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Treatment of achalasia in the era of high-resolution manometry

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Abstract

Esophageal achalasia is a primary motility disorder characterized by impaired lower esophageal sphincter relaxation and absence of esophageal peristalsis leading to impaired bolus transit, manifested with symptoms such as dysphagia, regurgitation, retrosternal pain, and weight loss. The standard diagnostic tool is esophageal manometry which demonstrates incomplete relaxation of the lower esophageal sphincter and impaired esophageal peristalsis. Recently, a new advanced technique, high-resolution manometry (HRM) with the addition of pressure topography plotting, using multiple sensors to capture the manometric data as a spatial continuum, allows a detailed pressure recording of the esophageal motility. This technique, currently the gold standard for the diagnosis of achalasia, has led to a subclassification of three manometric types that seem to have different responsiveness to treatment. Because its pathogenesis is as yet unknown, achalasia treatment options are not curative. Type II achalasia patients respond better to treatment compared to those with types I and III. Low-risk patients with type I or II achalasia have good outcome with both graded pneumatic dilatations and laparoscopic Heller myotomy, while type III achalasia patients respond better to laparoscopic Heller myotomy. Although, type III achalasia patients responds less in comparison to types I and II to laparoscopic Heller myotomy. Peroral endoscopic myotomy is a promising new technique but long-term follow-up studies for its safety and efficacy must be performed. This article reviews the current therapeutic options, highlighting the impact of HRM to predict the outcome and the new insights for the treatment of achalasia.

Keywords Achalasia, high-resolution manometry, botox, pneumatic dilatation, laparoscopic Heller myotomy, peroral endoscopic myotomy

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Introduction

Achalasia is a rare primary esophageal motor disorder characterized by the absence of peristalsis and a defective relaxation of the lower esophageal sphincter (LES) resulting in impaired bolus transport and food stasis in the esophagus [1]. Achalasia occurs equally in men and women with an incidence of 1 in 100,000 individuals and a prevalence of 10 in 100,000. The peak incidence occurs between 30 and 60 years of age [2,3]. The most frequent symptoms of achalasia are dysphagia for both solids and liquids, regurgitation of saliva and undigested food, respiratory complications (nocturnal cough and aspiration), chest pain, heartburn, and weight loss [4]. Heartburn can mimic gastroesophageal reflux disease (GERD). Dysphagia and regurgitation usually respond to treatment, but chest pain is much more difficult to treat [5]. The Eckardt symptom score is the grading system most frequently used for the evaluation of symptoms, stages and efficacy of achalasia treatment. A symptom score of 0-1 corresponds to clinical stage 0, a score of 2-3 to stage I, a score of 4-6 to stage II, and a score >6 to stage III. Stages 0 and I indicate remission of the disease. On the other hand, stages II and III represent failure of treatment (Table 1) [6,7]. The pathogenesis of achalasia is not well understood but it is believed to be due to an inflammatory neurodegenerative process with possible viral involvement. Measles and herpes viruses have been suggested as causal candidates. However, molecular techniques have failed to confirm these claims and the causative agent remains undiscovered [8]. It has been hypothesized that an autoimmune process triggered by a still unidentified cause results, in a genetically predisposed subject, in chronic inflammatory process leading to neuronal damage [9]. This chronic inflammation within the esophagus leads to the loss of postganglionic inhibitory neurons in the myenteric plexus and a consequent reduction in the inhibitory transmitters, nitric oxide and vasoactive intestinal peptide. The excitatory neurons remain unaffected; this causes an imbalance between excitatory and inhibitory neurons

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Table 1 Eckardt score: clinical scoring for achalasia

