DISEASES OF THE ESOPHAGUS

Guideline

The 2018 ISDE achalasia guidelines

G. Zaninotto,[1] C. Bennett,[2] G. Boeckxstaens,[3] M. Costantini,[4] M. K. Ferguson,[5] J. E. Pandolfino,[6] M. G. Patti,[7] U. Ribeiro, Jr,[8] J. Richter,[9] L. Swanstrom,[10] J. Tack,[3] G. Triadafilopoulos,[11] S. R. Markar,[1] R. Salvador,[4] L. Faccio,[12] N. A. Andreollo,[13] I. Cecconello,[14] G. Costamagna,[15] J. R. M. da Rocha,[8] E. S. Hungness,[16] P. M. Fisichella,[17] K. H. Fuchs,[18] I. Gockel,[19] R. Gurski,[20] C. P. Gyawali,[21] F. A. M. Herbella,[22] R. H. Holloway,[23] M. Hongo,[24] B. A. Jobe,[25] P. J. Kahrilas,[6] D. A. Katzka,[26] K. S. Dua,[27] D. Liu,[28] A. Moonen,[3] A. Nasi,[14] P. J. Pasricha,[29] R. Penagini,[30] S. Perretta,[31] R. A. A. Sallum,[8] G. Sarnelli,[32] E. Savarino,[4] F. Schlottmann,[33] D. Sifrim,[34] N. Soper,[16] R. P. Tatum,[35] M. F. Vaezi,[36] M. van Herwaarden-Lindeboom,[37] T. Vanuytsel,[3] M. F. Vela,[35] D. I. Watson,[38] F. Zerbib,[39] S. Gittens,[40] C. Pontillo,[41] S. Vermigli,[41] D. Inama,[41] D.E. Low[42]

[1] *Department of Surgery and Cancer, Imperial College, London, UK,* [2] *Office of Research and Innovation, Royal College of Surgeons in Ireland, Ireland,* [3] *Department of Chronic Diseases, Metabolism and Ageing (Chrometa), Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Leuven, Belgium,* [4] *Department of Surgical, Oncological and Gastroenterologica Sciences, University of Padua, Padua, Italy,* [5] *Department of Surgery, University of Chicago, Chicago, Illinois, USA,* [6] *Department of Medicine, Northwestern University, Chicago, Illinois, USA,* [7] *Department of Medicine and Surgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA,* [8] *Department of Gastroenterology, Division of Surgery, University of Sao Paulo, Sao Paulo, Brazil,* [9] *Department of Medicine, Temple University, Philadelphia, Pennsylvania, USA,* [10] *Institute of Image-Guided Surgery, Strasbourg, France; Interventional Endoscopy and Foregut Surgery, Oregon Health Science University, Portland, Oregon, USA,* [11] *Division of Gastroenterology and Hepatology, Stanford Esophageal Multidisciplinary Program in Innovative Research Excellence (SEMPIRE), Stanford University, Stanford, California, USA,* [12] *Division of Surgery, Padova University Hospital, Padova, Italy,* [13] *Faculty of Medical Science, State University of Campinas, Campinas, São Paulo, Brazil,* [14] *Digestive Surgery Division, University of São Paulo School of Medicine, São Paulo, Brazil,* [15] *Digestive Endoscopy Unit, A. Gemelli Hospital, Catholic University, Rome, Italy,* [16] *Department of Surgery, Northwestern University, Chicago, Illinois, USA,* [17] *Department of Surgery, Brigham and Women's Hospital and Boston VA Healthcare System, Harvard Medical School, Boston, Massachusetts, USA,* [18] *Department of Surgery, AGAPLESION-Markus-Krankenhaus, Frankfurt, Germany,* [19] *Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig, Leipzig, Germany,* [20] *Department of Surgery, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil,* [21] *Division of Gastroenterology, Washington University School of Medicine, St Louis, Missouri, USA,* [22] *Department of Surgery, School of Medicine, Federal University of São Paulo, São Paulo, Brazil,* [23] *Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, The University of Adelaide, Adelaide, Australia,* [24] *Department of Medicine, Kurokawa Hospital, Taiwa, Kurokawa, Miyagi, Japan,* [25] *Esophageal and Lung Institute, Allegheny Health Network Cancer Institute, Pittsburgh, Pennsylvania, USA,* [26] *Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA,* [27] *Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA,* [28] *Department of Gastroenterology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China,* [29] *Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA,* [30] *Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico; Department of Pathophysiology and Transplantation; Università degli Studi, Milan, Italy,* [31] *Institute for Image Guided Surgery IHU-Strasbourg, Strasbourg, France,* [32] *Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Naples, Italy,* [33] *Department of Surgery, Hospital Alemán of Buenos Aires, Buenos Aires, Argentina,* [34] *Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK,* [35] *Department of Surgery, University of Washington School of Medicine, Seattle, Washington, USA,* [36] *Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA,* [37] *Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands,* [38] *Department of Surgery, Flinders University, Adelaide, Australia,*

Address correspondence to: Prof. Giovanni Zaninotto, M.D., Department of Surgery and Cancer, Imperial College, London, UK.
Email: g.zaninotto@imperial.ac.uk

[39] *Department of Gastroenterology, University of Bordeaux, Bordeaux, France,* [40] *ECD Solutions, Atlanta, Georgia, USA,* [41] *ALMA (Association of patients with achalasia, ONLUS), Naples, Italy, and* [42] *Department of Thoracic Surgery Virginia Mason Medical Center, Seattle, Washington, USA*

SUMMARY. **Achalasia is a relatively rare primary motor esophageal disorder, characterized by absence of relaxations of the lower esophageal sphincter and of peristalsis along the esophageal body. As a result, patients typically present with dysphagia, regurgitation and occasionally chest pain, pulmonary complication and malnutrition. New diagnostic methodologies and therapeutic techniques have been recently added to the armamentarium for treating achalasia. With the aim to offer clinicians and patients an up-to-date framework for making informed decisions on the management of this disease, the International Society for Diseases of the Esophagus Guidelines proposed and endorsed the Esophageal Achalasia Guidelines (I-GOAL). The guidelines were prepared according the Appraisal of Guidelines for Research and Evaluation (AGREE-REX) tool, accredited for guideline production by NICE UK. A systematic literature search was performed and the quality of evidence and the strength of recommendations were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Given the relative rarity of this disease and the paucity of high-level evidence in the literature, this process was integrated with a three-step process of anonymous voting on each statement (DELPHI). Only statements with an approval rate >80% were accepted in the guidelines. Fifty-one experts from 11 countries and 3 representatives from patient support associations participated to the preparations of the guidelines. These guidelines deal specifically with the following achalasia issues: Diagnostic workup, Definition of the disease, Severity of presentation, Medical treatment, Botulinum Toxin injection, Pneumatic dilatation, POEM, Other endoscopic treatments, Laparoscopic myotomy, Definition of recurrence, Follow up and risk of cancer, Management of end stage achalasia, Treatment options for failure, Achalasia in children, Achalasia secondary to Chagas' disease.**

KEY WORDS: **esophageal achalasia, Chagas disease.**

SUMMARY TABLE OF STATEMENTS AND RECOMMENDATIONS

Topic and number	Statement	Consensus agreement score	Recommendation
Diagnosis of achalasia			
	1 High-resolution manometry is the test of choice for the diagnosis of achalasia (compared to conventional manometry)	**94.2%**	We recommend the use of HRM for the diagnosis of esophageal achalasia. Conditional recommendation; GRADE low.
	2 The Chicago Classification is a useful tool to define the clinically relevant phenotypes of achalasia.	**90.4%**	We recommend classification of achalasia according to the Chicago Classification. Good practice recommendation
	3 The timed barium esophagram offers an objective evaluation of the diseases and of the outcome after treatment (compared to traditional barium esophagram).	**90%.**	We recommend the adoption of TBS in the diagnostic pathway of achalasia and to evaluate the outcome of treatment. Conditional recommendation; GRADE low.
	4 Endoscopy should be performed in patients with suspected achalasia to exclude malignancy of the esophagogastric junction.	**98.1%**	We recommend performing UGI endoscopy in adult with the suspected diagnosis of achalasia to exclude neoplastic pseudoachalasia. Good practice recommendation.
	5 The Eckardt score is a simple tool to measure symptom severity in achalasia patients, but it should be integrated with objective measures such esophagogram and manometry.	**86.5%**	We recommend the use of the Eckardt score as part of the initial and follow-up assessment in patients with achalasia. Good practice recommendation.
Treatment of achalasia Medical treatment with nitrates, calcium blockers, or phosphodiesterase			
	6 There is no convincing evidence that medical treatment with nitrates is effective for symptomatic relief in adults with achalasia.	**86.5%**	We recommend against the use of nitrates, calcium blockers, or phosphodiesterase treatment for achalasia. GRADE: low.

Topic and number	Statement	Consensus agreement score	Recommendation
	7 There is no convincing evidence that medical treatment with calcium blockers is effective for (short term) symptomatic relief in adults with achalasia.	**88.2%**	
	8 In adults with achalasia, there is no evidence that medical treatment with phospho-diesterase inhibitors is effective for symptomatic relief.	**84.3%**	
Botulinum toxin injection (BTI)			
	9 BTI has limited application in young patients (aged less than 50 years).	**92.3%**	We recommend against the use of BTI in patients under 50 years of age, for control of symptoms. GRADE: very low: We recommend against BTI as an effective therapy (control of symptoms) for achalasia in patients fit for surgery (LHM) or pneumatic dilatation GRADE: moderate.
	10 BTI should be reserved for patients who are unfit for surgery or as a bridge to more effective therapies, such as surgery or endoscopic dilation	**94.3%**	
	11 Repeat treatments with Botox are safe, but less effective than initial treatment	**82.4%**	Recommendation: Botox injection can be safely repeated, but the clinician and the patients should be aware that their efficacy is lower than in initial treatment. Conditional recommendation. GRADE: low.
	12 There is no evidence for supporting the injection of Botox in the lower esophageal body (in addition to injection in the LES) in type III achalasia patients.	**92.1%**	We recommend against BTI in the esophageal body, even in the presence of type III achalasia. GRADE: very low.
	13 There is no evidence that patients undergoing repeat BTI of the LES should be treated with increasing dosage of BT.	**96.1%**	We recommend against the use of increasing BT dosage at retreatment. GRADE: very low.
Pneumatic dilatation			
	14 In patients with achalasia, graded PD is an effective treatment in terms of improvement of symptoms and swallowing function.	**90.4%**	We recommend graded pneumatic dilatations as an effective treatment (control of symptoms including dysphagia) for esophageal achalasia. Strong recommendation GRADE: moderate. Patients wishing longer term remission may opt for surgical treatment.
	15 In patients with achalasia who have received PD, the best post procedural test to assess if a perforation occurred is a Gastrografin (iodine contrast) swallow.	**80.8%**	We recommend that after PD patients are observed for 4 hours. Water-soluble iodine contrast (Gastrografin) esophagogram (or CT scan with oral contrast) should be performed if any symptoms, even if moderate, suggest that perforation is present after dilatation. We recommend against the routine use of contrast esophagram or computed tomography shortly after PD. Conditional recommendation. GRADE: low.
	16 There is only limited evidence that pneumatic dilatation may be used as first-line therapy in megaesophagus (diameter >6 cm & sigmoid shaped).	**82.4%**	We make no recommendation about pneumatic dilatation as first-line therapy in megaesophagus GRADE: very low.
	17 There is no evidence that patients undergoing graded dilation should be treated with proton pump inhibitors as maintenance therapy after the procedure, unless symptomatic or positive at 24-hour pH-monitoring.	**94.3%**	We recommend against the prophylactic use of PPI after PD, unless GERD symptoms are present or objective evidence of reflux is demonstrated. Conditional recommendation GRADE: very low.
Peroral endoscopic myotomy (POEM)			
	18 Treatment of achalasia patients with POEM, results in similar outcomes on swallowing functions compared with alternative treatment (Heller myotomy or PD), at least at medium term follow-up (2–4 years).	**88.4%**	We recommend POEM as an effective therapy (control of symptoms) for achalasia both in short- and medium-term follow-up with results comparable to Heller myotomy for symptom improvement. Conditional recommendation. GRADE: very low. We recommend POEM as an effective therapy (control of symptoms) for achalasia both in short- and medium-term follow-up with results comparable to pneumatic dilations for control of symptoms. Conditional recommendation. GRADE: low.

ISDE The International Society for Diseases of the Esophagus

Continued

Topic and number	Statement	Consensus agreement score	Recommendation
	19 Treatment of achalasia with POEM is associated with a higher incidence of GERD compared to alternative therapies (Heller myotomy with fundoplication or PD).	**96.2%**	We recommend that pretreatment information on the risk of GERD should be provided to the patient and follow-up acid suppression therapy considered after POEM. Good practice recommendation. Patients who seek a nonsurgical treatment (PD) or surgical treatment with a lower incidence of postprocedure GERD (Heller myotomy) should be counseled that these options exist.
	20 There is no evidence that previous treatment of patients with achalasia with PD or Botox reduces the technical feasibility of POEM and results in poorer outcomes.	**86.6%**	We recommend POEM as feasible and effective for symptom relief in patients previously treated with previous endoscopic therapies. Conditional recommendation; GRADE: very low.
	21 POEM is an appropriate treatment for symptom persistence/recurrence after laparoscopic myotomy.	**88.2%**	We recommend the use of POEM for symptom relief, as an option for treating recurrences after LHM. Conditional recommendation. GRADE: low.
	22 Attaining proficiency with the POEM procedure involves a stepwise approach to education and a defined learning curve for both medical and surgical endoscopists.	**90.2%**	We recommend that appropriate training with in vivo/in vitro animal model and adequate proctorship should be considered before starting a clinical program of POEM. Good practice recommendation.
Alternative treatments: retrievable stents and intrasphincteric injection with ethanolamine oleate or polidocanol			
	23 There is little evidence to support that modified retrievable stent placement at the LES is an effective treatment for patients with achalasia.	**98%**	We recommend against temporary (retrievable or absorbable) stents and intrasphincteric injection with ethanolamine oleate for achalasia. Conditional recommendation. GRADE: low.
	24 There is no or little evidence to support the use of endoscopic sclerotherapy with ethanolamine oleate or polidocanol as an effective first treatment for patients with achalasia.	**96%**	We recommend against temporary (retrievable or absorbable) stents and intrasphincteric injection with ethanolamine oleate or polidocanol for achalasia. Conditional recommendation. GRADE: low.
Laparoscopic Heller myotomy			
	25 The best outcomes for LHM are achieved in (Chicago) type I & type II achalasia patients.	**90.4%**	We recommend laparoscopic Heller myotomy for control of symptoms in Chicago type I and type II achalasia. Strong recommendation. GRADE: moderate.
	26 Laparoscopic Heller myotomy should include a myotomy 6 cm into the esophagus and 2 to 3 cm into the stomach as measured from the GEJ, for effective symptom control in achalasia patients.	**94.2%**	We recommend that Laparoscopic Heller cardiomyotomy should be extended at least (6 cm proximal to the GEJ and at least 2 cm distal to the GEJ. Conditional recommendation. GRADE: low.
	27 Partial fundoplication should be added to laparoscopic myotomy in patients with achalasia to reduce the risk of subsequent gastroesophageal reflux.	**94.2%**	We recommend that a partial (posterior or anterior fundoplication) but not a complete 360° wrap should be added to reduce the long-term risk (5 years) of developing gastroesophageal reflux and dysphagia after myotomy. Strong recommendation. GRADE: moderate.
	28 Laparoscopic Heller myotomy with a partial fundoplication is as effective at improving swallowing function as laparoscopic Heller myotomy alone.	**82.7%**	We recommend a partial fundoplication should be used when performing Heller myotomy to prevent subsequent development of gastro-esophageal reflux without compromising the adequate control of dysphagia. We recommend against LHM alone due to the risk development of gastro-esophageal reflux. Strong recommendation. GRADE: High.
	29 LHM (or other therapies as POEM or PD) should be considered as the first-line treatment option in achalasia patients with sigmoid esophagus (compared to esophagectomy).	**86.5%**	We recommend standard endoscopic or surgical therapies in surgically naïve achalasia patients with sigmoid-shaped esophagus, leaving esophagectomy as secondary option in case of failure of first line therapy. Conditional recommendation. GRADE: very low.

Continued

Topic and number	Statement	Consensus agreement score	Recommendation
Recurrence of achalasia after treatment			
	30 Symptom improvement is the most relevant clinical parameter for defining the success of surgical or endoscopic treatment for achalasia.	**90.4%**	We recommend assessment of symptomatic improvement as the best measure of success after treatment of achalasia. Good practice recommendation.
	31 In adults with achalasia, there is no universal definition of failure after any treatment.	**88.4%**	Recommendation: see next statement.
	32 Recurrent symptoms after achalasia treatment should routinely undergo repeat objective testing.	**100%**	We recommend objective testing in patients who suffer recurrent symptoms after treatment of achalasia including UGI endoscopy, barium swallow, manometry, and 24-hour pH monitoring. Good practice recommendation.
	33 The timed barium swallow objectively demonstrates the failure of achalasia treatment in patients with persistent/recurrent symptoms.	**82.7%**	We recommend TBS as a reliable method to assess recurrence of achalasia. Conditional recommendation. GRADE: Low.
Risk of cancer			
	34 Achalasia patients carry a moderately increased risk of development of squamous esophageal cancer 10 years or more from the primary treatment of achalasia.	**86.5%**	We recommend that achalasia patients should be informed that a moderately increased risk of esophageal cancer is present in male after at least 10 years from the initial treatment of the disease. Good practice recommendation. We make no recommendation about routine endoscopy or endoscopy intervals after any treatment.
Management of treatment failures			
	35 Patients with achalasia who do not respond to initial treatment with graded PD, should be referred for Heller myotomy or POEM.	**94.2%**	We recommend that in patients who are fit for surgery and have symptomatic recurrences after several pneumatic dilations, Heller myotomy, or POEM should be considered. Conditional recommendation. GRADE: of evidence low.
	36 Laparoscopic esophageal myotomy is a safe, feasible and effective treatment after failed Botox injection for achalasia.	**96.2%**	We recommend LHM as an effective therapy for symptom recurrence after primary treatment with BTI. Conditional recommendation. GRADE: very low.
	37 PD, compared with repeat myotomy or POEM, is the first option for treatment after failed Heller myotomy for achalasia.	**80.8%**	We recommend pneumatic dilation as a safe and effective treatment of symptom recurrences after LHM. Conditional recommendation. GRADE: Low.
	38 There is insufficient evidence that laparoscopic myotomy or redo POEM offer better results than PDs after failed POEM.	**82.4%**	We make no recommendation about laparoscopic myotomy or redo POEM offering better symptomatic relief than pneumatic dilations after failed POEM. Further research is recommended to provide high-quality data and guide clinical decisions.
Diagnosis and treatment of end stage achalasia			
	39 Barium swallow esophagram, compared with manometry, is the best diagnostic method for defining end stage achalasia (i.e. that which requires esophagectomy).	**94.1%**	We recommend the use of barium swallow as the most accurate investigation to properly define end-stage achalasia. Good practice recommendation.
	40 Esophagectomy is indicated in patients with persistent or recurrent achalasia after failure of previous less invasive treatments (PD, POEM, LHM) and radiologic progression of the disease.	**80.8%**	We recommend esophagectomy in patients with end-stage achalasia who have failed other less invasive interventions. Conditional recommendation. GRADE: Low.
Achalasia in children			
	41 Children with suspected achalasia should follow the same diagnostic pathway as that of adult patients.	**96%**	We recommend that children with a provisional diagnosis of achalasia should undergo the same work-up as in the adult population. Good practice recommendation.
	42 Surgical or endoscopic myotomy (compared to dilation) is the preferred treatment for pediatric patients with idiopathic achalasia (IA), especially for those aged 5 years or more.	**80%**	We recommend myotomy (either through a laparoscopic or flexible endoscopy approach as the preferred treatment in children). Conditional recommendation. Grade: very low.

