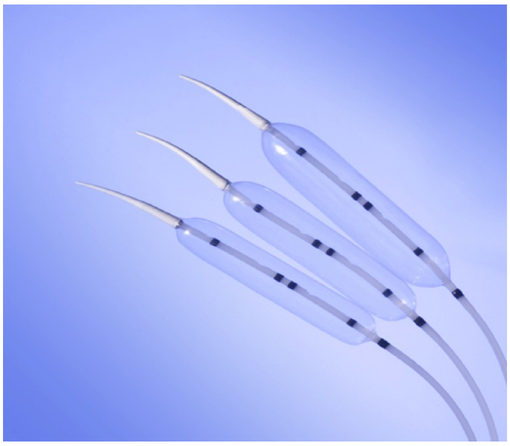

Fig 6 Rigiflex pneumatic dilation balloons; courtesy of Boston Scientific Marlborough, Massachusetts, USA

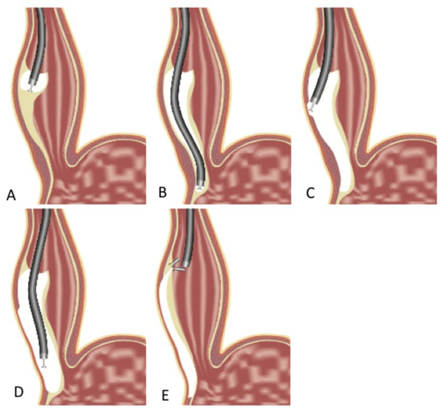

Fig 7 Peroral endoscopic myotomy (POEM) technique. A: After submucosal (SM) saline injection, mucosotomy is performed and dissection of SM tunnel is initiated. B: Dissection of SM tunnel is extended to gastric cardia. C: Myotomy initiation and dissection of circular layer. D: Extension of myotomy to muscle of the cardia with approximately 2 cm long cardiomyotomy. E: Closure of mucosotomy (entrance to SM tunnel) using endoscopic clips. Reproduced with permission from Winthrop University Hospital

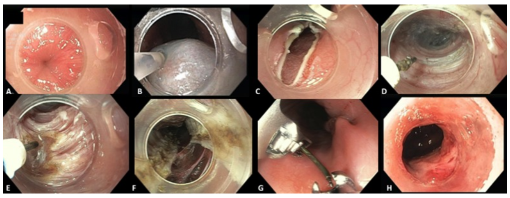

Fig 8 Peroral endoscopic myotomy (POEM). A: Very tight lower esophageal sphincter (LES) at esophagogastric junction (EGJ). B: Submucosal bleb created by injection of saline into submucosa with needle injector. C: Mucosal incision allowing entry into submucosal space. D: Dissection of submucosal tunnel with electrosurgical knife protruding from endoscope; circular fibers of muscularis propria can be seen at 6 o’clock; submucosal fibers being dissected are stained blue by methylene blue stained saline that is being used for submucosal injection; roof of tunnel which is composed of esophageal mucosa can be seen at 12 o’clock (underside of mucosa with some adherent submucosal fibers is seen from within submucosal tunnel). E: Initiation of myotomy (dissection of muscle fibers with elecrosurgical knife is shown). F: Completion of myotomy; cauterized edges of esophageal muscle are seen on right and left; roof of tunnel (mucosa) is seen at 12 o’clock; at base of myotomy, exposed mediastinal pleura is seen with vessels traversing muscle defect. G: Mucosal incision forming entrance to submucosal tunnel has been closed with endoscopic suturing device shown; closure can be seen as converging apposed folds of tissue at 2 o’clock. H: Endoscopic examination of EGJ shows greatly improved orifice with patulous LES and gastric lumen seen beyond (greatly improved compared with tight EGJ with lumen effacement seen in A)