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

that prevents LES relaxation [10,11]. The first diagnostic step is to exclude a benign or malignant obstruction using endoscopy or radiology. In early stages, both tests may be completely normal. In advanced cases, the esophagus will be dilated with retained food and saliva; endoscopically, the esophagogastric junction will have a rosette appearance sometimes with increased resistance to scope passage into the stomach. Barium studies show a "bird beak" appearance from the non-relaxing LES, varying degrees of esophageal dilation up to sigmoid esophagus, aperistalsis and sometimes an air-fluid level and absence of the gastric air bubble. To assess esophageal emptying, a timed barium swallow can be done, in which the height of the barium column at 5 min after ingesting 8 oz (236 mL) of barium is a good measure of esophageal emptying [5]. Manometry is still the gold standard diagnostic test for achalasia [12]. On conventional manometry, the main features of achalasia are: absence of peristalsis, sometimes with increased intraesophageal pressure, and incomplete relaxation of the LES on deglutition (residual pressure >10 mmHg) [13]. An increase in the resting tone of the LES is often observed [4]. However, the accuracy of these traditional studies has been challenged by the recent emergence of advanced techniques for the diagnosis of esophageal achalasia such as high-resolution manometry (HRM) and the addition of pressure topography plotting [12]. The use of multiple high-sensitivity sensors to capture manometric data as a spatial continuum allows a detailed pressure recording from the pharynx to the stomach and is regarded as the gold standard for diagnosis of achalasia [4,14]. Diagnostic algorithms for defining conventional manometric diagnoses of achalasia are improved with HRM, primarily due to the objectivity and accuracy with which it identifies impaired esophagogastric junction relaxation and the metric of peristaltic contraction [14]. The use of HRM has led to the subclassification of achalasia (Chicago classification) into three clinically relevant groups based on the contractility pattern in the esophageal body (Table 2, Fig. 1):

Type I (classic achalasia) no significant pressurization within the esophageal body and impaired LES relaxation

Type II (achalasia with compression or compartmentalization in the distal esophagus >30 mm Hg) rapid panesophageal pressurization with water swallows

Type III (spastic achalasia) rapidly propagated pressurization attributable to an abnormal lumen obliterating contraction

Additionally, HRM introduced a new parameter for quantification of the LES relaxation: integrated relaxation pressure, which calculates the mean post-swallow LES pressure of a 4 sec period during which the LES pressure was the lowest, skipping periods of crural contractions if necessary. The upper normal limit for the integrated relaxation pressure is 10 mmHg for type I achalasia, 15 mmHg for type II and 17 mmHg for type III achalasia, which differentiates best the impaired relaxation in achalasia from non-achalasia individuals and from patients with diffuse esophageal spasm [15].

Table 2 Manometric subtypes of achalasia according to Chicago classification

Type I	Absence of peristalsis, no pressurization within the esophageal body, high integrated relaxation pressure
Type II	Absence of peristalsis, and contractile activity, panesophageal pressurization >30 mmHg, and high integrated relaxation pressure
Type III	Absence of peristalsis, and two or more spastic contractions with or without periods of compartmentalized pressurization and a high integrated relaxation pressure

Treatment of achalasia

Because of the unknown pathogenesis of achalasia, a healing treatment is not available nowadays. Palliative treatment options are aimed to reduce the gradient across the LES, relieving the primary symptoms of dysphagia and regurgitation, improving esophageal emptying, and preventing the development of megaesophagus [16]. Treatment modalities include: pharmacological therapy, endoscopic injection of botulinum toxin (Botox), pneumatic dilatation (PD), laparoscopic Heller myotomy (LHM), and peroral endoscopic esophageal myotomy (POEM) [3,4]. No intervention significantly affects esophageal peristalsis and despite therapeutic interventions LES hypertonicity returns overtime, requiring repeated procedures [2].

Pharmacological therapy

Pharmacological management usually has a minor role in the treatment of esophageal achalasia because is the least effective option [17]. The two most commonly used pharmacological agents are nitrates and calcium channel blockers. Nitrates inhibit normal LES contraction by increasing nitric oxide concentration in smooth muscle cells, which, in turn, increases cyclic adenosine monophosphate levels promoting muscle relaxation. Wen *et al* in a recent review identified only two randomized studies assessing the success of nitrates in the treatment of achalasia. They concluded that no solid recommendations could be given [18]. Calcium antagonists block calcium entry and hence esophageal muscle contraction. Nifedipine, in sublingual doses of 10-20 mg, 15-30 min before meals is the most used oral drug for achalasia. It inhibits LES contraction