Continued

Topic and number	Statement	Consensus agreement score	Recommendation
	43 BTI is not an appropriate first-line therapy in very young children with achalasia.	**81.6%**	We recommend against BTI as a first-line therapy in very young children with achalasia (with exceptions for those children who are medically frail and at high-risk for surgical intervention). Conditional recommendation. Grade: very low.
	44 The long-term outcome of achalasia treatment in children should be assessed by symptoms, function, physical growth, and general development.	**94.4%**	We recommend that the long-term outcome of achalasia treatment in children should be closely monitored by symptoms, swallowing function, physical growth, and general development. Good practice recommendation.
Diagnosis and management of achalasia secondary to Chagas disease			
	45 There are minor differences between the clinical presentation of IA and achalasia secondary to Chagas disease.	**86.2%**	We recommend that diagnostic techniques used for IA should also be used for CDE, due to the similarities in manometric and clinical features. Conditional recommendation. GRADE: low.
	46 There are no differences in the treatment of idiopathic achalasia and achalasia specific to Chagas disease.	**90%**	We recommend that all treatments for IA may be used for CDE for symptom relief. Conditional recommendation. GRADE: low.

INTRODUCTION

Achalasia is a relatively rare esophageal motor disorder characterized by the absence of swallow-induced relaxation of the lower esophageal sphincter (LES) and by absence of peristalsis along the esophageal body. Consequently, the transit of the food into the stomach is impaired and the patient typically experiences dysphagia. Other symptoms reported are regurgitation of saliva or undigested food, respiratory symptoms (nocturnal cough, recurrent aspiration, and pneumonia), heartburn, and chest pain.[1] The most common form of achalasia is idiopathic and is mostly observed sporadically. In idiopathic achalasia (IA), the disease occurs secondary to the destruction of the myenteric plexus that coordinates both peristaltic contraction and LES relaxations.[2-4] A similar clinical picture can be present in patients with local or distant cancer (pseudoachalasia)[5,6] or in patients with Chagas' disease,[7] both characterized by the destruction of the myenteric plexus either by infiltrating tumors or by circulating autoantibodies or by *Trypanosoma cruzi* infection.

The incidence of achalasia is similar in most countries, with no differences in gender and race, although its incidence increases with age. It has been consistently estimated that the incidence varies between 0.7 to 1.6 per 100,000 inhabitants/year.[8-11] The prevalence of achalasia was currently estimated to be 10 per 100,000 inhabitants. Newer studies in the era of high-resolution esophageal manometry (HRM) suggest that these numbers are low, and that the actual incidence is 2 to 3/100,000 with a much higher prevalence.[12-14]

Achalasia is a chronic disease and all the current treatment options can only palliate symptoms, but not cure the disease. As a result, many achalasia patients undergo multiple treatments throughout their lifetime.[1]

The diagnosis of achalasia is based on tests which include: esophageal manometry that measures the pressure generated in the LES and in the esophageal body; barium esophagram and upper gastrointestinal endoscopy, mainly to rule out the presence of cancer (pseudoachalasia) and possible complications of the disease (candidiasis).

Achalasia treatments are aimed at reducing the pressure of the LES either using medication like botulinum toxin injection (BTI) into the LES or disrupting the LES muscle by stretching its fibers with dilators or by dividing it surgically or endoscopically (myotomy).[15]

However, over the last 10 years, there has been significant evolution of the management of achalasia with the introduction of new diagnostic tools as high-resolution manometry (HRM)[16,17] and treatment options as peroral endoscopic myotomy (POEM)[18], temporary stent insertion and injection of chemical substances in the LES.

Achalasia is a disease treated by both gastroenterologists and surgeons and two American scientific societies of gastroenterologists and surgeons (ACG & SAGES) have produced guidelines for achalasia.[19,20] This new ISDE Clinical Guideline for Achalasia (I-GOAL), however, is distinctive in that it is interdisciplinary and international. Our guideline aims to offer all stakeholders (physicians and surgeons, patients, and health policy managers) a useful and up-to-date resource for applying the best evidence-based principles to the diagnosis and management of achalasia, and achalasia of Chagas' disease. The guideline is also based on a unique interactive methodology

that allows the development of statements on diseases where there are few high-quality studies and scant evidence to support strong recommendations.[21]

METHODS

All forms of achalasia (adult, pediatric, achalasia related to Chagas disease and achalasia related to triple A, Down syndrome, or other genetic diseases) were considered.

The 'Working Group' comprised 51 members from medical and surgical specialties and included three patient representatives and two conveners (GZ and DL). Participants were selected among ISDE members with a specific interest in managing achalasia by the two conveners. Other members of the team included a scientific consultant who coordinated the process and edited submitted statements (CB), and a web developer (SG). CB and SG (non-voting group members) initially developed the process to be applied during the development of the guidelines. The group was geographically diverse with members from the USA (19), Italy (8), UK (3), Belgium (4), Australia (2), Brazil (7), Germany (2), France (2), Netherlands (1), Japan (1), China (1), Argentina (1). Panels were created by inviting participants from both gastroenterology and surgery to work in study groups led by a Chairperson.

We systematically searched for evidence, selected evidence, and integrated this with three rounds of an eDelphi process to obtain consensus on key areas:

- Diagnostic workup,
- Definition of the disease,
- Severity of presentation,
- Medical treatment,
- BTI,
- Pneumatic dilatation (PD),
- POEM,
- Other endoscopic treatments,
- Laparoscopic myotomy,
- Definition of recurrence,
- Follow up and risk of cancer,
- Management of end stage achalasia,
- Treatment options for failure,
- Achalasia in children,
- Achalasia secondary to Chagas' disease
- Achalasia secondary to genetic diseases.

We excluded 'secondary achalasia' as this is not a well-defined condition.

Our approach combined the principles of evidence-based medicine supported by systematic literature reviews with the use of an iterative anonymous voting process[22-24] and the method used is accredited for guideline production by NICE UK.[25] The online platform permitted anonymous individual feedback and changes of views during the process, together with controlled feedback of evidence regulated by the coordinator (CB) and the consensus chair (GZ). The group was initially asked to identify areas where there is uncertainty in management and to provide clinical questions, structured by population, intervention, comparator, and outcome (PICO).

Keywords identified from the clinical questions were used to construct literature searches in electronic databases (Appendix of search strategies),

The principal steps in the process were: (1) selection of the consensus group and identification of clinical questions; (2) development of draft statements by the panels; (3) systematic literature reviews to identify evidence to support each statement; (4) production of evidence-based discussions using the selected evidence; (5) 3 rounds of iterative voting and commenting. The initial stage was the development of statements followed by a comprehensive literature review. Statements were prepared that described the population, the intervention or management strategy, whether a comparison strategy was applicable, and the outcomes being assessed. Participants were assigned to panels corresponding to statements and developed pertinent summaries for each statement using the available literature. These summaries were written by the panel members and included all the relevant evidence identified for each statement, making specific reference to any studies that were assessed but which did not contribute additional evidence. The Summary Statements were then posted online for voting and feedback to guide refinement.

The respondents were asked to choose one of the following for each statement; agree strongly (A+), agree with reservation (A), undecided (U), disagree (D) or disagree strongly (D+). Participants voted on statements, assessments were made on the basis of the participants' comments and judgments were informed of the supporting evidence. We defined consensus as 80% of respondents strongly agree or agree with reservation. When agreement was not reached, we rephrased the statement to see if this would provoke stronger agreement. If no strong agreement was reached after at least two rounds of voting, it was eliminated.

We electronically collected conflict of interest declarations at each stage of the voting process, electronically, at voting. The study is a secondary analysis of published work and did not involve human subjects or interventions therefore it did not require ethics committee review. However, the study was overseen by the ISDE and was subject to the review of ISDE's ethics committee.

GRADE

We used the GRADE system[26,27] to describe the quality of the evidence and the strength of recommendation. We used GRADE terminology for statements and recommendations.[28] The lack of effect estimates

and potential selection bias inherent in the included observational studies meant that much of the evidence was very low or low-quality evidence.

Evidence from randomized controlled trial (RCT) data is initially given a high-quality rating but is downgraded if the study methodology has a risk of bias i.e. there is unexplained clinically relevant heterogeneity, evidence is indirect, there is important uncertainty around the estimate of effect or there is evidence for publication bias. As a result, it is possible for RCT data to have a very low quality of evidence if several of these concerns are present. Evidence from observational studies starts at low quality but can be upgraded if the effect size is large, there is a dose response and all plausible confounding would act in the opposite direction to the effect noted. After completion of the consensus process, we used the GRADE approach to make recommendations, producing grade profiles[29] and we quantified the strength of recommendations.[30,31] A strong recommendation suggests that the intervention should be offered to most patients most of the time whereas a conditional recommendation suggests that there is either lower quality evidence, the balance between benefits and downsides is closely balanced and/or important uncertainty about patients' values and preferences exists. GRADE ratings were not applied when recommendations were considered to refer to universally accepted good practice[32] rather than evidence-based decisions on two or more competing management strategies.

Systematic literature search

Three authors (MS, RS, and LF) independently searched electronic databases MEDLINE (via Pubmed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 2000 to December 2016 for English-language articles. Exclusion criteria included studies on esophageal spastic motor disorders other than achalasia, case series reporting outcomes with less than ten patients and case reports. We used the PICO scheme to build our search strategy using search terms describing the patient and intervention. An updated search using the MeSH term '[esophageal achalasia]' was repeated in December 2017 and newly published articles or requested by participants were added to the main database up to January 2018 which coincided with our third and final round of voting. The references of the included articles were hand-searched to identify additional relevant studies. Participants were allowed to suggest more references (also outside the original time frame period) if they deemed them appropriate for the study.

Prior to the first voting round, users were able to select from this database and the convener (GZ) and a research assistant (SM) used these bibliographies to provide evidence-based discussions to associate with each statement available for review by the panel. Participants were also invited to add new literature at each round of the process. In this way, the group identified a list of primary references specific to each statement and these were used to develop the statement discussion. Panel chairs were responsible for the final selection of evidence and editing statement discussions, with moderation by CB and GZ. The literature search technique permitted inclusion of additional articles during the consensus process that might have been missed during initial searches (including newly published articles added at updates). Before including articles for citation, the articles were reviewed by panel members and the convener (GZ). GZ reviewed the studies obtained at the updated search in December 2017 and add relevant studies to the online database; these were then included in the evidence-based discussions. Appendix 1 describes the precise search terms used for each PICO statement and the PRISMA search strategy and flowchart generated.

RESULTS

Literature search

Out of 3183 articles were initially retrieved (including 61 articles added with the updated 2017 search) and 128 were added by the panelists; 22 articles were added after the updated literature search in January 2018. In total, 466 articles were considered for the preparation of the Guidelines. A detailed PRISMA figure for each of the key areas is provided in the online supplement (Figs. S1–15)

We found that the overall GRADE quality of evidence related to all the statements was low, or at best moderate although the consensus process resulted in a high level of consensus for many statements. At the final round of consensus, we achieved consensus (≥80% agreement) on 47/57 statements, 10 statements were not accepted. Of these 10, at least 50% of the participants who voted agreed with the statement, but they failed to reach consensus according to our criteria. Two statements (on PD for treatment of recurrence after surgery) were similar in content and were combined for the purposes of this guideline manuscript.

We selected, on the basis of the agreement level and clinical relevance, 46 statements that represent the following key clinically relevant areas: 1. Diagnosis of achalasia, 2. Management of primary disease; 3. Definition of failures; 4. Risk of cancer and follow-up of achalasia patients; 5 Management of failures; 6. Definition diagnosis and treatment of 'end stage achalasia'; 7. Management of achalasia in children; 8. Diagnosis and management of achalasia in Chagas disease. These 46 statements form the basis of this guideline. All the statements were archived: (http://www.mdpub.org/igoal).

Diagnosis of achalasia

1. **HRM is the test of choice for the diagnosis of achalasia (compared to conventional manometry).**

Agree: 94.2% [D + (2%); D (0); U (3.8%); A (26.9%); A + (67.3%)]

HRM records intraluminal pressures circumferentially at 1 cm intervals over a 36 cm segment along the length of the esophagus. These pressure data are transformed into a topographic color contour plot. HRM is easier to perform than conventional manometry, the learning curve for recognizing the color contour patterns is shorter, and inter-rater and intra-rater agreement for the Chicago classification of achalasia subtypes is very good to excellent.[33,34] HRM has generated a new metric for esophagogastric junction (EGJ) relaxation known as the "integrated relaxation pressure" (IRP) measured within the swallowing window from the initiation of a swallow and Upper Esophageal Sphincter (UES) relaxation until the arrival of the peristaltic contraction at the LES or after 10 seconds in absence of peristalsis. Relaxation pressure is reported as the lowest value persisting for 4 seconds after the swallow and can distinguish between the LES and crural diaphragm components.[35] One study found a two-fold increase in the diagnosis of achalasia compared to conventional manometry from 12% to 26%.[36] Based on a series of 62 patients with well-defined achalasia 4-second IRP >15 mmHg as had a sensitivity of 97% and only 3% false negative rate. This was a considerable diagnostic improvement over the single sensor nadir >7 mmHg, which only had a sensitivity of 52% with a striking 48% false negative rate.[37] Despite evidence supporting the use of HRM, this test has not yet been widely adopted, especially in nonacademic hospitals.[38]

Recommendation: we conditionally recommend the use of HRM for the diagnosis of esophageal achalasia (compared to conventional manometry). GRADE: low.

2. The Chicago Classification is a useful tool to define the clinically relevant phenotypes of achalasia.

Agree: 90.4% [D + (1.9%); D (1.9%); 3 (5.8%); A (44.2%); A + (46.2%)]

The Chicago Classification 3.0 was created to define clinically relevant phenotypes for esophageal motor patterns that are associated with the chief complaint of dysphagia using 10 5 mL water swallows. By utilizing the integrated relaxation pressure, specific metrics of propagation and pressurization patterns, the Chicago Classification 3.0 provides a systematic classification scheme that can define achalasia into distinct subtypes (I, II, III) and variants that may indicate evolving/early achalasia (EGJ outflow obstruction) or achalasia in the context of a low LES pressure (absent contractility).[16,39] The subtypes of achalasia are defined on the basis of the patterns of esophageal body contractility and pressurization once an elevated integrated relaxation pressure establishes that there is resistance to bolus transit at the esophagogastric junction. This approach provides a more systematic mechanism for classifying achalasia based on an algorithm with specific criteria and a high level of agreement between interpreters. Thus, the Chicago Classification 3.0 is a more robust and standardized method to classify achalasia compared to conventional manometry and barium esophagraphy, which fail to distinguish patterns beyond vigorous achalasia. This classification scheme does not capture all achalasia patients as early achalasia can be seen with propagating contractions and an elevated IRP (EGJ outflow obstruction)[39] and in the late stages where esophageal dilatation occurs and intraesophageal pressures are too low to generate an elevated IRP in the context of absent contractility.

Type II achalasia has the best prognosis and while type III tends to have the worst prognosis.[16,40-44] Type I may represent a more advanced stage of achalasia and its prognosis is variable, but in general is worse than Type II.

Recommendation: we recommend classification of achalasia according to the Chicago Classification. Good practice recommendation.

3. The timed barium esophagram offers an objective evaluation of the diseases and of the outcome after treatment (compared to traditional barium esophagram).

Agree: 90%. [D + (2%); D (4%); U (4%); A (50%); A + (40%)]

In the timed barium esophagram (also known as the timed barium swallow (TBS)),[45] the patient drinks 100–200 mL of low density (45% weight by volume) barium sulfate over one minute in the upright position. Frontal spot films of the esophagus are obtained at 0, 1, 2, and 5 minutes. The height of the barium column is measured from the distal esophagus, identified by the 'bird-beak' appearances of barium, to the top of the distinct barium column. Width (diameter) of the esophagus can be measured at the widest part of the barium column perpendicular to the long axis of the esophagus. The degree of esophageal emptying is estimated either qualitatively by comparing the barium height on images taken at 1 and 5 min or by measuring the height and width of each image, calculating a rough area for both and determining the percent change in area.[46] The TBS is a reproducible technique for estimating esophageal emptying with almost perfect interobserver agreement.[45] TBS predicts the likelihood of symptom recurrence after pneumatic dilation or surgical myotomy.[47] Rohof *et al.* observed that the esophageal retention was a good predictor of treatment failure in long-standing achalasia and proposed using the TBS rather than manometry to decide on retreatment.[48] TBS is not

yet widely adopted, however, and many centers still use barium swallow esophagogram.