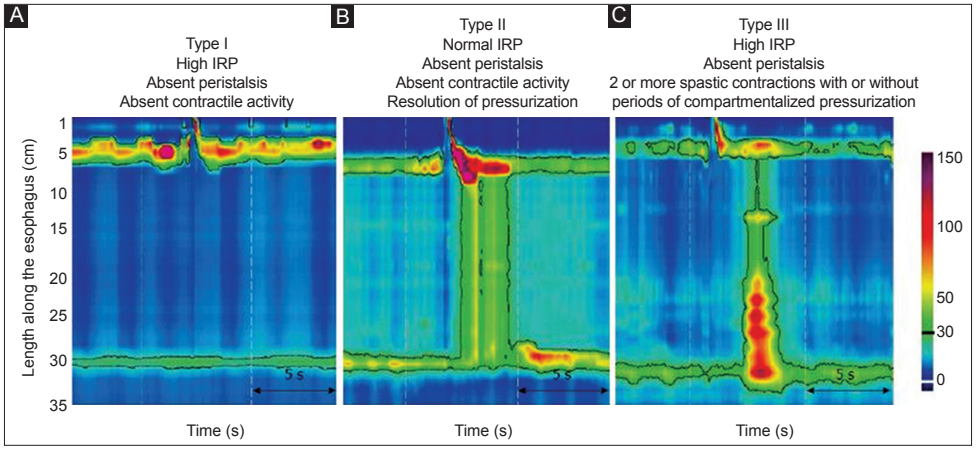

Figure 1 Achalasia subtypes according to Chicago classification. (A) Type I (classic achalasia) refers to patients with absence of peristalsis, no pressurization within the esophageal body, high integrated relaxation pressure (IRP). (B) Type II (achalasia with compression) refers to patients with absence of peristalsis, and contractile activity, panesophageal pressurization >30 mmHg, and high IRP. (C) Type III patient (spastic achalasia), refers to patients with absence of peristalsis, and two or more spastic contractions with or without periods of compartmentalized pressurization and a high IRP

and decreases his resting pressure up to 60% [17]. The clinical response is of short duration because drug tolerance develops rapidly; symptoms improvement is incomplete and side effects such as headache, hypotension and leg edema are common limiting factors in their use. Thus, these drugs are commonly reserved for patients who cannot or refuse to undergo other more invasive therapies and for those in whom Botox has failed [2].

Endoscopic injection of Botox

Botox is a biological neurotoxin derived from *Clostridium botulinum* that causes paralysis of both voluntary and involuntary muscles by blocking the release of acetylcholine from the nerve terminal endings. Its action persists for 3 to 4 months on average [19]. There are five commercial formulations of Botox with varying potencies. The majority of the studies report the use of Botox (Allergan Inc., Irvine, California, USA) and studies comparing Botox and Dysport (Ipsen Pharma, Boulogne-Billancourt, France) described similar clinical outcomes as far as the dose is adjusted according to the variable potency of the different formulations [20]. Botox A is injected at a dose of 80-100 U in four quadrants just above the Z line into the LES through a sclerotherapy needle during an upper gastrointestinal endoscopy. Botox injection is safe with only minor complications such as transient pain (25% of the patients) and reflux symptoms (less than 5%). Serious side effects such as mediastinitis and allergic reactions related to egg protein are rare. Doses higher than 100 U have not been proven to be more effective [21,22]. More than 75% of cases have an initial clinical response but the success rate fades rapidly to less than 60% at one year. About 50% of patients relapse and require repeat treatments at 6-24 months after the first treatment [21-23]. Prolonged responses have been reported in older patients with a vigorous manometric pattern [22], however, this may be more akin to the type II pattern associated with panesophageal pressurization by HRM [24]. Five randomized trials comparing Botox injection to PD and one to LHM have shown that there is initially a comparable relief from dysphagia but a rapid deterioration in the group of the patients treated with Botox injection after 6-12 months [23,25-29]. Additionally, serial Botox injections are more expensive than PD [16]. There is some evidence that multiple Botox injections into the LES could affect the results of a subsequent surgical myotomy [25]. Considering these limitations, the use of Botox injections should be restricted to elderly patients and those with comorbidities who are not candidates for PD and LHM.

PD

PD of the LES is considered the most effective nonsurgical treatment for achalasia [30]. PD uses air pressure to dilate intraluminally and disrupt the circular muscle fibers of the LES. The most commonly used dilator is the Micro-invasive Rigiflex Balloon system (Boston Scientific Corp, Boston, Massachusetts, USA). These balloons are available in three diameters (30, 35 and 40 mm) mounted on a flexible catheter placed over an endoscopic guidewire. Under sedation and under fluoroscopic guidance the balloon is positioned across the LES and gradually inflated until the waist is planed, using 7-15 psi of air, held for 15-60 sec [16]. The actual protocol varies across centers [13]. The most used protocol is a graded dilatation starting with a 30 mm balloon and subsequent dilations spaced over variable time intervals (2-4 weeks) on the basis of clinical symptom relief (Eckardt symptom score) or repeat LES pressure measurements or esophageal emptying improvement [31-35]. After the procedure the patients should undergo a gastrografin radiograph followed by barium esophagogram to exclude esophageal perforation [36]. However,

it is our opinion that radiographic testing with gastrografin or barium should not be performed if the patient has pain and a perforation is suspected. In fact, in this case, gastrografin may increase the diameter of a small esophageal perforation and the resulting mediastinal contamination may make non-surgical management impossible. In such cases, a computed tomography to identify free air might represent a better choice. PD may be performed as an outpatient procedure. Patients without suspicion of esophageal perforation may undergo radiographic testing after an observation of 4-6 h and could be discharged if negative. Patients can return to normal activities the next day. However, patients should be instructed to pursue immediate care if they reveal severe chest pain with or without fever as delayed perforation has been reported possibly related to postprocedure vomiting [2]. Many studies suggest that by using graded dilator approach, good to excellent relief of symptoms is possible in 50-93% of the treated patients [2,37-39]. Richter *et al*, in a review of nearly 1200 patients from 24 studies with an average follow up of 37 months, reported that PD with Rigiflex balloon resulted in good to excellent relief of the symptoms in 74%, 86% and 90% of patients treated with 30, 35 and 40 mm balloon, respectively. One third of the patients will have a relapse of their symptoms over a 5-year period, however a long-term remission can be achieved in most of the patients by "on demand" repeat PD based on symptom recurrence [40,41]. Predictors of the best clinical outcomes after PD include: age older than 40 years, women, LES pressure after dilatation <10 mmHg and type II pattern by HRM [5,6,12,31,34,42,43]. Thirty three percent of patients experience procedure-related complications, but most of them are minor such as chest pain, bleeding, aspiration pneumonia, fever, esophageal hematoma, and mucosal tear without perforation [44]. The most serious complication associated with PD is esophageal perforation with an overall median rate in experienced hands of 1.9% (range 0-16) [31,34]. Conservative therapy with antibiotic and parenteral nutrition may be effective in small perforations and painful deep tears, but surgical repair through thoracotomy is the best approach for large perforations with extensive mediastinal contamination [45]. Most of the perforations occur during the first dilatation. The difficulty of keeping the balloon in an appropriate position seems to be a potential risk factor [46]. Boeckxstaens *et al* in their achalasia trial reported more perforations, primarily in older patients, when the first PD was performed with a 35 mm versus a 30 mm balloon [6]. GERD may occur after PD in a range of 15-35% of the patients and PPI therapy can improve their reflux-related symptoms [40]. PD is the most cost-effective treatment for achalasia over a 5-10-year follow-up period [47,48].