TBS studies provide data for diagnosis and to predict improvement after treatment. A 50% improvement in emptying and >5 cm of stasis at 5 minutes[48] were good predictors of treatment failure and recurrence. A recent study on 188 achalasia patients, 46 EGJ outlet obstruction, and 146 patients with dysphagia from other causes, based on ROC analysis, barium column height of 5 cm at 1 minute showed the highest sensitivity of 86% and specificity of 71%, while the barium column height of 2 cm at 5 minutes had the highest sensitivity of 80% and specificity of 86% in differentiating achalasia for the other two groups.[49] Two studies, however, do not support the positive prognostic ability of TBS.[50,51]

Recommendation: we conditionally recommend the use of TBS in the diagnostic pathway of achalasia and to evaluate the outcome of treatment. GRADE: low.

4. Endoscopy should be performed in patients with suspected achalasia to exclude malignancy of the esophagogastric junction.

Agree: 98.1% [D + (0%); D (0%); U (1.9%); A (9.6%); A + (88.5%)]

Endoscopy has a low diagnostic yield[52] in the diagnostic workup of achalasia and its primary role is in ruling out a pseudoachalasia (secondary achalasia) or mechanical obstruction.[53-58] Three clinical features are thought to be suggestive of cancer as a cause of pseudoachalasia: short duration of dysphagia (<1 year), serious weight loss (>6.8 kg), and age over 55 years. The presence of any of these features should raise a suspicion of cancer, even though they have a low predictive accuracy.[19,59] Mucosal ulceration or nodularity, reduced compliance of the gastroesophageal junction, or an inability to pass the endoscope into the stomach are the most common EGD findings of pseudoachalasia. Endoscopic biopsy is used for the diagnosis of secondary pseudoachalasia.[60-64]

Recommendation: We recommend performing UGI endoscopy in adult with the suspected diagnosis of achalasia to exclude neoplastic pseudoachalasia. Good practice recommendation.

5. The Eckardt score is a simple tool to measure symptom severity in achalasia patients, but it should be integrated with objective measures such esophagogram and manometry.

Agree: 86.5% [D + (0%); D (2%); U (11.5%); A (42.3%) A + (44.2%)]

The Eckardt score (ES) is a simple measure to assess achalasia outcome and focuses on 4 symptom components: dysphagia, regurgitation, retrosternal pain, and weight loss. The 4 components are graded from 0 to 3, and patients are classified as having a good outcome if ES is <3 or a poor outcome if ES ≥3.[65] Although this measure is the most widely used and accepted questionnaire for achalasia disease severity, it has not been validated outside of comparisons with physiologic measures and has not been vetted as a patient reported outcome measure.[66,67] In a paper published after the consensus process ended, it was reported that the Eckardt score did not fulfill criteria for a validated symptom score, and the chest pain and weight loss components may decrease the reliability and validity of this score.[68]

Recommendation: we recommend the use of the Eckardt score as part of the initial and follow-up assessment in patients with achalasia. Good practice recommendation.

Treatment of achalasia

Medical treatment

6. There is no convincing evidence that medical treatment with nitrates is effective for symptomatic relief in adults with achalasia. Agree: 86.5%

[D + (3.8%); D (5.5%); U (6.9%); A (56.9%); A + (26.9%)]

7. There is no convincing evidence that medical treatment with calcium blockers is effective for (short term) symptomatic relief in adults with achalasia.

Agree: 88.2% [D + (0%); D (2%); U (9.8%); A (54.9%); A + (33.3%)]

8. In adults with achalasia, there is no evidence that medical treatment with phosphodiesterase inhibitors is effective for symptomatic relief.

Agree: 84.3% [D + (0%); D (2%); U (13.7%); A (54.9%); A + (29.4%)]

There is no convincing evidence for using any of these medications for short term relief of achalasia symptoms.[69-83]

Recommendations: we recommend against the use of nitrates, calcium blockers or phosphodiesterase inhibitors treatment for symptomatic relief of achalasia. GRADE: low.

Botulinum toxin injection 'Botox' (BTI)

9. BTI has limited application in young patients (aged less than 50 years).

Agree: 92.3% [D + (0%); D (5.8%); U (1.9%); A (42.3%); A + (50%)]

We found no evidence to support the use of BTI in patients <50 years.[84-90] We did not specifically address its utility in patients under 50 years of age who are at high-risk for surgical or other procedures.

10. BTI should be reserved for patients who are unfit for surgery or as a bridge to more effective therapies, such as surgery or endoscopic dilation.

Agree: 94.3% [D + (0%); D (3.8%); U (1.9%); A (46.2%); A + (48.1%)]

BTI in the LES in achalasia has a very high safety profile and even mild adverse event with heartburn or chest pain are observed in less than 10% of patients treated.[91] In a RCT comparing Heller myotomy with BTI, the results in the 2 groups were comparable at 6 months, although symptom scores improved more in surgical patients (82% vs. 66%). At 2-year follow-up, only 34% of BTI patients versus 87.5% of the Heller patients were asymptomatic.[92] Similarly, four randomized trials and a Cochrane meta-analysis comparing BTI with pneumatic dilations (PD) consistently reported a higher cumulative rate of remission rate at 1 year after treatment.[85,86,93-96]

Recommendations: we recommend against the use of BTI in patients under 50 years of age, for control of symptoms. GRADE: very low:

We recommend against BTI as an effective therapy (control of symptoms) for achalasia in patients fit for surgery (LHM) GRADE: moderate.

We recommend against BTI as an effective therapy (control of symptoms) for achalasia in patients fit for pneumatic dilatation GRADE: moderate.

11. Repeat treatments with BTI are safe, but less effective than initial treatment.

We found that repeated treatments may be successful, if there are contraindications to invasive, but more durable treatments. BTI efficacy, however, may decrease over time. In an open study[97] followed up 35 patients treated with BTI, 12 (34.3%) relapsed and were retreated, 4 out of 12 did not respond after retreatment. In a controlled trial,[85] 7 of the 8 patients in the botulinum toxin group required a second injection because of recurrent dysphagia, the effect of the second injection lasted for at least 6 months in all treated patients, compared with only two thirds in the trials by Pasricha in 1994[98] and was still evident in 80% of this series at 1 year of follow-up. In this study, symptoms recurred in the long-term responders about 1 year after the initial injection. However, in such patients, further injections at this stage retained their efficacy. In a retrospective[89] study of 25 patients with achalasia of the 16 patients who responded to the initial injection, two were lost to follow-up and in the remaining 14 patients, the outcome was still satisfactory in nine patients after a mean of 2.5 years. The five patients who experienced only a short-term clinical success received a second or third injection of botulinum toxin, but their symptoms never improved substantially for more than 6 months. In a pilot, open trial by Martinek in 2003,[99] anterograde and retrograde BTIs were given. After a single BTI, 11 responders reported a relapse and 2 patients remained asymptomatic. The median symptom-free interval was 17 months (range: 8–28). Five patients with a relapse underwent BT reinjection. Three of them remained asymptomatic and two experienced the second relapse. After BT reinjection, the median symptom-free interval was 16 months (range: 10–19). All other patients with a relapse and without BT reinjection were treated with either balloon dilation or surgery and remained asymptomatic.[84,85,89,98,99]

Agree: 82.4%, [D + (2%); D (2%); U (13.6%); A (60.8%); A + (21.6%)]

Recommendation: we conditionally recommend that for symptom relief, BTI injection can be safely repeated, but clinicians and patients should be aware that their efficacy is lower than in initial treatment. GRADE: low.

12. There is no evidence that patients with 3 type III achalasia should receive additional Botox injections in the lower esophagus in addition to injections in the LES to improve function and symptoms.

Agree: 92.1% [D + (0%); D (2%); U (5.9%); A (68.6%); A + (23.5%)]

We found no direct evidence to support the use of BTI in the lower esophagus in patients with type III achalasia).[17,91-93,100]

Recommendation: we recommend against BTI in the esophageal body, even in the presence of type III achalasia. GRADE: very low.

13. There is no evidence that patients undergoing repeat BTI of the LES should be treated with increasing dosage of Botulinum toxin.

Agree: 96.1% [D + (0%); D (0%); U (3.9%); A (56.9%); A + (39.2%)]

We found no evidence to support an increasing dosage of (BT) when patients need retreatment.

Recommendation: we recommend against the use of increasing (BT) dosage at retreatment. GRADE: very low.

Pneumatic dilatation

14. In patients with achalasia, graded PD is an effective treatment in terms of improvement of symptoms and swallowing function.

Agree: 90.4% [D + (0%); D (3.8%); U (5.8%); A (32.7%); A + (57.7%)]

Graded PD consists of a series of dilations starting with a 30 mm balloon, and depending on the response, followed by dilations using 35 mm and in some cases, a 40-mm balloon. Dilation is aimed at reducing the LES pressure in achalasia and reducing the resistance to bolus flow with consequent improvement in symptoms. There is no evidence about optimum duration

of inflation, the balloon pressure to be applied or the interval between the successive dilations.

Graded PD is effective as an initial treatment in terms of symptoms including dysphagia, but success rates decline over time and retreatment may be required. Success rates largely vary depending on the criteria used to define success and the duration of follow-up and they are significantly increased by allowing redilation in case of recurrent symptoms.[101-104] In the European RCT comparing PD versus laparoscopic Heller's myotomy for idiopathic achalasia, 96% of patients responded successfully to the initial series of pneumatic dilation.[105] Success rates (intention-to-treat) dropped from 90% at 1 year to 86% at 2 years and 82% at 5 years.[105] West *et al*. in 2002 showed a further reduction with even longer follow-up, with success rates dropping to 60%, 50%, and 40% in patients with a follow-up between 5 and 9 years, 10 and 14 years and >15 years.[106]

One quarter to one third of dilated patients will require redilation during the following 4–5 years.[101,105] An Australian study reported that 18% will relapse by 2 years, 41% by 5 years, and 60% by 10 years.[107] Furthermore, a review summarizing four studies of patients who had two or more dilations showed that 92%, 84%, 78%, and 64% patients were in remission at 1, 2, 3, and 5 years.[108]

In comparison with surgical therapy (LHM) in a RCT,[109] the clinical response and the variables related to good results in 92 patients with achalasia who were randomized to receive either PD or laparoscopic Heller myotomy (LHM) with partial fundoplication were evaluated. Three months after treatment, 73% of the patients from PD group and 84% of the surgery group had good results ($P = 0.19$). After 2 years of follow-up, 54% of the PD group and 60% of the surgery group (P = not significant) were symptom free. They concluded that surgical treatment and PD for achalasia are equally effective after 2 years of follow-up. However, some randomized trials comparing PD and LHM[110-112] showed better control of the outcomes of symptom control, GERD, and dysphagia respectively, after LHM. For symptom remission, LHM was not superior to PD in one meta-analysis,[113] however, other meta-analyses[114,115] have shown better treatment success,[114] and response rate (control of symptoms)[115] for LHM.

Recommendation: we recommend graded pneumatic dilatations as an effective treatment (control of symptoms including dysphagia) for esophageal achalasia. GRADE: moderate. Patients wishing longer term remission (without further dilatation) may opt for surgical treatment.

15. In patients with achalasia who have received pneumatic dilation, the best postprocedural test to assess if a perforation occurred is a Gastrografin (iodine contrast) swallow.

Agree: 80.8% [D + (1.9%); D (5.8%); U (11.5%); A (48.1%); A + (32.7%)]

Perforation is a serious complication of PD and should be diagnosed immediately to prevent soiling of the mediastinum or thoracic cavity with luminal contents. The rate of perforation after PD varies from 2% to 5.4% and is associated with patients who are older than 65 years, high amplitude of contraction in the distal esophagus and the use of Witzel dilators.[116] Perforation symptoms include epigastric pain, chest pain, left shoulder pain, dyspnea, fever, and moderate amount of hematemesis.[117] Intake of water will typically elicit epigastric or chest pain. Whether all patients should undergo postprocedure X-ray of the esophagus is unclear: one study by Zori 2016 compared elective radiological evaluation based on clinical suspicion versus routine esophagograms in all patients in a total population of 119 patients.[118] Although only three perforations occurred, no perforations were missed in the group where an esophagogram was taken if there was clinical suspicion of perforation, suggesting that the radiological evaluation could be performed only in case of clinical suspicion.

Recommendation: we recommend that after PD patients are observed for 4 hours, water-soluble iodine contrast (Gastrografin) esophagogram (or CT scan with oral contrast) should be performed if any symptoms, even if moderate, suggest that perforation is present after dilatation. We recommend against the routine use of contrast esophagram or computed tomography shortly after PD. GRADE: low.

16. There is only limited evidence that pneumatic dilatation may be used as first-line therapy in megaesophagus (diameter >6 cm & sigmoid shaped).

Khan *et al.* reported their experience in 9 patients with megaesophagus (>7 cm diameter) out of 110 who underwent pneumatic dilation. In this cohort, it was possible to dilate adequately, in all nine cases without complications, with good symptomatic improvement at 12-month follow-up.[119] Although there are no studies that definitively show that esophageal diameter determines outcome, pneumatic dilation is considered difficult in patients with sigmoid esophagus and associated with a higher rate of complications.

Agree: 82.4% [D + (2%); D (2%); 7 (13.6%); A (66.7%); A + (15.7%)]

Recommendation: we make no recommendation about pneumatic dilatation as first line therapy in megaesophagus. GRADE: very low.

17. There is no evidence that patients undergoing graded dilation should be treated with proton pump inhibitors as maintenance therapy after the procedure, unless symptomatic or positive at 24-hour pH-monitoring.

There are several studies which report on the development of GERD-related disease following pneumatic dilation and other treatments.[105,112,120-123] However, none of these studies provided information, which would result in all patients being treated prophylactically with acid suppressive therapy after such interventions. The utility of wireless pH monitoring to detect GERD was confirmed in a case series, (not included in our initial assessment of the literature).[124] In such cases, or when symptoms are present, PPI therapy should be offered. In conclusion, none of the examined studies reported the necessity on using PPI after PD as prophylaxis but given the high risk of GERD in such patients, the threshold for suspecting it should be low and PPI should be prescribed whenever symptoms occur, or GERD is confirmed by pH monitoring.

Agree: 94.3 [D + (0%); D (1.9%); U (3.8%); A (63.5%); A + (30.8%)]

Recommendation: we recommend against the prophylactic use of PPI after PD, unless GERD symptoms are present or objective evidence of reflux is demonstrated[124] GRADE: very low.

Peroral endoscopic myotomy

18. Treatment of achalasia patients with POEM, results in similar outcomes on swallowing functions compared with alternative treatment (Heller myotomy or pneumatic dilation), at least at medium-term follow-up (2–4 years).

Agree: 88.4 % [D + (0%); D (5.8%); U (5.8%); A (55.8%); A + (32.6%)]

The efficacy of POEM procedure has been mainly evaluated with changes in the Eckardt score to assess symptom improvement and timed barium esophagogram and manometry to assess the functional outcomes. Published studies report therapeutic success in 82–100% of patients, with dramatic reductions in the Eckardt score as well as the LES pressure.[37,125,126] Medium-term outcomes for POEM are now available in the literature with the longest follow-up now at 5 years.[127] The NOSCAR white paper[128] reports an >82% clinical success rate among 16 expert centers (841 patients) and a meta-analysis of 1122 patients shows a pooled overall failure rate (Eckardt >3) between 3.2% and 8%.[128–130] While there are multiple institutional and pooled retrospective comparisons between LHM and POEM,[130-136] there have been no comparable comparisons between POEM outcomes and achalasia balloon dilation other than an abstract of a RCT, (which was not included in our initial literature review as it was an abstract), with 133 patients who were therapy-naïve randomly assigned to POEM or PD, and which showed higher 1 year therapeutic success in the POEM group.[137] Most authors make an indirect inference to the relative equivalence of PD and LHM.

Comparative studies between POEM and LHM have uniformly shown equivalence or slight superiority to POEM in most intraoperative or postoperative domains.[131,133,135] Zhang *et al*. recently reported the outcome of POEM in a cohort of 33 patients with type III achalasia: at a median follow-up of 27 months 29 patients (87.8%) were asymptomatic with an Eckardt score >3.[132] Guo *et al*. analyzed the long-term outcome of POEM in 67 patients (mean follow-up: 40.1 ± 2.8 months) and reported a good symptomatic result (Eckardt score <3) in 59 patients (88%).[138] However, patients with type III achalasia were more likely to experience treatment failure. To date there is still insufficient evidence that POEM results in similar improvement in function and symptoms in all achalasia subtypes due to the paucity of data, short follow-up period, and lack of objective postoperative esophageal testing.[139]

Recommendations: we conditionally recommend POEM as an effective therapy (control of symptoms) for achalasia both in short- and medium-term follow-up with results comparable to Heller myotomy for symptom improvement. GRADE: very low.

We conditionally recommend POEM as an effective therapy (control of symptoms) for achalasia both in short- and medium-term follow-up with results comparable to pneumatic dilations for control of symptoms. GRADE: low

19. Treatment of achalasia with POEM is associated with a higher incidence of GERD compared to alternative therapies (Heller myotomy with fundoplication or pneumatic dilation).

Agree: 96.2% [D + (0%); D (1.9%); U (1.9%); A (46.2%); A + (50%)]

When performing surgical myotomy of the LES both the longitudinal and the circular fibers are divided, and a partial fundoplication is typically added to prevent gastroesophageal reflux (Dor or Toupet procedure). This raises the question if POEM is associated with high incidence of postoperative GERD. Outcome data regarding the incidence of GERD after POEM are currently limited. The NOSCAR 2015 white paper on POEM cites 12 studies with only 3 reporting pH monitoring data, on objective testing, the rate of GERD after POEM was 20% to 46%.[140] Patel in 2016 reviewed 22 studies (19 case series and 3 comparative studies) and reported only two additional studies that employed esophageal ambulatory pH monitoring in POEM. One study on 41 patients demonstrated GERD in 4/13 (30.7%) and another study on 100 patients documented GERD in 39/73 (53.4%).[130] Bhayani in 2014, however, reported on 101 patients who underwent postoperative 24-hour pH testing following Heller (48%) and POEM (76%).[131] Postoperatively, 39% of POEM and 32% of HM had abnormal acid exposure ($P = 0.7$).