LHM

The surgical procedure most widely used to treat achalasia is Heller myotomy, first described in 1913 by Ernst Heller and used ever since with a few technical modifications [49]. The two changes that modified the initial Heller procedure are cutting of the anterior side of the cardia muscle fibers only and the association of a fundoplication to reduce the development of GERD [50,51], the most frequent complication after myotomy without fundoplication. The technique evolved initially with a laparotomy approach followed by a successful thoracoscopic approach. However, in 1991 Shimi *et al* described a minimally invasive technique for LHM that has become the preferred method because of lower morbidity and faster recovery [52,53]. A recent meta-analysis by Campos *et al* demonstrated that a LHM (3086 patients) improved the symptoms significantly more than the thoracoscopic approach (211 patients) (89.3% vs. 77.6, P=0.048) and reduced the incidence of postoperative GERD (14.9% vs. 28.3%, P=0.03). Campos *et al* also showed that the addition of an antireflux procedure such as fundoplication on LHM, reduced significantly further the gastroesophageal reflux symptoms (31.5% vs. 8.8%) with a similar therapeutic success [38]. Richards *et al* demonstrated the benefit of adding a fundoplication on LHM in a double-blind randomized trial comparing myotomy with or without fundoplication [54]. There is less certainty on the type of fundoplication applied to obtain a better outcome. Postoperative dysphagia is significantly higher after a Nissen fundoplication than after partial anterior approach [55]. A recent multicenter randomized controlled trial comparing anterior Dor and posterior Toupet approach suggested that both provide similar control of reflux after LHM [56,57]. Overall, LHM with partial fundoplication is a very safe operation with a mortality rate of 0.1% [4]. Clinical success rates are very high, with a mean success rate of 89% (range 76-100%) at a follow up of 35 months [38]. However, the success rates after 5 years drop to 65-85%, probably as a result of disease progression [58,59]. Younger men (<40 years), a LES pressure greater than 30 mmHg and a straight esophagus (without distal tortuosities) are positive prognostic factors for a successful LHM [60,61]. As for PD, the manometric subtype also affects the success rates of LHM. Patients with type II HRM achalasia pattern have the best outcome [62]. There is no difference in clinical success rates between PD and LHM for patients with types I and type II achalasia, but the type III pattern responds better to surgery than to PD, probably because of the more extensive proximal disruption of the esophageal muscle [42,62]. It is important to be very cautious in patients treated previously with intrasphincteric injection of Botox, as fibrosis can be present at the level of gastroesophageal juction. In these cases, myotomy has an increased risk of mucosal perforation. Portale *et al* reported that patients who previously underwent Botox injection and PD had less successful outcome in LHM than the patients who had not had such treatments [54,63,64].

The most common complication of LHM is perforation of the esophageal or gastric mucosa (average 6.3%) during the myotomy, usually repaired without clinical consequences [65]. Recurrence of dysphagia usually develops after LHM within 12-18 months. Most often the cause is an incomplete myotomy on the gastric side where the dissection is more complicated, late scarring of the myotomy and an obstructive antireflux wrap [13, 66]. Recurrences after LHM can be treated with success with PD and in case of failure of this with a new LHM [66].

PD versus LHM

At present, PD and LHM are the most effective treatment options for achalasia. The decision of which approach to undertake is difficult because of the lack of a large randomized controlled trial. Campos *et al* in their review of case series reported an improvement rate of 68% in 1065 patients treated with PD versus an 89% improvement rate of LHM in 3086 patients [38]. In 2006, a cross-sectional study by Vela *et al* showed similar success rates for PD and LHM. 106 patients underwent PD and 73 patients were treated with LHM. Success rates, defined as regurgitation or dysphagia less than three times per week or no alternative treatments, were 96% for PD group vs. 98% for LHM group at 6 months of follow up. The success rates were decreased to 44% vs. 57% at 6 years [31]. In 2007 Kostic *et al* performed a randomized controlled trial that compared PD with Rigiflex balloon to LHM with Toupet fundoplication [67]. The results showed a superiority of the surgery procedure, but the limitations were that only 51 patients were studied with a limited follow up of only 1 year [67]. Finally, in 2011 Boeckstaens *et al* reported the results of the European Achalasia Trial, a prospective randomized clinical trial comparing PD and LHM with Dor fundoplication. 201 patients were randomized to receive either PD with Rigiflex balloon (30 and 35 mm with up to three repeat dilatations) or LHM. Therapeutic success was defined as a reduction in the Eckardt symptom score below 4. After two years of follow up, comparable therapeutic success rates of 86% and 90% were observed for PD and LHM respectively. Both barium emptying and LES pressure improved to similar extents in both groups. Redilatation was performed in 23 of 95 patients (25%). Based on these data, the authors concluded that LHM does not achieve superior rates of therapeutic success compared with PD as primary treatment for achalasia, at least after a mean follow up of 43 months, and, therefore, either one can be recommended as an initial therapy.

POEM

Although the current treatments for achalasia are effective, PD is associated with the necessity of retreatment (25%) and surgical myotomy still requires laparoscopy and dissection of the gastroesophageal junction. Thus, there has been interest in developing a new technique that incorporates an endoscopic approach with principles of natural orifice transluminal endoscopic surgery to perform a myotomy. This technique is termed POEM [68]. A 2 cm longitudinal mucosal incision is made on the mucosal surface to create a mucosal entry to the submucosal space. Then a submucosal tunnel is made to reach the LES and to dissect the circular muscle fibers over a 7 cm esophageal and 2 cm gastric length. Inoue *et al* studied 17 patients and reported a success rate of 100% and a significant reduction of LES pressure [2,6]. A series of other studies confirmed the high success rate (85-100%) even after several previous PD, even though the follow up was only 6 months [39,69-72]. Moreover, because no antireflux procedure is included in this technique, the risk to develop GERD is up to 46% [39]. Longer follow up and randomized prospective controlled trials with standard LHM and/or PD are needed before accepting POEM as a new treatment option for achalasia.

Other therapies

Self-expanding metallic stents

A few studies have reported the utility of self-expanding metallic stents for the treatment of achalasia. The stents gradually expand at body temperature over 24 h, resulting in more predictable tearing of the cardia muscle, less tissue scarring, and a lower rate of stenosis after the removal of the stent [73,74]. Recently, a prospective randomized study evaluating the long-term efficacy of a partially covered removable metallic stent versus PD was reported from a group in China. Li *et al* reported a clinical success rate of 83% for the 30 mm stent at 10 years, whereas the success rate for 20 mm stent and PD was 0%. However, the dilatation protocol was less aggressive than the standard technique used in Europe with a maximal diameter of 32 mm [74]. In another, single-center long-term prospective study, Zhao *et al* reported, using a 30 mm metallic stent, a clinical success rate of >80%. No perforation or mortality was reported, but stent migration occurred in 5% of patients, GERD in 20%, and chest pain in 38.7% [73]. Although these results appear promising, this technique needs to be evaluated more and tested in comparison with the therapeutic protocols of PD and LHM used in Europe and the US.

Endoscopic sclerotherapy

Recently, different studies of Spanish and Iranian investigators reported the use of ethanolamine oleate to treat achalasia [75,76]. Moreto *et al* performed injections ever 2-4 weeks until dysphagia resolved in 103 patients over the last 20 years. The primary outcome was dysphagia relief. Secondary outcomes were LES pressure, esophagogram, gastroesophageal reflux, and endoscopic ultrasonography. They reported a 90% of cumulative expectancy of being free of recurrence at 50 months [76]. There is skepticism about this procedure because the fibrotic stricture might make more traditional therapies difficult to perform [16].

Future therapies

All the present approaches for the treatment of achalasia are targeting the disruption of the esophagus rather than trying to correct the underlying abnormality and restore the motility function. In view of the fact that the enteric

neurons innervating the esophagus and the LES could disappear due to an autoimmune mechanism, theoretically immunosuppressive therapy could be considered to prevent disease progression [77]. However, at the time of diagnosis, the number of neurons is already decreased, leading to significant dysfunction and symptoms. Another experimental study in mice suggested that transplantation of neuronal stem cells might be a future therapeutic option [78]. The neurospheres, as they called the neural stem cells, can be isolated and cultured from mucosal biopsies as proven by Metzger *et al*. They generated neurosphere-like bodies capable of proliferating and generating multiple neuronal subtypes; when transplanted, they colonized cultured aganglionic human hindgut to generate ganglia-like structures and enteric neurons and glia [79]. Unfortunately, after *in vivo* transplantation into the mice pylorus these neurosphere-like bodies failed to adopt a neuronal phenotype. Similar findings were reported from other groups. Clearly, more research is required to develop optimized therapies and techniques of stem cell therapy to restore the functional anatomy of the LES.