Inoue reported on their series of 500 patients (no pH monitoring) and demonstrated that 268 of 414 patients (64.7%) had endoscopic findings of reflux esophagitis and (16.8%) complained of GERD symptoms such as heartburn or regurgitation.[127] In a multicenter trial of 205 patients in total,[37] of 197 patients with available clinical data, 18%% had reflux esophagitis after POEM and 37.5% had abnormal esophageal acid exposure.[141] A systematic review by Schlottmann[142] compared data between LHM and POEM and showed that while POEM was more effective in relieving dysphagia, the patients were more likely to develop GERD symptoms (OR 1.69, 95% CI 1.33–2.14, $P < 0.0001$), GERD related erosive esophagitis (OR 9.31, 95% CI 4.71–18.85 $P < 0.0001$, and abnormal pH monitoring (OR 4.30, 95% CI 2.96–6.27, $P < 0.0001$).[141,143,144]

Recommendation: Pretreatment information on the risk of GERD should be provided to the patient and follow-up acid suppression therapy) considered after POEM. Good practice recommendation.

Patients who seek a nonsurgical treatment (PD) or surgical treatment with a lower incidence of postprocedure GERD (Heller myotomy) should be counseled that these options exist.

20. There is no evidence that previous treatment of patients with achalasia with pneumatic dilation or BTI reduces the technical feasibility of POEM and results in poorer outcomes.

Agree: 86.6% [D + (0%); D (1.9%); U (11.5%); A (71.2%); A + (15.4%)]

Technical feasibility of POEM and outcome after dilatation or BTI treatment have never been specifically addressed by a prospective study. There are case series[145-150] reporting on patients with prior PD or BTI. These studied the outcomes and/or technical difficulty of POEM in those cases to achalasia patients without prior treatment. All of them reported that previous treatment did not affect the performance or early outcome of POEM.

Recommendation: we recommend POEM as feasible and effective for symptom relief in patients previously treated with previous endoscopic therapies. Conditional recommendation; GRADE: very low.

21. POEM is an appropriate treatment for symptom persistence/recurrence after laparoscopic myotomy.

Agree: 88.2% [D + (0%); D (7.8%); U (4%); A (64.7%); A + (23.5%)]

There are several studies that have examined the use of POEM in the treatment of recurrent achalasia after the failure of an initial intervention: these studies demonstrate that POEM is effective after initial failed intervention with minimal complications; the sample size in each individual study has been typically small (typically 2 to 3 patients).[140,148,151] In studies specifically identifying patients with failed LHM, positive outcomes and minimal complications with POEM as second-line intervention were observed.

In a case study of 12 patients with failed LHM undergoing POEM as second-line treatment, 91.7% had improvement of dysphagia based on the Eckardt score.[152] In a recent retrospective multicenter cohort study of 180 achalasia,[37] a significantly lower proportion of patients in the HM group had a clinical response to POEM (81%) than in the non-HM group (94% $P = 0.01$). POEM may be less effective as a second-line treatment after LHM than in naïve patients but remains a viable option after failed LHM.[153,154]

Recommendation: we conditionally recommend the use of POEM for symptom relief, as an option for treating recurrences after LHM. GRADE: low.

22. Attaining proficiency with the POEM procedure involves a stepwise approach to education and a defined learning curve for both medical and surgical endoscopists.

Agree: 90.2% [D + (0%); D (0%); U (9.8%); A (25.5%); A + (64.7%)]

POEM is a complex procedure that requires mastering specific endoscopic skills and understanding certain visual cues to completely and safely achieve an appropriate myotomy. The current literature is limited and definition of a minimal learning curve with current recommendations ranging between 7 and 40 procedures is needed to achieve proficiency.[155-158] Preclinical training using videos, experience using cadaver or animal models, observations of human cases and mentoring by experts have all been recommended when introducing POEM in clinical practice (NOSCAR 2014).[129]

Recommendation: appropriate training with in vivo / in vitro animal model and adequate proctorship is recommended before starting a clinical program of POEM. Good clinical practice.

Alternative treatments: retrievable stents and intrasphincteric injection with ethanolamine oleate or polidocanol

23. There is little evidence to support that modified retrievable stent placement at the LES is an effective treatment for patients with achalasia.

Agree: 98% [D + (0%); D (0%); U (2%); A (52.9%); A + (45.1%)]

24. There is no or little evidence to support the use of endoscopic sclerotherapy with ethanolamine oleate or polidocanol as an effective first treatment for patients with achalasia.

Agree: 96% [D + (0); D (0); U (5.8%); A (29.4%); A + (66.6%)].

Despite the number of studies retrieved in our searches, there is no convincing evidence for using any of these treatments for relief of achalasia symptoms.[159-171]

Recommendation: We recommend against temporary (retrievable or absorbable) stents and intrasphincteric injection with ethanolamine oleate or polidocanol for achalasia. GRADE: low.

Laparoscopic Heller myotomy

25. The best outcomes for LHM are achieved in (Chicago) type I & type II achalasia patients.

Agree: 90.4% [D + (0%); D (3.8%); U (5.8%); A (46.2%); A + (44.2%)]

A meta-analysis of three randomized controlled trials[105,110,112] found that LHM was significantly more effective than PBD after 12-month follow-up.[115]

Type II achalasia patients were significantly more likely to respond to pneumatic dilatation and LHM (100%), as compared to type I (56%) and type III (29%).[17] In 246 consecutive patients who underwent LHM and found that treatment failure rates were significantly different among the subtypes of achalasia: type I 14.6%, type II 4.7%, and type III 30.4% ($P = 0.0007$).[41] In a post-hoc analysis of the European RCT, a higher percentage of patients with type II achalasia were treated successfully with PD or LHM than patients with type I or III achalasia.[40] Both LHM and PD have a lower effectiveness in type III, but LHM has a better outcome of PD in type III. This was confirmed by a meta-analysis encompassing nine observational studies, and 727 patients which showed that type II achalasia was associated with the best prognosis after LHM, while type III achalasia had the worst prognosis: 'The pooled OR between the subtypes of achalasia after PBD or LHM showed that the best and worse treatment outcomes were found in patients with type II and III achalasia, respectively (type I vs. type II after PBD: OR 0.16, 95% CI 0.08–0.36, $P = 0.000$; type I vs. type III after PBD: OR 3.64, 95% CI 1.55–8.53, $P = 0.003$; type II vs. type III after PBD: OR 27.18, 95% CI 9.08–81.35, $P = 0.000$; type I vs. type II after LHM: OR 0.26, 95% CI 0.12–0.56, $P = 0.001$; type I vs. type III after LHM: OR 1.89, 95% CI 0.80–4.50, $P = 0.148$; type II vs. type III after LHM: OR 6.86, 95% CI 2.72–17.28, $P = 0.000$).'[172]

'Spastic' forms of achalasia (Type III according to the Chicago classification) are rare and they represent approximately 10 to 15% of all patients with achalasia; there are no specific trials comparing other treatments to LHM in type III. All the trials comparing PD to LHM consistently show that LHM is at least as effective as PD, and that this effect is durable (5-year follow-up)[111] and three meta-analyses [114,115,172] suggest that LHM is even more effective than PD, meaning that in 90% of achalasia patients LHM is very effective.

Recommendation: we recommend laparoscopic Heller myotomy for control of symptoms in Chicago type I and type II achalasia. Strong recommendation. GRADE: moderate.

26. Laparoscopic Heller myotomy should include a myotomy 6 cm into the esophagus and 2 to 3 cm into the stomach as measured from the GEJ, for effective symptom control in achalasia patients.

Agree: 94.2% [D + (2%); D (0%); U (3.8%); A (40.4%); A + (53.8%)]

The primary aim of surgical myotomy is to divide the muscle bundles of the LES complex, to reduce the esophageal outflow obstruction.[16,173,174] Anatomical, and physiological studies using manometry and endoscopic ultrasonography or in combination showed that the EGJ muscle complex and the sling fibers contribute substantially to the high-pressure zone and should therefore be included in the myotomy.[174,175] The need to perform an adequate myotomy distally onto the stomach should be emphasized.[176,177] (The most appropriate length of the myotomy may depend on the direction in which it is performed: the sling fibers have a different width on the left and right gastric sides of the cardia, and slightly diverting the myotomy leftward (as is normally done), in the narrower portion, ensures that most of the bundles constituting the sling fibers are divided with a myotomy 2 cm long.[173-178] Two studies supported extending the myotomy up to 3 cm in the stomach and claimed a reduction of dysphagia recurrence in patients.[179,180] The proximal extent of the myotomy during LHM is typically 6 to 8 cm cephalad to the EGJ, but no study has compared outcomes between differential proximal myotomy lengths.[174] This proximal extent is typically the maximum length that can be safely achieved via a laparoscopic, transhiatal approach, but has little physiologic basis, as the high-pressure zone of the EGJ complex is on average less than 4 cm in total length, with less than 2 cm lying cephalad to the squamocolumnar junction.

Recommendation: we conditionally recommend that Laparoscopic Heller cardiomyotomy should be extended at least (6 cm proximal to the GEJ and at least 2 cm distal to the GEJ. GRADE: low.

27. Partial fundoplication should be added to laparoscopic myotomy in patients with achalasia to reduce the risk of subsequent gastro-esophageal reflux.

Agree: 94.2% [D + (0%); D (2%); U (3.8%); A (21.2%); A + (73.1%)]

Symptomatic gastroesophageal reflux has been reported to occur in up to 48% of patients after myotomy for achalasia.[143,180-187] While some studies advocated a Nissen (360°) fundoplication after myotomy,[184,185] there is a general consensus that a complete 360° wrap can lead to an increased rate of postoperative dysphagia.[186-189] A RCT comparing

anterior partial fundoplication (Dor) versus 360° fundoplication (Nissen) confirmed that the recurrence rate of dysphagia was significantly higher among patients who received a 360° fundoplication without a significant difference in reflux control.[190] There is no consensus regarding the choice between anterior Dor (180°) and posterior Toupet (270°) (partial) fundoplications.[191-193]

Recommendation: we recommend that a partial (posterior or anterior fundoplication) but not a complete 360° wrap should be added to reduce the long-term risk (5years) of developing gastroesophageal reflux and dysphagia after myotomy. GRADE: moderate.

28. Laparoscopic Heller myotomy with a partial fundoplication is as effective at improving swallowing function as laparoscopic Heller myotomy alone.

Agree: 82.7% [D + (7.7%); D (3.8%); U (5.8%); A (36.5%); A + (46.2%)]

Laparoscopic cardiomyotomy (Heller's procedure) with antireflux fundoplication has been shown to result in effective relief of dysphagia symptoms with a low incidence of postoperative GERD resulting in an improved quality of life and the relief of dysphagia is not hampered by the addition of a partial fundoplication.[192,194,195] LHM was compared with LHM and Dor anterior partial 180° fundoplication in a RCT; there were no differences in the baseline characteristics between study groups. Pathologic gastroesophageal reflux occurred in 10 of 21 patients (47.6%) after LHM and in 2 of 22 patients (9.1%) after LHM plus Dor fundoplication ($P = 0.005$).[143] The Eckardt postoperative dysphagia score and the postoperative resting and nadir pressure of the LES were similar in the two groups. A systematic review[195] compared the safety and efficacy of endoscopic and surgical treatments for esophageal achalasia. Other studies assessing the same issue have shown that the incidence of postoperative GER was lower when a fundoplication was added to a laparoscopic myotomy (31.5% without a fundoplication versus 8.8% with; OR 6.3; 95% CI, 2.0 to19.4; $P = 0.003$) and the control of dysphagia was similar.[177,191,195-198,193,199]

Recommendation: we recommend a partial fundoplication should be used when performing Heller myotomy to prevent subsequent development of gastro-esophageal reflux without compromising the adequate control of dysphagia.

We recommend against LHM alone due to the risk development of gastro-esophageal reflux. GRADE: High.

29. LHM (or other therapies such as POEM or PD) should be considered as the first-line treatment option in achalasia patients with sigmoid esophagus (compared to esophagectomy).

Agree: 86.5% [D + (0%); D (0%); U (13.5%); A (42.3%); A + (44.2%)]

A severely dilated and sigmoid-shaped esophagus is considered the final endpoint associated with long-standing untreated esophageal achalasia or the result of recurrences after failure of previous treatments. In these patients, esophagectomy is considered a definitive treatment, but this option carries a high morbidity and an increased risk of mortality. Some studies have shown good results of LHM even in advanced phase of the disease suggesting that esophagectomy should be reserved for patients who have failed cardiomyotomy and other interventions.[144,200-203] Mineo *et al*. reported their experience in six patients and LHM proved to be effective in improving subjective, objective, and quality of life outcome measures in patients with sigmoid esophagus.[200] In a larger series of 33 patients with sigmoid achalasia, Faccani *et al* reported that LHM was effective in relieving dysphagia in these patients.[202] Sweet and colleagues showed that the outcome of LHM was not influenced by the degree of esophageal dilation.[203] Excellent or good results were obtained in 91% of patients, and none required esophagectomy. More recently, Panchanatheeswaran *et al*. showed that LHM provided significant improvement of dysphagia, regurgitation, and quality of life in a small study of eight patients with sigmoid esophagus.[201] The results of LHM in such patients are not as good as in less advanced disease.[177] Occasionally, a good outcome of POEM in sigmoid esophagus has been reported, but the experience level with this approach is low since the procedure in this setting is technically difficult.[204]

Recommendation: we conditionally recommend standard endoscopic or surgical therapies in surgically naïve achalasia patients with sigmoid-shaped esophagus, leaving esophagectomy as secondary option in case of failure of first line therapy. GRADE: very low.

Recurrence of achalasia after treatment

30. Symptom improvement is the most relevant clinical parameter for defining the success of surgical or endoscopic treatment for achalasia.

Agree: 90.4% [D + (0%); D (3.8%); U (5.8%); A (57.7%); A + (32.7%)]

The aim of therapy in achalasia is to palliate the symptoms of dysphagia and regurgitation. Therefore, symptom scores have been introduced to assess outcomes of such treatments, including BTI, PD (PD), surgical (LHM) or endoscopic myotomy (POEM). The most widely used is the Eckardt score.[205] Adequate relief of patients' symptoms (i.e., a good treatment outcome) is usually defined by a decrease in the Eckardt score to 3 or less, whereas a score higher than 3 is usually associated with treatment failure.[105,141,206,207] Some authors have also used a less

strict definition for failure by setting the threshold level for failure to 4,[207] or have used different symptom scores,[111,177,208-211] none of which have been widely accepted.

Recommendation: we recommend assessment of symptomatic improvement as the best measure of success after treatment of achalasia. Good practice recommendation

31. In adults with achalasia, there is no universal definition of failure after any treatment.

Agree: 88.4% [D + (0%); D (5.8%); U (5.8%); A (59.6%); A + (28.8%)]

Achalasia recurrence may occur after any treatment although with variable rates.[42,65,99,101,102,104,212-226] Achalasia recurrence is defined as the development of symptoms compatible with achalasia after initial improvement resulting from an endoscopic (BTI, PD, peroral esophageal myotomy (POEM)) or surgical intervention (laparoscopic or open myotomy).[42,214,227] Possible etiologies of recurrent symptoms include scarring across the myotomy, an incorrect or too tight fundoplication, GERD, peptic stricture, end-stage achalasia, and malignancy.[228] Many reports do not differentiate between persistence and recurrence of symptoms by separating patients who have experienced initial improvement from those whose symptoms never sufficiently improved.[227,229,230] Moreover persistence or recurrence of symptoms is differently defined in some cases as an Eckardt score that fails to fall to 3 or less with treatment or increases to >3 following initial successful therapy.[42,231] Others have used failure to reduce a symptom score by at least 50%.[232] A thorough evaluation of such patients is performed with esophageal manometry, upper endoscopy, contrast esophagraphy,[153,229,233-235] and sometimes computed tomography and/or esophageal pH testing.[154,228] These are important to document and quantify symptoms of recurrence, although there is no universal definition of failure of treatment.

Recommendation: see next statement.

32. Recurrent symptoms after achalasia treatment should routinely undergo repeat objective testing.

Agree: 100% [D + (0%); D (0%); U (0%); A (34.6%); A + (56.4%)].

Symptoms are typically interpreted in the framework of a standard scoring system originally designed for assessment of untreated achalasia.[65] However, recurrent symptoms may be more etiologically complex and difficult to interpret, and a standard scoring system may fail to adequately account for other components such as acid reflux[101,104,212,213,215-219] or differentiate recurrent achalasia from a peptic stricture. A careful evaluation of the nature of the recurrent symptoms, aimed at understanding the physiology and anatomy, by means of upper endoscopy, manometry, and a contrast esophagraphy is required before the diagnosis of recurrent achalasia is made.[104,153,228] A correct diagnosis of recurrent achalasia provides the foundation for the decision as to whether the reintervention is indicated, and the type of intervention in order to accomplish a high success rate. The decision to investigate further should be balanced carefully with potential risks and costs of further investigations. For example, patients undergoing first PD after confident diagnosis of achalasia may need a second dilatation (35 mm) and it may be logical to proceed with that, before undertaking further investigation.[104,153,227,228,233,236,42,65,99,101,102,212-226]

Symptom recurrence is not necessarily related to failure of achalasia therapy, and evaluation is required to determine the etiology of such symptoms. Recurrent symptoms may indicate recurrence of achalasia, but since no universal definition of recurrent achalasia exists and given the complexity of the disease, objective tests are warranted. Note: persistent symptoms such as those which persist after initial PD may be viewed differently and patients could proceed to the second dilatation before investigations.

Recommendation: we recommend objective testing in patients who suffer recurrent symptoms after treatment of achalasia including UGI endoscopy, barium swallow, manometry, and 24-H pH monitoring. Good practice recommendation

33. The timed barium swallow objectively demonstrates the failure of achalasia treatment in patients with persistent/recurrent symptoms.