Concluding remarks

The recent emergence of the HRM as a diagnostic tool has helped identify three subtypes of achalasia that show different responsiveness to endoscopic or surgical therapies. This subclassification has facilitated choosing the appropriate treatment for each different patient, thereby increasing overall treatment efficacy. In our opinion, high-risk older patients and those with severe comorbidities should undergo Botox, while all the other patients may be considered as low risk and offered surgical or endoscopic treatment (Fig. 2). The choice between PD or surgery may depend on local expertise.

The role of POEM as a valuable substitute of the traditional therapeutic options will be defined in the immediate future after randomized prospective comparison trials and long-term follow-up studies are published. Pharmacological therapy could be administered to patients waiting for an endoscopic or surgical treatment and to those with high surgical risk whenever the approach with Botox is not possible or has failed. While current treatment of achalasia still focuses on mechanical disruption of the LES, future therapies are anticipated aiming at restoring its function.

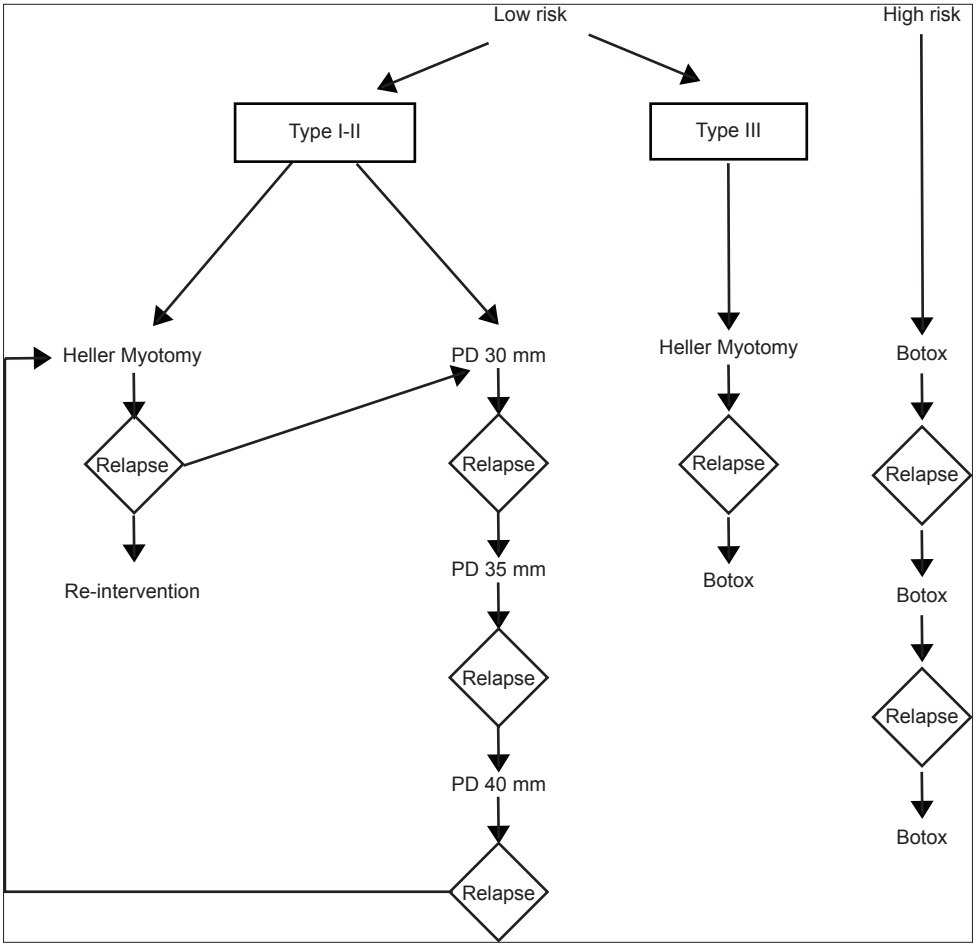

Figure 2 Therapeutic algorithm for achalasia patients

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