Agree: 82.7% [D + (1.9%); D (5.8%); U (9.6%); A (55.8%); A + (26.9%)]

Several reports have confirmed the usefulness of the TBS as the best assessment of failure after treatment of achalasia with botulinum toxin,[237] PD,[154,229,230,235,238] Heller myotomy,[235] or POEM.[154,230] Vaezi *et al.*[232] showed that TBS was a better predictor of long-term success after PD than symptom assessment, but recent study by van Hoeij did not support this finding.[239] Other studies have also questioned the value of TBS for predicting recurrence.[123]

Recommendation: we conditionally recommend TBS as a reliable method to assess recurrence of achalasia. GRADE: Low

Risk of cancer

34. Achalasia patients carry a moderately increased risk of development of squamous esophageal cancer 10 years or more from the primary treatment of achalasia.

Agree: 86.5% [D + (1.9%); D (5.8%); U (7.7%); A (61.5%); A + (25%)]

There has been an historic association between esophageal achalasia and cancer. Two early studies

reported a high percentage of patients with achalasia dying of esophageal cancer (6 out of 125, 5%) or developing cancer during a 5-year follow-up (4 out of 124, 2%), with a 140-fold increased risk of developing cancer.[106,240] In more recent and better designed studies, the risk of cancer appears to be only 10 to 50 times higher compared than seen in the general population.[177,241,242]

Esophageal cancer may arise from the chronic inflammation of the esophageal mucosa due to food debris and saliva stasis, especially in presence of suboptimal treatment. Hypothetically, this inflammation will lead to epithelial hyperplasia, dysplasia, and eventually to squamous cancer. An alternative etiology is that the posttreatment gastroesophageal reflux causes the development of Barrett's esophagus and adenocarcinoma.[121,243,244] One large Dutch study on 448 patients (who underwent primary treatment pneumatic dilatation) with a follow-up of 15 years, showed an increased risk for esophageal cancer of 28 (CI 17–46). The majority of these cancers (12) were squamous, except three adenocarcinomas.[245] Two studies examined the mortality for esophageal cancer in achalasia patients: the first study was conducted in Italy and involved the follow-up of a single-center cohort of 229 patients treated with Heller myotomy (follow-up 12 years). The second study was conducted in Sweden on a national cohort of 2897 achalasia patients with a mean follow-up of 9.9 years.[242,246] Despite their relatively short follow-up, both studies reported a similar increase in the standardized incidence ratio of death for esophageal squamous cancer only in males of 11 (95% CI 1.33–39.7) and 13.8 (95% CI 8.1–20.4), respectively. The incidence of cancer in the Swedish study did not vary with different treatments approaches; and the excess risk was limited to squamous cancer. Pertinently, there was a long interval reported in all these studies between the diagnosis/mortality for esophageal cancer and the initial treatment of achalasia. Although we found no evidence about routine endoscopy in this group of patients, endoscopy may be used on a single patient basis and/or in case of suboptimal control of symptoms.

Recommendation: we recommend that achalasia patients should be informed that a moderately increased risk of esophageal cancer is present in male after at least 10 years from the initial treatment of the disease. Good practice recommendation.

We make no recommendation about routine endoscopy surveillance or endoscopy intervals after any treatment.

Management of treatment failures

35. Patients with achalasia who do not respond to initial treatment with graded pneumatic dilation, should be referred for Heller myotomy or POEM.

Agree: 94.2% [D + (0%); D (0%); U (5.8%); A (32.7%); A + (61.5%)]

In general, patients with achalasia have an excellent response to graded PDs;[1,101] when symptomatic recurrence after graded PD occurs, and if patients are fit for surgery, Heller myotomy is effective.[15,19,104,247] However, Snyder *et al*. compared the failure rates of laparoscopic Heller myotomy in patients who underwent no or only one preoperative endoscopic intervention compared to multiple interventions.[247,248] The incidence of surgical failure was 7% in the first group compared to 28% in the latter. Finley *et al*. performed a multivariate regression controlling for age and sex and showed that the preoperative dilation and injection of botulinum toxin were associated with significantly worse late postoperative dysphagia.[249] In a large series of 400 patients treated with laparoscopic Heller myotomy, success rates were lower if patients had prior endoscopic treatment of either both BTI or PD albeit not statistically significant.[177] Finally, in a series of 200 LHM patients,[250] multivariate analysis identified an increased failure in patients with prior endoscopic treatments (17% vs. 4%). It is however unclear from these studies to what extent previous botulinum toxin or PD is responsible for this reduction in the success rate.

Recommendation: we conditionally recommend that in patients who are fit for surgery and have symptomatic recurrences after several pneumatic dilations, Heller myotomy, or POEM should be considered. GRADE: of evidence low.

36. Laparoscopic esophageal myotomy is a safe, feasible, and effective treatment after failed BTI for achalasia.

Agree: 96.2% [D + (0%); D (0%); U (3.8%); A (38.5%); A + (57.7%)]

BTI in the LES is a safe and effective treatment for esophageal achalasia, but its effect is not durable. PDs,[251] LHM, and POEM may be used in patients with recurrences after BTI. In a study comparing BTI and LHM,[92] 10 out of 25 patients with recurrent symptoms after BTI were treated with LHM, with good results in 9. It must be emphasized that some reports have shown that LHM after BTI is more difficult,[252,253] leading to higher incidence of intraoperative complications including mucosal injury although these findings were not confirmed by others.[254,255] Less satisfactory outcomes were reported in patients undergoing LHM after BTI,[253,256] as compared to patients undergoing surgery as primary treatment. In another study,[255] the logistic regression analysis showed that prior treatment with two BTI sessions, or the combination of BTI with PD, were significantly associated with unsatisfactory outcomes after subsequent surgery. In conclusion, LHM is effective treatment after failed BTI but prior BTI may

affect outcomes and the incidences of perioperative complications.

Recommendation: we conditionally recommend LHM as an effective therapy for symptom recurrence after primary treatment with BTI. GRADE: very low.

37. PD, compared with repeat myotomy or POEM, is the first option for treatment after failed Heller myotomy for achalasia.

Agree: 80.8% [D + (0%); D (5.7%), U (13.5%); A (59.1%); A + (21.7%)]

Following LHM, 10–20% of patients with achalasia will relapse in the mid- to long-term and need further treatment. There is no consensus in the literature on the best way to approach these patients: PD, BTI, POEM, redo-myotomy, or even esophagectomy have all been reported.

PD is safe and effective in relieving achalasia symptoms after failed myotomy in 50% to 95% of patients.[223,236,257-261] All these reports were retrospective and were limited in the number of treated patients (12 to 30 cases). In a large series of 400 patients, there were 39 failures of LHM treated with PD. Patients received 2 or more PDs. The success rate was 75%.[177]

This success rate is still lower than rates reported in patients treated with PD as primary treatment (50% to 67% vs. 74% to 86%),[90,104,259] in spite of the more frequent use of the 4.0 cm dilator. The best success rate (78% to 95%) was reported by adopting an 'on demand' dilation protocol, by offering further PD on relapse.[223,236,257] In all reported series, the procedure was very safe with no perforations. In 2017 Schlottmann *et al.* reported their experience treating patients after failure of LHM: of the 19 patients with LHM failure 12 responded to PDs (63%) and 4 to PD and BTIs (20%); overall, 84% of the patients were successfully managed by endoscopic treatments.[262] Comparing patients treated with PD after failed myotomy to patients directly undergoing additional surgery showed that the efficacy of PD and redo-surgery in treating symptoms and improving esophageal emptying (as evaluated by timed barium swallow) were similar.[90] In comparison, Ngamruengphong *et al.* reported on 90 patients with failed LHM treated by POEM and demonstrated clinical success rate in 81% of patients.[37] Therefore, PD is a safe and effective treatment of recurrence after LHM (although to a lesser degree than in patients undergoing primary dilation treatment), therefore it is reasonable to offer the patient this possibility before planning more invasive therapies as LHM or POEM.

Recommendation: we conditionally recommend pneumatic dilation as a safe and effective treatment of symptom recurrences after LHM. GRADE: Low

38. There is insufficient evidence that the laparoscopic myotomy or re-do POEM offer better results than pneumatic dilations after failed POEM.

Agree: 82.4% [D + (0%); D (5.8%); U (11.8%); A (66.7%); A + (15.7%)]

Recurrent or persistent symptoms following POEM do occur and there is no general agreement as to how these relapsing patients should be managed. One recent paper from Shanghai[234] reported on 15 patients with recurrent symptoms after POEM (Eckardt score >3), (1% of 1454 patients in whom POEM was performed). All 15 were treated with repeat POEM as salvage therapy. Relief of symptoms at 11 ± 6 months was reported in all the patients expressed as mean Eckardt score decreasing from 5.6 ± 1.1 to 1.2 ± 1.1. In two European and 1 North-American tertiary-care hospitals, evaluating patients enrolled in ongoing trials,[227,263] 43 patients with recurrent symptoms after POEM were identified, representing 9.8% of 441 treated patients. PDs up to 35 mm were performed in 15 of these patients with effective outcomes seen in only 3. Further dilations with a 40-mm balloon were not effective. Eight patients underwent a repeat POEM, which was effective in 5, and 11 underwent rescue LHM, that was effective in 5. Although these numbers failed to reach statistical significance for the small sample size, PD showed poor efficacy in treating patients with a failed POEM, as compared to LHM or redo POEM. After a failed POEM, repeated treatment with a new POEM or LHM appears to be better options than PD. It should be noted, however, that most studies highlighted that repeated POEM may be technically demanding, due to fibrosis from the initial treatment.[227,263]

Recommendation: we make no recommendation about laparoscopic myotomy or redo POEM offering better symptomatic relief than pneumatic dilations after failed POEM. Further research is recommended to provide high quality data and guide clinical decisions.

Diagnosis and treatment of end stage achalasia

39. Barium swallow esophagram, compared with manometry, is the best diagnostic method for defining end stage achalasia (i.e. that which requires esophagectomy).

Agree: 94.1% [D + (2%); D (2%); U (2%); A (59.5%); A + (34.6%)]

Barium esophography provides the best information regarding esophageal anatomy associated with end-stage achalasia. Anatomic features are better appreciated on esophagogram as compared to endoscopy and include assessment of esophageal diameter, retention of food and saliva, a sigmoid appearance of the esophageal body and a sump-shaped portion of the distal esophagus and of the

gastroesophageal junction.[264] The presence of extensive esophageal debris may also signal the need for drainage and anesthesia assistance prior to endoscopic evaluation. Several reports have utilized barium studies to assess end-stage achalasia and indicate the need for esophagectomy.[265-267] Other tests had only a secondary role in defining end-stage achalasia, for example, endoscopy to assess for stasis esophagitis, reflux stricture, or cancer.[264-266] Manometry may prove difficult because of the technical challenges with insertion in a dilated, tortuous, fluid, and food filled esophagus.[268]

Recommendation: we recommend the use of barium swallow as the most accurate investigation to properly define end-stage achalasia. Good practice recommendation.

40. Esophagectomy is indicated in patients with persistent or recurrent achalasia after failure of previous less invasive treatments (PD, POEM, LHM) and radiologic progression of the disease.

Agree: 80.8% [D + (0%); D (3.8%); U (15.4%); A (40.4%); A + (40.4%)]

When all conservative strategies failed, esophagectomy is the last resort to manage achalasia. Esophagectomy is associated with a high rate of complications and surgical mortality rate. All effort must therefore be focused on managing patients with recurrent symptoms after surgery with less invasive treatments, such as POEM or repeated myotomy or 'on demand' PD. However, patients should be carefully followed up to promptly identify when esophagectomy is necessary, before a patient's condition and nutritional status deteriorates and increases the risk and complexity of esophageal resection. Good or excellent results of esophagectomy in 37 achalasia patients were reported by Miller[269] in the 'open' surgical era, but the complication rate associated with esophagectomy was high (32.4%) and the perioperative mortality was 5.4%. A predictive factor for the need of esophagectomy is the presence of a massively dilated esophagus (>6 cm).[235,270] Loviscek subdivided his patients with esophagus >6 cm into those with a tortuous megaesophagus and all the patients who underwent an esophagectomy (4/504) were in this last group. Overall, esophagectomy was required in less than 1% of their entire population of 504 patients, but it was ultimately required in 17% of those who relapsed after previous surgical treatment.[235]

Recommendation: we conditionally recommend esophagectomy in patients with end-stage achalasia who have failed other interventions. GRADE Low

Achalasia in children

41. Children with suspected achalasia should follow the same diagnostic pathway as that of adult patients.

Agree: 96% [D + (0%); D (2%); U (2%); A (66%); A + (30%)]

There are no systematic studies defining the optimal diagnostic regime in children. Older children (aged 10 to 17) can and should undergo a work-up similar to adults; with endoscopy, high-resolution manometry and a standard or timed barium swallow study.

Obtaining some of these studies in infants and small children may be difficult due to size mismatch and compliance. In a cohort of 42 pediatric patients,[271] all had a barium study and endoscopy. 38 patients had manometry with 4 being too young to tolerate the test. Unlike adults, biopsies of the GEJ are not mandatory for the pediatric population due to low risk of cancer in this population.

Recommendation: we recommend that children with a provisional diagnosis of achalasia should undergo the same work-up as in the adult population. Good practice recommendation.

42. Surgical or endoscopic myotomy (compared to dilation) is the preferred treatment for pediatric patients with idiopathic achalasia, especially for those aged 5 years or more.

Agree: 80% [D + (0%); D (6%); U (14%); A (56%); A + (24%)]

All treatments for achalasia have been shown to be safe and effective in the pediatric population.[272-276] Transthoracic open or thoracoscopic approaches[275] have been mostly abandoned due to access trauma, poor outcomes in the adult experience and inability to add a partial fundoplication. Instead, an open abdominal or laparoscopic approach is now the only accepted method accepted in pediatric patients.

While open Heller myotomy is long established and safe, most centers have converted to less invasive laparoscopic access. Pastor *et al*., in a large single center retrospective study documents this institutional conversion from open to laparoscopic Heller and confirms its equal effectiveness and patient benefit.[277] Pneumatic balloon dilation remains a popular option for the pediatric population, though less so than for adults due, once again, to concerns over the potential need of multiple reinterventions over the patient's lifespan. Another concern is the issue of balloon size mismatch for the younger children, which limits application of balloon dilation to children over the age of 5 years. DiNardo *et al*. reported an 87% success rate of PD in pediatric patients >5 years with 6 years follow-up although patients required an average of three treatments.[274] LHM is often considered the first-line treatment for pediatric achalasia. Numerous papers have shown it to be a safe and effective therapy. Similar to laparoscopic adult surgery, it is usually accompanied by a partial fundoplication, with no conclusion regarding the superiority of a Dor or Toupet fundoplication. Lee *et al*. presented a retrospective comparison between surgery or PD.[278] They concluded that, in the

pediatric population, laparoscopic Heller with partial fundoplication was the best treatment for achalasia.

Today, there are several case series describing POEM in the pediatric population and showing it is both feasible and safe[273,279,280] but there are only a few series from pediatric hospitals introducing the new approach into their treatment algorithm.[279] Outcomes were the same regardless of who performed the procedure. As with PD, there were concerns that the size of therapeutic endoscopic instrumentation might be too large for small infants although the youngest patients in case series are 5 years old and in anecdotal patients as young as 2 years have been done. Data to date has shown POEM to be equivalent if not better than PD or LHM in relief of dysphagia.[273,281] While some investigators have suggested that the reflux prevention may be less essential in the pediatric population,[282,283] it may be that POEM is the ultimate preferred initial strategy in the pediatric population, but it should be borne in mind that abnormal reflux after POEM has the potential to lead to dysplasia or adenocarcinoma in the esophagus in later life.

Recommendation: we conditionally recommend myotomy (either through a laparoscopic or flexible endoscopy approach) as the preferred treatment in children. GRADE: very low.

43. BTI is not an appropriate first-line therapy in very young children with achalasia.

Agree: 81.6% [D + (0%); D (6.2%); U (12.2%); A (36.7%); A + (44.9%)]

BTI likewise has good short-term effect (Ip 2000) but the short duration of its efficacy (Ip 2000), makes it unappealing in pediatric patients.[271,273,281,283,284]

Recommendation: we recommend against BTI as a first-line therapy in very young children with achalasia, with exceptions for those children who are medically frail and at high-risk for surgical intervention. Conditional recommendation. GRADE: very low.

44. The long-term outcome of achalasia treatment in children should be assessed by symptoms, function, physical growth, and general development.

Agree: 94% [D + (0%); D (0%); U (6%); A (46%); A + (48%)]

All series of pediatric achalasia treatments have in common that the treatment immediately improves the patients' QOL and reverses weight loss and failure to thrive.[285-287] Most patients will need repeat treatments over time, particularly patients having BTI or PD as an initial treatment. Smits *et al.*, described the longitudinal experience in the Netherlands where 88% of PD treated patients had repeat treatment therapy required in 22% of patients after Heller myotomy.[287] A further 26-year single institution series showed that 83% of PD treated patients had repeated interventions versus 30% of the myotomy patients.[277] In this series, of the 83% who had repeated interventions, 53% of the initial PD patients had repeated PD and 30% went on eventually to myotomy. The initial myotomy patients who required repeated interventions had either redo myotomy or in one case, an esophagectomy. Long term follow-up demonstrates a recurrent need for interventions and a relatively high incidence of residual or recurrent symptoms. In the Dutch longitudinal study, with 10-year follow-up, Eckardt scores >3 was seen in 45% of patients (equal between PD and HM). GERD symptoms were also common at long-term follow-up with 76% of initial Heller patients reporting GERD symptoms and 33% of post PD patients. These symptoms impact QOL with scores for general and achalasia specific QOL being lower in almost all domains compared to age matched population norms.[287]

Recommendation: we recommend that the long-term outcome of achalasia treatment in children should be closely monitored by symptoms, swallowing function, physical growth, and general development. Good practice recommendation.

Diagnosis and management of achalasia secondary to Chagas disease

45. There are minor differences between the clinical presentation of idiopathic achalasia and achalasia secondary to Chagas disease.

Agree: 86.2% [D + (0%); D (2%); U (11.8%); A (64.7%); A + (21.5%)]

Chagas disease esophagopathy (CDE) is caused by the infection of the flagellated protozoan *Trypanosoma cruzi*, which causes the destruction of the esophageal autonomic nervous system leading to a clinical presentation similar to IA.[288-291] Although IA and CDE are very similar, some differences have been observed between them. The common pathological pathways in IA and CDE are the loss of neurons of the myenteric plexus of the esophagus.[291,292] However, in IA there is a selective loss of inhibitory neurons, whereas in CDE both excitatory and inhibitory neurons are compromised. Several studies have shown that LES pressure in IA is increased,[289,291,293,294] conversely, in CDE, LES pressure may be decreased, normal or increased.[288,293,295-298] The two diseases present a hypersensitivity of the LES to gastrin, and a predominance of alfa-adrenergic innervation,[289,293] but a different response to botulinum toxin injection that causes the pressure to decrease in IA but only a partial response in CDE. From a manometric point of view, most patients with CDE have low amplitude contractions.

These differences in the two diseases do not significantly influence the clinical presentation: solid food dysphagia is the most prevalent symptom (98.8% of cases); regurgitation, halitosis, pyrosis, and chest pain were present in more than 60% of CDE patients.[299]

In patients with IA, the age of presentation is similar between both nonadvanced and advanced achalasia, although symptom duration is significantly longer in the latter. Given that the two diseases have similar motor abnormalities of the LES and esophageal body, the possibilities of treatment are much the same and the choice of the best option for each patient depends on the clinical and radiological presentation and on the experience of the medical service that will perform the therapy.[288,290,292,293] In conclusion, IA and CDE present some minor differences in esophageal motility, but manometric and clinical findings are similar.

Recommendation: we conditionally recommend that diagnostic techniques used for IA should also be used for CDE, due to the similarities in manometric and clinical features. GRADE: low.

46. There are no differences in the treatment of idiopathic achalasia and achalasia specific to Chagas disease.

Agree: 90% [D + (0%); D (2%); U (8%); A (62%); A + (28%)]

All treatments for IA may be used in patients with CDE. In these patients, however, a careful preoperative evaluation is mandatory for the associated involvement of heart, colon, and gallbladder.[7,300] While the progression of CDE is slow, late presentation is common and most of these patients present with esophageal dilation in which can be massive in 10 to 40% of them. In one study[87] BTI was effective in 58% of patients at 6 month follow-up. Good and/or excellent results have been obtained by PD, though a recurrence rate up to 30% was reported.[7,300-302] Heller myotomy (or some modification of it) with anterior or posterior partial fundoplication has been adopted.[300,303-305] A significant number of patients with CDE present for the first time to treatment with end-stage disease, with atonic and dilated esophagus, and esophagectomy is required as primary therapy,[306-309] although several groups opted for a first less invasive approach.[310] Given the high number of patients with a massively dilated esophagus and the risk of esophagectomy, alternative procedures have been suggested including: cardioplasty plus truncal vagotomy and Roux-en-Y partial gastrectomy, Thal-Hatafuku operation, or Merendino operation.[7,307,311-313] Currently, the indications for esophageal resection are: end-stage disease, both as the initial treatment or after failure of conservative operations; concomitant premalignant or malignant lesions of the esophagus; and esophageal perforation unsuitable for repair during diagnostic tests, therapeutic endoscopy or intraoperatively.[7,300,306,308,309]

Recommendation: we conditionally recommend that all treatments for IA may be used for CDE for symptom relief. GRADE: low.

Appendix 1: search strategies

The search strategy for Medline included the following key-words: 'Esophageal achalasia' 'AND/OR' 'Esophageal Manometry' 'High Resolution Esophageal manometry'; 'Chicago classification'; 'Barium Swallow'; 'Timed barium swallow'; 'Endoscopy'; 'Pseudoachalasia'; 'Symptom' 'Score Symptom' 'Medical treatment'; 'Nitrates'; 'Calcium blockers'; 'Sildenafil'; 'Botulinum Toxin'; 'Pneumatic Dilatation'; Graded Pneumatic Dilatation'; 'Esophageal Perforation'; 'Complication'; 'Per-oral endoscopic myotomy (POEM)'; 'Heller Myotomy'; 'Laparoscopic Heller Myotomy'; 'Fundoplication'; 'Recurrence'; 'Failure'; Megaesophagus' 'End-stage Achalasia'; 'Esophagectomy'; 'Esophageal Resection'; 'Re-intervention'; 'Chagas Disease'; 'Children'; Genetic Disease.

The search strategies for the other databases were adapted to the specific vocabulary of each database. In December 2017, we conducted a further search limited to the year 2017 (up to December 2017) to update the references (using the MeSH term: esophageal achalasia).

ACKNOWLEDGMENTS

These Guidelines were funded by:

ISDE International Society for Esophageal Diseases

Morgagni Foundation –ESO- ONLUS

Department of Surgical, Oncological and Gastroenterologica Sciences, University of Padua, Padua, Italy.

ALMA –ONLUS (Association of Patients with Achalasia)

(in order of contribution)

The Guidelines were endorsed by:

ISDE International society for Esophageal Diseases

Coordinamento Malattie Rare Regione Veneto

References

1 Boeckxstaens G E, Zaninotto G, Richter J E. Achalasia. Lancet 2014; 383: 83–93.
2 Clark S B, Rice T W, Tubbs R R, Richter J E, Goldblum J R. The nature of the myenteric infiltrate in achalasia: an immunohistochemical analysis. Am J Surg Pathol 2000; 24: 1153–8.
3 Goldblum J R, Rice T W, Richter J E. Histopathologic features in esophagomyotomy specimens from patients with achalasia. Gastroenterology 1996; 111: 648–54.
4 Villanacci V, Annese V, Cuttitta A *et al.* An immunohistochemical study of the myenteric plexus in idiopathic achalasia. J Clin Gastroenterol 2010; 44: 407–10.
5 Tracey J P, Traube M. Difficulties in the diagnosis of pseudoachalasia. Am J Gastroenterol 1994; 89: 2014–8.
6 Hejazi R A, Zhang D, McCallum R W. Gastroparesis, pseudoachalasia and impaired intestinal motility as paraneoplastic manifestations of small cell lung cancer. Am J Med Sci 2009; 338: 69–71.

7 Herbella F A, Aquino J L, Stefani-Nakano S *et al.* Treatment of achalasia: lessons learned with Chagas' disease. Dis Esophagus 2008; 21: 461–7.
8 Farrukh A, DeCaestecker J, Mayberry J F. An epidemiological study of achalasia among the south asian population of leicester, 1986–2005. Dysphagia 2008; 23: 161–4.
9 Sadowski D C, Ackah F, Jiang B, Svenson L W. Achalasia: incidence, prevalence and survival. A population-based study. Neurogastroenterol Motil 2010; 22: e256–61.
10 Birgisson S, Richter J E. Achalasia in Iceland, 1952–2002: an epidemiologic study. Dig Dis Sci 2007; 52: 1855–60.
11 Gennaro N, Portale G, Gallo C *et al.* Esophageal achalasia in the Veneto region: epidemiology and treatment. Epidemiology and treatment of achalasia. J Gastrointest Surg 2011; 15: 423–8.
12 van Hoeij F B, Ponds F A, Smout A J, Bredenoord A J. Incidence and costs of achalasia in The Netherlands. Neurogastroenterol Motil 2018; 30 (2) doi: 10.1111/nmo.13195.
13 Duffield J A, Hamer P W, Heddle R, Holloway R H, Myers J C, Thompson S K. Incidence of achalasia in South Australia based on esophageal manometry findings. Clin Gastroenterol Hepatol 2017; 15: 360–5.
14 Samo S, Carlson D A, Gregory D L, Gawel S H, Pandolfino J E, Kahrilas P J. Incidence and prevalence of achalasia in Central Chicago, 2004–2014, since the widespread use of high-resolution manometry. Clin Gastroenterol Hepatol 2017; 15: 366–73.
15 Triadafilopoulos G, Boeckxstaens G E, Gullo R *et al.* The Kagoshima consensus on esophageal achalasia. Dis Esophagus 2012; 25: 337–48.
16 Pandolfino J E, Ghosh S K, Rice J, Clarke J O, Kwiatek M A, Kahrilas P J. Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. Am J Gastroenterol 2008; 103: 27–37.
17 Pandolfino J E, Kwiatek M A, Nealis T, Bulsiewicz W, Post J, Kahrilas P J. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology 2008; 135: 1526–33.
18 Inoue H, Minami H, Kobayashi Y *et al.* Peroral endoscopic myotomy (POEM) for esophageal achalasia. Endoscopy 2010; 42: 265–71.
19 Vaezi M F, Pandolfino J E, Vela M F. ACG clinical guideline: diagnosis and management of achalasia. Am J Gastroenterol 2013; 108: 1238–49; quiz 50.
20 Stefanidis D, Richardson W, Farrell T M, Kohn G P, Augenstein V, Fanelli R D. SAGES guidelines for the surgical treatment of esophageal achalasia. Surg Endosc 2012; 26: 296–311.
21 Pai M, Iorio A, Meerpohl J *et al.* Developing methodology for the creation of clinical practice guidelines for rare diseases: a report from RARE-Bestpractices. Rare Dis 2015; 3: e1058463.
22 Bennett C, Moayyedi P, Corley D A *et al.* BOB CAT: a large-scale review and Delphi consensus for management of Barrett's esophagus with no dysplasia, indefinite for, or low-grade dysplasia. Am J Gastroenterol 2015; 110: 662–82; quiz 83.
23 Bennett C, Vakil N, Bergman J *et al.* Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process. Gastroenterology 2012; 143: 336–46.
24 Rutter M D, Senore C, Bisschops R *et al.* The European Society of Gastrointestinal Endoscopy quality improvement initiative: developing performance measures. United Eur Gastroenterol J 2016; 4: 30–41.
25 NICE. NICE accrediation decision. 'Final accrediation report': https://www.nice.org.uk/Media/Default/About/accreditation/accreditation-decisions/BAD-CAT-consensus-group-final-decision.pdf. 2012.
26 Guyatt G, Oxman A D, Akl E A *et al.* GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011; 64: 383–94.
27 Guyatt G H, Oxman A D, Vist G E *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336: 924–6.
28 GRADEproGDT. GRADEpro Guideline Development Tool [Software]. McMaster University: Evidence Prime, Inc., 2015.
29 Guyatt G H, Oxman A D, Kunz R *et al.* Going from evidence to recommendations. BMJ 2008; 336: 1049–51.
30 Andrews J, Guyatt G, Oxman A D *et al.* GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013; 66: 719–25.
31 Andrews J C, Schunemann H J, Oxman A D *et al.* GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. J Clin Epidemiol 2013; 66: 726–35.
32 Guyatt G H, Schunemann H J, Djulbegovic B, Akl E A. Guideline panels should not GRADE good practice statements. J Clin Epidemiol 2015; 68: 597–600.
33 Richter J E. High-resolution manometry in diagnosis and treatment of achalasia: help or hype. Curr Gastroenterol Rep 2014; 16: 420.
34 Carlson D A, Lin Z, Kahrilas P J *et al.* The functional lumen imaging probe detects esophageal contractility not observed with manometry in patients with achalasia. Gastroenterology 2015; 149: 1742–51.
35 Pandolfino J E, Fox M R, Bredenoord A J, Kahrilas P J. High-resolution manometry in clinical practice: utilizing pressure topography to classify oesophageal motility abnormalities. Neurogastroenterol Motil 2009; 21: 796–806.
36 Roman S, Huot L, Zerbib F *et al.* High-resolution manometry improves the diagnosis of esophageal motility disorders in patients with dysphagia: a randomized multicenter study. Am J Gastroenterol 2016; 111: 372–80.
37 Ngamruengphong S, Inoue H, Chiu P W *et al.* RETRACTED: long-term outcomes of per-oral endoscopic myotomy in patients with achalasia with a minimum follow-up of 2 years: an international multicenter study. Gastrointest Endosc 2017; 85: 927–933.e2.
38 Niebisch S, Hadzijusufovic E, Mehdorn M *et al.* Achalasia—an unnecessary long way to diagnosis. Dis Esophagus 2017; 30: 1–6.
39 Kahrilas P J, Bredenoord A J, Fox M *et al.* The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015; 27: 160–74.
40 Rohof W O, Salvador R, Annese V *et al.* Outcomes of treatment for achalasia depend on manometric subtype. Gastroenterology 2013; 144: 718–25; quiz e13-4.
41 Salvador R, Costantini M, Zaninotto G *et al.* The preoperative manometric pattern predicts the outcome of surgical treatment for esophageal achalasia. J Gastrointest Surg 2010; 14: 1635–45.
42 Yamashita H, Ashida K, Fukuchi T *et al.* Predictive factors associated with the success of pneumatic dilatation in Japanese patients with primary achalasia: a study using high-resolution manometry. Digestion 2013; 87: 23–28.
43 Katada N, Sakuramoto S, Yamashita K *et al.* Comparison of the Heller–Toupet procedure with the Heller–Dor procedure in patients who underwent laparoscopic surgery for achalasia. Surg Today 2014; 44: 732–9.
44 Kumbhari V, Saxena P, Messallam A A *et al.* Fluoroscopy to document the extent of cardiomyotomy during peroral endoscopic myotomy. Endoscopy 2014; 46: E369–70.
45 de Oliveira J M, Birgisson S, Doinoff C *et al.* Timed barium swallow: a simple technique for evaluating esophageal emptying in patients with achalasia. Am J Roentgenol 1997; 169: 473–9.
46 Kostic S V, Rice T W, Baker M E *et al.* Timed barium esophagogram: a simple physiologic assessment for achalasia. J Thorac Cardiovasc Surg 2000; 120: 935–46.
47 Andersson M, Lundell L, Kostic S *et al.* Evaluation of the response to treatment in patients with idiopathic achalasia by the timed barium esophagogram: results from a randomized clinical trial. Dis Esophagus 2009; 22: 264–73.
48 Rohof W O, Lei A, Boeckxstaens G E. Esophageal stasis on a timed barium esophagogram predicts recurrent symptoms in patients with long-standing achalasia. Am J Gastroenterol 2013; 108: 49–55.
49 Blonski W, Kumar A, Feldman J, Richter J E. Timed barium swallow: diagnostic role and predictive value in untreated achalasia, esophagogastric junction outflow obstruction, and non-achalasia dysphagia. Am J Gastroenterol 2018; 113: 196–203.
50 van Hoeij F B, Bredenoord A J. Clinical application of esophageal high-resolution manometry in the diagnosis of

esophageal motility disorders. J Neurogastroenterol Motil 2016; 22: 6–13.
51 Krieger-Grubel C, Tutuian R, Borovicka J. Correlation of esophageal clearance and dysphagia symptom assessment after treatment for achalasia. United Eur Gastroenterol J 2016; 4: 55–61.
52 Reynolds J C, Parkman H P. Achalasia. Gastroenterol Clin North Am 1989; 18: 223–55.
53 Vaezi M F. The American college of gastroenterology's new guidelines on achalasia: What clinicians need to know. Curr Gastroenterol Rep 2013; 15: 358.
54 O'Neill O M, Johnston B T, Coleman H G. Achalasia: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2013; 19: 5806–12.
55 Stavropoulos S N, Friedel D, Modayil R, Parkman H P. Diagnosis and management of esophageal achalasia. BMJ 2016; 354: i2785.
56 Krill J T, Naik R D, Vaezi M F. Clinical management of achalasia: current state of the art. Clin Exp Gastroenterol 2016; 9: 71–82.
57 Tucker H J, Snape W J, Jr, Cohen S. Achalasia secondary to carcinoma: manometric and clinical features. Ann Intern Med 1978; 89: 315–8.
58 Woodfield C A, Levine M S, Rubesin S E, Langlotz C P, Laufer I. Diagnosis of primary versus secondary achalasia: reassessment of clinical and radiographic criteria. Am J Roentgenol 2000; 175: 727–31.
59 Sandler R S, Bozymski E M, Orlando R C. Failure of clinical criteria to distinguish between primary achalasia and achalasia secondary to tumor. Digest Dis Sci 1982; 27: 209–13.
60 Abubakar U, Bashir M B, Kesieme E B. Pseudoachalasia: a review. Niger J Clin Pract 2016; 19: 303–7.
61 Vaezi M F, Felix V N, Penagini R *et al.* Achalasia: from diagnosis to management. Ann NY Acad Sci 2016; 1381: 34–44.
62 Kahrilas P J. Treating achalasia: more than just flipping a coin. Gut 2016; 65: 726–7.
63 Bryant R V, Holloway R H, Nguyen N Q. Gastrointestinal: role of endoscopic ultrasound in the evaluation of pseudoachalasia. J Gastroenterol Hepatol 2012; 27: 1128.
64 Ponds F A, van Raath M I, Mohamed S M M, Smout A, Bredenoord A J. Diagnostic features of malignancy-associated pseudoachalasia. Aliment Pharmacol Ther 2017; 45: 1449–58.
65 Eckardt V F, Gockel I, Bernhard G. Pneumatic dilation for achalasia: late results of a prospective follow up investigation. Gut 2004; 53: 629–33.
66 Patel D A, Sharda R, Hovis K L *et al.* Patient-reported outcome measures in dysphagia: a systematic review of instrument development and validation. Dis Esophagus 2017; 30: 1–23.
67 Urbach D R, Tomlinson G A, Harnish J L, Martino R, Diamant N E. A measure of disease-specific health-related quality of life for achalasia. Am J Gastroenterol 2005; 100: 1668–76.
68 Taft T H, Carlson D A, Triggs J *et al.* Evaluating the reliability and construct validity of the Eckardt symptom score as a measure of achalasia severity. Neurogastroenterol Motil 2018; 30: e13287.
69 Gelfond M, Rozen P, Gilat T. Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. Gastroenterology 1982; 83: 963–9.
70 Wen Z H, Gardener E, Wang Y P. Nitrates for achalasia. Cochrane Database Syst Rev 2004: Cd002299.
71 Bassotti G, Annese V. Review article: pharmacological options in achalasia. Aliment Pharmacol Ther 1999; 13: 1391–6.
72 Storr M, Allescher H D. Esophageal pharmacology and treatment of primary motility disorders. Dis Esophagus 1999; 12: 241–57.
73 Annese V, Bassotti G. Non-surgical treatment of esophageal achalasia. World J Gastroenterol 2006; 12: 5763–6.
74 Roman S, Kahrilas P J. Management of spastic disorders of the esophagus. Gastroenterol Clin North Am 2013; 42: 27–43.
75 Triadafilopoulos G, Aaronson M, Sackel S, Burakoff R. Medical treatment of esophageal achalasia. Digest Dis Sci 1991; 36: 260–7.
76 Bortolotti M, Labo G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. Gastroenterology 1981; 80: 39–44.
77 Nasrallah S M, Tommaso C L, Singleton R T, Backhaus E A. Primary esophageal motor disorders: clinical response to nifedipine. South Med J 1985; 78: 312–5.
78 Traube M, Dubovik S, Lange R C, McCallum R W. The role of nifedipine therapy in achalasia: results of a randomized, double-blind, placebo-controlled study. Am J Gastroenterol 1989; 84: 1259–62.
79 Maradey-Romero C, Gabbard S, Fass R. Treatment of esophageal motility disorders based on the Chicago classification. Curr Treat Options Gastroenterol 2014; 12: 441–55.
80 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.
81 Simren M, Silny J, Holloway R, Tack J, Janssens J, Sifrim D. Relevance of ineffective oesophageal motility during oesophageal acid clearance. Gut 2003; 52: 784–90.
82 Eherer A J, Schwetz I, Hammer H F *et al.* Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. Gut 2002; 50: 758–64.
83 Fox M, Sweis R, Wong T, Anggiansah A. Sildenafil relieves symptoms and normalizes motility in patients with oesophageal spasm: a report of two cases. Neurogastroenterol Motil 2007; 19: 798–803.
84 Allescher H D, Storr M, Seige M *et al.* Treatment of achalasia: botulinum toxin injection vs. pneumatic balloon dilation. A prospective study with long-term follow-up. Endoscopy 2001; 33: 1007–17.
85 Annese V, Basciani M, Perri F *et al.* Controlled trial of botulinum toxin injection versus placebo and pneumatic dilation in achalasia. Gastroenterology 1996; 111: 1418–24.
86 Bansal R, Nostrant T T, Scheiman J M *et al.* Intrasphincteric botulinum toxin versus pneumatic balloon dilation for treatment of primary achalasia. J Clin Gastroenterol 2003; 36: 209–14.
87 Brant C, Moraes-Filho J P, Siqueira E *et al.* Intrasphincteric botulinum toxin injection in the treatment of chagasic achalasia. Dis Esophagus 2003; 16: 33–38.
88 Muehldorfer S M, Schneider T H, Hochberger J, Martus P, Hahn E G, Ell C. Esophageal achalasia: intrasphincteric injection of botulinum toxin A versus balloon dilation. Endoscopy 1999; 31: 517–21.
89 Neubrand M, Scheurlen C, Schepke M, Sauerbruch T. Long-term results and prognostic factors in the treatment of achalasia with botulinum toxin. Endoscopy 2002; 34: 519–23.
90 Vela M F, Richter J E, Wachsberger D, Connor J, Rice T W. Complexities of managing achalasia at a tertiary referral center: use of pneumatic dilatation, Heller myotomy, and botulinum toxin injection. Am J Gastroenterol 2004; 99: 1029–36.
91 van Hoeij FB Tack J F, Pandolfino J E *et al.* Complications of botulinum toxin injections for treatment of esophageal motility disorders dagger. Dis Esophagus 2017; 30: 1–5.
92 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.
93 Vaezi M F, Richter J E, Wilcox C M *et al.* Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomised trial. Gut 1999; 44: 231–9.
94 Ghoshal U C, Chaudhuri S, Pal B B, Dhar K, Ray G, Banerjee P K. Randomized controlled trial of intrasphincteric botulinum toxin A injection versus balloon dilatation in treatment of achalasia cardia. Dis Esophagus 2001; 14: 227–31.
95 Mikaeli J, Fazel A, Montazeri G, Yaghoobi M, Malekzadeh R. Randomized controlled trial comparing botulinum toxin injection to pneumatic dilatation for the treatment of achalasia. Aliment Pharmacol Ther 2001; 15: 1389–96.
96 Leyden J E, Moss A C, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Cochrane Database Syst Rev 2014: Cd005046.
97 D'Onofrio V, Miletto P, Leandro G, Iaquinto G. Long-term follow-up of achalasia patients treated with botulinum toxin. Dig Liver Dis 2002; 34: 105–10.
98 Pasricha P J, Ravich W J, Hendrix T R, Sostre S, Jones B, Kalloo A N. Treatment of achalasia with intrasphincteric

injection of botulinum toxin: a pilot trial. Ann Intern Med 1994; 121: 590–1.
99 Martinek J, Spicak J. A modified method of botulinum toxin injection in patients with achalasia: a pilot trial. Endoscopy 2003; 35: 841–4.
100 Pasricha P J, Rai R, Ravich W J, Hendrix T R, Kalloo A N. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology 1996; 110: 1410–5.
101 Zerbib F, Thetiot V, Richy F, Benajah D A, Message L, Lamouliatte H. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. Am J Gastroenterol 2006; 101: 692–7.
102 Hulselmans M, Vanuytsel T, Degreef T *et al.* Long-term outcome of pneumatic dilation in the treatment of achalasia. Clin Gastroenterol Hepatol 2010; 8: 30–35.
103 Bravi I, Nicita M T, Duca P *et al.* A pneumatic dilation strategy in achalasia: prospective outcome and effects on oesophageal motor function in the long term. Aliment Pharmacol Ther 2010; 31: 658–65.
104 Vela M F, Richter J E, 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.
105 Boeckxstaens G E, Annese V, des Varannes S B *et al.* Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. N Engl J Med 2011; 364: 1807–16.
106 West R L, Hirsch D P, Bartelsman J F *et al.* Long term results of pneumatic dilation in achalasia followed for more than 5 years. Am J Gastroenterol 2002; 97: 1346–51.
107 Elliott T R, Wu P I, Fuentealba S, Szczesniak M, de Carle D J, Cook I J. Long-term outcome following pneumatic dilatation as initial therapy for idiopathic achalasia: an 18-year single-centre experience. Aliment Pharmacol Ther 2013; 37: 1210–9.
108 Katzka D A, Castell D O. Review article: an analysis of the efficacy, perforation rates and methods used in pneumatic dilation for achalasia. Aliment Pharmacol Ther 2011; 34: 832–9.
109 Borges A A, Lemme E M, Abrahao L J, Jr *et al.* Pneumatic dilation versus laparoscopic Heller myotomy for the treatment of achalasia: Variables related to a good response. Dis Esophagus 2014; 27: 18–23.
110 Kostic S, Kjellin A, Ruth M *et al.* Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. World J Surg 2007; 31: 470–8.
111 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.
112 Novais P A, Lemme E M. 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.
113 Cheng J W, Li Y, Xing W Q, Lv H W, Wang H R. Laparoscopic Heller myotomy is not superior to pneumatic dilation in the management of primary achalasia: conclusions of a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2017; 96: e5525.
114 Schoenberg M B, Marx S, Kersten J F *et al.* Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. Ann Surg 2013; 258: 943–52.
115 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.
116 Borotto E, Gaudric M, Danel B *et al.* Risk factors of oesophageal perforation during pneumatic dilatation for achalasia. Gut 1996; 39: 9–12.
117 Vanuytsel T, Lerut T, Coosemans W *et al.* Conservative management of esophageal perforations during pneumatic dilation for idiopathic esophageal achalasia. Clin Gastroenterol Hepatol 2012; 10: 142–9.
118 Zori A G, Kirtane T S, Gupte A R *et al.* Utility of clinical suspicion and endoscopic re-examination for detection of esophagogastric perforation after pneumatic dilation for achalasia. Endoscopy 2016; 48: 128–33.
119 Khan A A, Shah S W, Alam A, Butt A K, Shafqat F, Castell D O. Massively dilated esophagus in achalasia: response to pneumatic balloon dilation. Am J Gastroenterol 1999; 94: 2363–6.
120 Leeuwenburgh I, Van Dekken H Scholten P *et al.* Oesophagitis is common in patients with achalasia after pneumatic dilatation. Aliment Pharmacol Ther 2006; 23: 1197–203.
121 Leeuwenburgh I, Scholten P, Calje T J *et al.* Barrett's esophagus and esophageal adenocarcinoma are common after treatment for achalasia. Dig Dis Sci 2013; 58: 244–52.
122 Min Y W, Lee J H, Min B H, Lee J H, Kim J J, Rhee P L. Association between gastroesophageal reflux disease after pneumatic balloon dilatation and clinical course in patients with achalasia. J Neurogastroenterol Motil 2014; 20: 212–8.
123 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.
124 Mauro A, Franchina M, Elvevi A *et al.* Yield of prolonged wireless pH monitoring in achalasia patients successfully treated with pneumatic dilation. United Eur Gastroenterol J 2017; 5: 789–95.
125 Von Renteln D Fuchs K H, Fockens P *et al.* Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. Gastroenterology 2013; 145: 309–11. e1-3.
126 Swanstrom L L, Kurian A, Dunst C M, Sharata A, Bhayani N, Rieder E. Long-term outcomes of an endoscopic myotomy for achalasia: the POEM procedure. Ann Surg 2012; 256: 659–67.
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.
128 Stavropoulos S N, Modayil R J, 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.
129 Stavropoulos S N, Desilets D J, Fuchs K H *et al.* Per-oral endoscopic myotomy white paper summary. Gastrointest Endosc 2014; 80: 1–15.
130 Patel K, Abbassi-Ghadi N, Markar S, Kumar S, Jethwa P, Zaninotto G. Peroral endoscopic myotomy for the treatment of esophageal achalasia: systematic review and pooled analysis. Dis Esophagus 2016; 29: 807–19.
131 Bhayani N H, Kurian A A, Dunst C M, Sharata A M, Rieder E, Swanstrom L L. 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.
132 Zhang Y, Wang H, Chen X *et al.* Per-oral endoscopic myotomy versus laparoscopic Heller myotomy for achalasia: a meta-analysis of nonrandomized comparative studies. Medicine (Baltimore) 2016; 95: e2736.
133 Schneider A M, Louie B E, Warren H F, Farivar A S, Schembre D B, Aye R W. A matched comparison of per oral endoscopic myotomy to laparoscopic heller myotomy in the treatment of achalasia. J Gastrointest Surg 2016; 20: 1789–96.
134 Kumagai K, Tsai J A, Thorell A, Lundell L, Hakanson B. Per-oral endoscopic myotomy for achalasia. Are results comparable to laparoscopic Heller myotomy? Scand J Gastroenterol 2015; 50: 505–12.
135 Docimo S, Jr, Mathew A, Shope A J, Winder J S, Haluck R S, Pauli E M. Reduced postoperative pain scores and narcotic use favor per-oral endoscopic myotomy over laparoscopic Heller myotomy. Surg Endosc 2017; 31: 795–800.
136 Zhang X C, Li Q L, Xu M D *et al.* Major perioperative adverse events of peroral endoscopic myotomy: a systematic 5-year analysis. Endoscopy 2016; 48: 967–78.
137 Ponds F A, Fockens P, Neuhaus H *et al.* Peroral endoscopic myotomy (POEM) versus pneumatic dilatation in therapy-naïve patients with achalasia: results of a randomized controlled trial. Gastroenterology 2017; 152: S139.
138 Guo H, Yang H, Zhang X *et al.* Long-term outcomes of peroral endoscopic myotomy for patients with achalasia: a retrospective single-center study. Dis Esophagus 2017; 30: 1–6.
139 Kumbhari V, Khashab M A. Peroral endoscopic myotomy. World J Gastrointest Endosc 2015; 7: 496–509.
140 Stavropoulos S N, Modayil R, Friedel D. Per oral endoscopic myotomy for the treatment of achalasia. Curr Opin Gastroenterol 2015; 31: 430–40.

141 Ngamruengphong S, von Rahden B H, Filser J *et al.* Intraoperative measurement of esophagogastric junction cross-sectional area by impedance planimetry correlates with clinical outcomes of peroral endoscopic myotomy for achalasia: a multicenter study. Surg Endosc 2016; 30: 2886–94.
142 Schlottmann F, Luckett D J, Fine J, Shaheen N J, Patti M G. Laparoscopic Heller myotomy versus peroral endoscopic myotomy (POEM) for achalasia: a systematic review and meta-analysis. Ann Surg 2018; 267: 451–60.
143 Richards W O, Torquati A, Holzman M D *et al.* Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg 2004; 240: 405–15; discussion 12-5.
144 Salvador R, Pesenti E, Gobbi L *et al.* Postoperative gastroesophageal reflux after laparoscopic Heller-dor for achalasia: true incidence with an objective evaluation. J Gastrointest Surg 2017; 21: 17–22.
145 Sharata A, Kurian A A, Dunst C M, Bhayani N H, Reavis K M, Swanstrom L L. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. J Gastrointest Surg 2013; 17: 1188–92.
146 Orenstein S B, Raigani S, Wu Y V *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.
147 Achim V, Aye R W, Farivar A S, Vallieres E, Louie B E. A combined thoracoscopic and laparoscopic approach for high epiphrenic diverticula and the importance of complete myotomy. Surg Endosc 2017; 31: 788–94.
148 Jones E L, Meara M P, Pittman M R, Hazey J W, Perry K A. Prior treatment does not influence the performance or early outcome of per-oral endoscopic myotomy for achalasia. Surg Endosc 2016; 30: 1282–6.
149 Bak Y T, Lorang M, Evans P R, Kellow J E, Jones M P, Smith R C. Predictive value of symptom profiles in patients with suspected oesophageal dysmotility. Scand J Gastroenterol 1994; 29: 392–7.
150 Ling T, Guo H, Zou X. Effect of peroral endoscopic myotomy in achalasia patients with failure of prior pneumatic dilation: a prospective case-control study. J Gastroenterol Hepatol 2014; 29: 1609–13.
151 Louie B E, Schneider A M, Schembre D B, Aye R W. Impact of prior interventions on outcomes during per oral endoscopic myotomy. Surg Endosc 2017; 31: 1841–8.
152 Zhou P H, Li Q L, Yao L Q *et al.* Peroral endoscopic remyotomy for failed Heller myotomy: a prospective single-center study. Endoscopy 2013; 45: 161–6.
153 Vigneswaran Y, Yetasook A K, Zhao J C, Denham W, Linn J G, Ujiki M B. Peroral endoscopic myotomy (POEM): feasible as reoperation following Heller myotomy. J Gastrointest Surg 2014; 18: 1071–6.
154 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.
155 Hungness E S, Sternbach J M, Teitelbaum E N, Kahrilas P J, Pandolfino J E, Soper N J. Per-oral endoscopic myotomy (POEM) after the learning curve: durable long-term results with a low complication rate. Ann Surg 2016; 264: 508–17.
156 Kurian A A, Dunst C M, Sharata A, Bhayani N H, Reavis K M, Swanstrom L L. Peroral endoscopic esophageal myotomy: defining the learning curve. Gastrointest Endosc 2013; 77: 719–25.
157 Teitelbaum E N, Soper N J, Arafat F O *et al.* Analysis of a learning curve and predictors of intraoperative difficulty for peroral esophageal myotomy (POEM). J Gastrointest Surg 2014; 18: 92–99; discussion 8-9.
158 Patel K S, Calixte R, Modayil R J, Friedel D, Brathwaite C E, Stavropoulos S N. 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.
159 Cheng Y S, Li M H, Chen W X, Chen N W, Zhuang Q X, Shang K Z. Selection and evaluation of three interventional procedures for achalasia based on long-term follow-up. World J Gastroenterol 2003; 9: 2370–3.
160 Cheng Y S, Ma F, Li Y D *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.
161 Coppola F, Gaia S, Rolle E, Recchia S. Temporary endoscopic metallic stent for idiopathic esophageal achalasia. Surg Innov 2014; 21: 11–14.
162 De Palma G D, lovino P, Masone S, Persico M, Persico G. Self-expanding metal stents for endoscopic treatment of esophageal achalasia unresponsive to conventional treatments. Long-term results in eight patients. Endoscopy 2001; 33: 1027–30.
163 Li Y D, Cheng Y S, Li M H, Chen N W, Chen W X, Zhao J G. Temporary self-expanding metallic stents and pneumatic dilation for the treatment of achalasia: a prospective study with a long-term follow-up. Dis Esophagus 2010; 23: 361–7.
164 Li Y D, Tang G Y, Cheng Y S, Chen N W, Chen W X, Zhao J G. 13-year follow-up of a prospective comparison of the long-term clinical efficacy of temporary self-expanding metallic stents and pneumatic dilatation for the treatment of achalasia in 120 patients. Am J Roentgenol 2010; 195: 1429–37.
165 Zeng Y, Dai Y M, Wan X J. Clinical remission following endoscopic placement of retrievable, fully covered metal stents in patients with esophageal achalasia. Dis Esophagus 2014; 27: 103–8.
166 Zhao H, Wan X J, Yang C Q. Comparison of endoscopic balloon dilation with metal stent placement in the treatment of achalasia. J Dig Dis 2015; 16: 311–8.
167 Rieder E, Asari R, Paireder M, Lenglinger J, Schoppmann S F. Endoscopic stent suture fixation for prevention of esophageal stent migration during prolonged dilatation for achalasia treatment. Dis Esophagus 2017; 30: 1–6.
168 Mikaeli J, Veisari A K, Fazlollahi N *et al.* Ethanolamine oleate versus botulinum toxin in the treatment of idiopathic achalasia. Ann Gastroenterol 2015; 28: 229–35.
169 Moreto 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.
170 Niknam R, Mikaeli J, Mehrabi N *et al.* Ethanolamine oleate in resistant idiopathic achalasia: a novel therapy. Eur J Gastroenterol Hepatol 2011; 23: 1111–5.
171 Niknam R, Mikaeli J, Fazlollahi N *et al.* Ethanolamine oleate as a novel therapy is effective in resistant idiopathic achalasia. Dis Esophagus 2014; 27: 611–6.
172 Ou Y H, Nie X M, Li L F, Wei Z J, Jiang B. High-resolution manometric subtypes as a predictive factor for the treatment of achalasia: a meta-analysis and systematic review. J Dig Dis 2016; 17: 222–35.
173 Mittal R K, Balaban D H. The esophagogastric junction. N Engl J Med 1997; 336: 924–32.
174 Teitelbaum E N, Soper N J, Pandolfino J E *et al.* An extended proximal esophageal myotomy is necessary to normalize EGJ distensibility during Heller myotomy for achalasia, but not POEM. Surg Endosc 2014; 28: 2840–7.
175 Salvador R, Caruso V, Costantini M *et al.* Shorter myotomy on the gastric site (</ = 2.5 cm) provides adequate relief of dysphagia in achalasia patients. Dis Esophagus 2015; 28: 412–7.
176 Di Martino N, Monaco L, Izzo G *et al.* The effect of esophageal myotomy and myectomy on the lower esophageal sphincter pressure profile: intraoperative computerized manometry study. Dis Esophagus 2005; 18: 160–5.
177 Zaninotto G, Costantini M, Rizzetto C *et al.* Four hundred laparoscopic myotomies for esophageal achalasia: a single centre experience. Ann Surg 2008; 248: 986–93.
178 Mattioli S, Pilotti V, Felice V, Di Simone M P, D'Ovidio F, Gozzetti G. Intraoperative study on the relationship between the lower esophageal sphincter pressure and the muscular components of the gastro-esophageal junction in achalasic patients. Ann Surg 1993; 218: 635–9.
179 Oelschlager B K, Chang L, Pellegrini C A. Improved outcome after extended gastric myotomy for achalasia. Arch Surg 2003; 138: 490–5; discussion 5–7.
180 Wright A S, Williams C W, Pellegrini C A, Oelschlager B K. Long-term outcomes confirm the superior efficacy of extended Heller myotomy with Toupet fundoplication for achalasia. Surg Endosc 2007; 21: 713–8.

181 Jara F M, Toledo-Pereyra L H, Lewis J W, Magilligan D J, Jr. Long-term results of esophagomyotomy for achalasia of esophagus. Arch Surg 1979; 114: 935–6.
182 Andreollo N A, Earlam R J. Heller's myotomy for achalasia: is an added anti-reflux procedure necessary? Br J Surg 1987; 74: 765–9.
183 Jamieson G G. Gastro-esophageal reflux following myotomy for achalasia. Hepatogastroenterology 1991; 38: 506–9.
184 Falkenback D, Johansson J, Oberg S *et al.* Heller's esophagomyotomy with or without a 360° floppy Nissen fundoplication for achalasia. Long-term results from a prospective randomized study. Dis Esophagus 2003; 16: 284–90.
185 Donahue P E, Schlesinger P K, Sluss K F *et al.* Esophagocardiomyotomy-floppy Nissen fundoplication effectively treats achalasia without causing esophageal obstruction. Surgery 1994; 116: 719–24; discussion 24–5.
186 Topart P, Deschamps C, Taillefer R, Duranceau A. Long-term effect of total fundoplication on the myotomized esophagus. Ann Thorac Surg 1992; 54: 1046–52; discussion 51-2.
187 Hunter J G, Trus T L, Branum G D, Waring J P. Laparoscopic Heller myotomy and fundoplication for achalasia. Ann Surg 1997; 225: 655–65; discussion 64–5.
188 Malthaner R A, Tood T R, Miller L, Pearson F G. Long-term results in surgically managed esophageal achalasia. Ann Thorac Surg 1994; 58: 1343–7; discussion 6-7.
189 Khajanchee Y S, Kanneganti S, Leatherwood A E, Hansen P D, Swanstrom L L. Laparoscopic Heller myotomy with Toupet fundoplication: outcomes predictors in 121 consecutive patients. Arch Surg 2005; 140: 827–33; discussion 33-4.
190 Rebecchi F, Giaccone C, Farinella E, Campaci R, Morino M. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia: long-term results. Ann Surg 2008; 248: 1023–30.
191 Lyass S, Thoman D, Steiner J P, Phillips E. Current status of an antireflux procedure in laparoscopic Heller myotomy. Surg Endosc 2003; 17: 554–8.
192 Rawlings A, Soper N J, 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.
193 Kurian A A, Bhayani N, Sharata A, Reavis K, Dunst C M, Swanstrom L L. Partial anterior vs partial posterior fundoplication following transabdominal esophagocardiomyotomy for achalasia of the esophagus: metaregression of objective postoperative gastroesophageal reflux and dysphagia. JAMA Surg 2013; 148: 85–90.
194 Ortiz A, de Haro L F, Parrilla P *et al.* Very long-term objective evaluation of heller myotomy plus posterior partial fundoplication in patients with achalasia of the cardia. Ann Surg 2008; 247: 258–64.
195 Campos G M, Vittinghoff E, Rabl C *et al.* Endoscopic and surgical treatments for achalasia: A systematic review and meta-analysis. Ann Surg 2009; 249: 45–57.
196 Patti M G, Feo C V, Diener U *et al.* Laparoscopic Heller myotomy relieves dysphagia in achalasia when the esophagus is dilated. Surg Endosc 1999; 13: 843–7.
197 Bonavina L. Minimally invasive surgery for esophageal achalasia. World J Gastroenterol 2006; 12: 5921–5.
198 Sharp K W, Khaitan L, Scholz S, Holzman M D, Richards W O. 100 consecutive minimally invasive Heller myotomies: lessons learned. Ann Surg 2002; 235: 631–9; discussion 8-9.
199 Wei M T, He Y Z, Deng X B *et al.* Is Dor fundoplication optimum after laparoscopic Heller myotomy for achalasia? A meta-analysis. World J Gastroenterol 2013; 19: 7804–12.
200 Mineo T C, Pompeo E. Long-term outcome of Heller myotomy in achalasic sigmoid esophagus. J Thorac Cardiovasc Surg 2004; 128: 402–7.
201 Panchanatheeswaran K, Parshad R, Rohila J, Saraya A, Makharia G K, Sharma R. Laparoscopic Heller's cardiomyotomy: a viable treatment option for sigmoid oesophagus. Interact Cardiovasc Thorac Surg 2013; 16: 49–54.
202 Faccani E, Mattioli S, Lugaresi M L, Di Simone M P, Bartalena T, Pilotti V. Improving the surgery for sigmoid achalasia: long-term results of a technical detail. Eur J Cardiothorac Surg 2007; 32: 827–33.
203 Sweet M P, Nipomnick I, Gasper W J *et al.* The outcome of laparoscopic Heller myotomy for achalasia is not influenced by the degree of esophageal dilatation. J Gastrointest Surg 2008; 12: 159–65.
204 Hu J W, Li Q L, Zhou P H *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.
205 Eckardt V F, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology 1992; 103: 1732–8.
206 Gutschow C A, Tox U, Leers J, Schafer H, Prenzel K L, Holscher A H. Botox, dilation, or myotomy? Clinical outcome of interventional and surgical therapies for achalasia. Langenbecks Arch Surg 2010; 395: 1093–9.
207 Ling T S, Guo H M, Yang T, Peng C Y, Zou X P, Shi R H. Effectiveness of peroral endoscopic myotomy in the treatment of achalasia: a pilot trial in Chinese Han population with a minimum of one-year follow-up. J Dig Dis 2014; 15: 352–8.
208 Sawas T, Ravi K, Geno D M *et al.* The course of achalasia one to four decades after initial treatment. Aliment Pharmacol Ther 2017; 45: 553–60.
209 Rosemurgy A, Downs D, Jadick G *et al.* Dissatisfaction after laparoscopic Heller myotomy: the truth is easy to swallow. Am J Surg 2017; 213: 1091–7.
210 Wood T W, Ross S B, Ryan C E *et al.* Reoperative Heller myotomy: more pain, less gain. Am Surg 2015; 81: 637–45.
211 Ruffatto A, Mattioli S, Lugaresi A M, D'Ovidio F, Antonacci F, Di Simone M P. Long term results after Heller-Dor operation for oesophageal achalasia. Eur J Cardiothorac Surg 2006; 29: 914–9.
212 Chan S M, Chiu P W, Wu J C *et al.* Laparoscopic Heller's cardiomyotomy achieved lesser recurrent dysphagia with better quality of life when compared with endoscopic balloon dilatation for treatment of achalasia. Dis Esophagus 2013; 26: 231–6.
213 Kroupa R, Hep A, Dolina J *et al.* Combined treatment of achalasia - botulinum toxin injection followed by pneumatic dilatation: long-term results. Dis Esophagus 2010; 23: 100–5.
214 Ghoshal U C, Rangan M, Misra A. Pneumatic dilation for achalasia cardia: reduction in lower esophageal sphincter pressure in assessing response and factors associated with recurrence during long-term follow up. Dig Endosc 2012; 24: 7–15.
215 Carter J T, Nguyen D, Roll G R, Ma S W, Way L W. Predictors of long-term outcome after laparoscopic esophagomyotomy and Dor fundoplication for achalasia. Arch Surg 2011; 146: 1024–8.
216 Codispoti M, Soon S Y, Pugh G, Walker W S. Clinical results of thoracoscopic Heller's myotomy in the treatment of achalasia. Eur J Cardiothorac Surg 2003; 24: 620–4.
217 Gaissert H A, Lin N, Wain J C, Fankhauser G, Wright C D, Mathisen D J. Transthoracic Heller myotomy for esophageal achalasia: analysis of long-term results. Ann Thorac Surg 2006; 81: 2044–9.
218 Kilic A, Schuchert M J, Pennathur A, Gilbert S, Landreneau R J, Luketich J D. Long-term outcomes of laparoscopic Heller myotomy for achalasia. Surgery 2009; 146: 826–33; discussion 31-3.
219 Werner Y B, Costamagna G, Swanstrom L L *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.
220 Alderliesten J, Conchillo J M, Leeuwenburgh I, Steyerberg E W, Kuipers E J. Predictors for outcome of failure of balloon dilatation in patients with achalasia. Gut 2011; 60: 10–16.
221 Cheng P, Shi H, Zhang Y *et al.* Clinical effect of endoscopic pneumatic dilation for achalasia. Medicine (Baltimore) 2015; 94: e1193.
222 Howard J M, Mongan A M, Manning B J *et al.* Original article: outcomes in achalasia from a surgical unit where pneumatic dilatation is first-line therapy. Dis Esophagus 2010; 23: 465–72.
223 Kumbhari V, Behary J, Szczesniak M, Zhang T, Cook I J. Efficacy and safety of pneumatic dilatation for achalasia in the treatment of post-myotomy symptom relapse. Am J Gastroenterol 2013; 108: 1076–81.
224 Spiliopoulos S, Sabharwal T, Inchingolo R *et al.* Fluoroscopically guided balloon dilatation for the treatment of

achalasia: long-term outcomes. Dis Esophagus 2013; 26: 213–8.
225 Dang Y, Mercer D. Treatment of esophageal achalasia with Heller myotomy: retrospective evaluation of patient satisfaction and disease-specific quality of life. Can J Surg 2006; 49: 267–71.
226 Mattioli S, Ruffato A, Lugaresi M, Pilotti V, Aramini B, D'Ovidio F. Long-term results of the Heller–Dor operation with intraoperative manometry for the treatment of esophageal achalasia. J Thorac Cardiovasc Surg 2010; 140: 962–9.
227 Li Q L, Yao L Q, Xu X Y *et al.* Repeat peroral endoscopic myotomy: a salvage option for persistent/recurrent symptoms. Endoscopy 2016; 48: 134–40.
228 Patti M G, Allaix M E. Recurrent symptoms after Heller myotomy for achalasia: evaluation and treatment. World J Surg 2015; 39: 1625–30.
229 Gockel I, Junginger T, Eckardt V F. Persistent and recurrent achalasia after Heller myotomy: analysis of different patterns and long-term results of reoperation. Arch Surg 2007; 142: 1093–7.
230 Fumagalli U, Rosati R, De Pascale S *et al.* Repeated surgical or endoscopic myotomy for recurrent dysphagia in patients after previous myotomy for achalasia. J Gastrointest Surg 2016; 20: 494–9.
231 Gockel I, Junginger T. The value of scoring achalasia: a comparison of current systems and the impact on treatment-the surgeon's viewpoint. Am Surg 2007; 73: 327–31.
232 Vaezi M F, Baker M E, Achkar E, Richter J E. Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. Gut 2002; 50: 765–70.
233 Duffy P E, Awad Z T, Filipi C J. The laparoscopic reoperation of failed Heller myotomy. Surg Endosc 2003; 17: 1046–9.
234 Li Y, LingHu E, Ding H *et al.* Peroral endoscopic myotomy with simultaneous submucosal and muscle dissection for achalasia with severe interlayer adhesions. Gastrointest Endosc 2016; 83: 651–2.
235 Loviscek M F, Wright A S, Hinojosa M W *et al.* Recurrent dysphagia after Heller myotomy: is esophagectomy always the answer? J Am Coll Surg 2013; 216: 736–43; discussion 43-4.
236 Legros L, Ropert A, Brochard C *et al.* Long-term results of pneumatic dilatation for relapsing symptoms of achalasia after Heller myotomy. Neurogastroenterol Motil 2014; 26: 1248–55.
237 Mikaeli J, Bishehsari F, Montazeri G *et al.* Injection of botulinum toxin before pneumatic dilatation in achalasia treatment: a randomized-controlled trial. Aliment Pharmacol Ther 2006; 24: 983–9.
238 Chuah S K, Hu T H, Wu K L, Chen T Y, Changchien C S, Lee C M. The role of barium esophagogram measurements in assessing achalasia patients after endoscope-guided pneumatic dilation. Dis Esophagus 2009; 22: 163–8.
239 van Hoeij F B, Smout A, Bredenoord A J. Esophageal stasis in achalasia patients without symptoms after treatment does not predict symptom recurrence. Neurogastroenterol Motil 2017; 29.
240 Brucher B L, Stein H J, Bartels H, Feussner H, Siewert J R. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. World J Surg 2001; 25: 745–9.
241 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.
242 Zaninotto G, Rizzetto C, Zambon P, Guzzinati S, Finotti E, Costantini M. Long-term outcome and risk of oesophageal cancer after surgery for achalasia. Br J Surg 2008; 95: 1488–94.
243 Csendes A, Braghetto I, Burdiles P, Korn O, Csendes P, Henriquez 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.
244 da Rocha J R, Ribeiro U, Jr, Sallum R A, Szachnowicz S, Cecconello I. Barrett's esophagus (BE) and carcinoma in the esophageal stump (ES) after esophagectomy with gastric pull-up in achalasia patients: a study based on 10 years follow-up. Ann Surg Oncol 2008; 15: 2903–9.
245 Leeuwenburgh I, Gerrits M M, Capello A *et al.* Original article: expression of p53 as predictor for the development of esophageal cancer in achalasia patients. Dis Esophagus 2010; 23: 506–11.
246 Zendehdel K, Nyren O, Edberg A, Ye W. Risk of esophageal adenocarcinoma in achalasia patients, a retrospective cohort study in Sweden. Am J Gastroenterol 2011; 106: 57–61.
247 Allaix M E, Patti M G. Endoscopic dilatation, Heller myotomy, and peroral endoscopic myotomy: treatment modalities for achalasia. Surg Clin North Am 2015; 95: 567–78.
248 Snyder C W, Burton R C, Brown L E, Kakade M S, Finan K R, Hawn M T. Multiple preoperative endoscopic interventions are associated with worse outcomes after laparoscopic Heller myotomy for achalasia. J Gastrointest Surg 2009; 13: 2095–103.
249 Finley C J, Kondra J, Clifton J, Yee J, Finley R. Factors associated with postoperative symptoms after laparoscopic Heller myotomy. Ann Thorac Surg 2010; 89: 392–6.
250 Schuchert M J, Luketich J D, Landreneau R J *et al.* Minimally invasive surgical treatment of sigmoidal esophagus in achalasia. J Gastrointest Surg 2009; 13: 1029–36; discussion 35–6.
251 Jung H E, Lee J S, Lee T H *et al.* Long-term outcomes of balloon dilation versus botulinum toxin injection in patients with primary achalasia. Korean J Intern Med 2014; 29: 738–45.
252 Horgan S, Hudda K, Eubanks T, McAllister J, Pellegrini C A. Does botulinum toxin injection make esophagomyotomy a more difficult operation? Surg Endosc 1999; 13: 576–9.
253 Smith C D, Stival A, Howell D L, Swafford V. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. Ann Surg 2006; 243: 579–86; discussion 84–6.
254 Bonavina L, Incarbone R, Reitano M, Antoniazzi L, Peracchia A. Does previous endoscopic treatment affect the outcome of laparoscopic Heller myotomy? Ann Chir 2000; 125: 45–49.
255 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.
256 Peracchia A, Bonavina L. Achalasia: dilation, injection or surgery? Can J Gastroenterol 2000; 14: 441–3.
257 Zaninotto G, Costantini M, Portale G *et al.* Etiology, diagnosis, and treatment of failures after laparoscopic Heller myotomy for achalasia. Ann Surg 2002; 235: 186–92.
258 Chen Z, Bessell J R, Chew A, Watson D I. Laparoscopic cardiomyotomy for achalasia: clinical outcomes beyond 5 years. J Gastrointest Surg 2010; 14: 594–600.
259 Guardino J M, Vela M F, Connor J T, Richter J E. Pneumatic dilation for the treatment of achalasia in untreated patients and patients with failed Heller myotomy. J Clin Gastroenterol 2004; 38: 855–60.
260 Saleh C M, Ponds F A, Schijven M P, Smout A J, Bredenoord A J. Efficacy of pneumodilation in achalasia after failed Heller myotomy. Neurogastroenterol Motil 2016; 28: 1741–6.
261 Amani M F N, Shirami S, Malekzadeh R, Mikaeli J. Assessment of pneumatic balloon dilation in patients with symptomatic relapse after failed Heller myotomy. Middle East J Dig Dis 2015; 8: 57–62.
262 Schlottmann F, Andolfi C, Kavitt R T, Konda V JA, Patti M G. Multidisciplinary approach to esophageal achalasia: a single center experience. J Laparoendosc Adv Surg Tech A 2017; 27: 358–62.
263 van Hoeij F B, Ponds F A, Werner Y *et al.* Management of recurrent symptoms after per-oral endoscopic myotomy in achalasia. Gastrointest Endosc 2018; 87: 95–101.
264 Lewandowski A. Diagnostic criteria and surgical procedure for megaesophagus - a personal experience. Dis Esophagus 2009; 22: 305–9.
265 Devaney E J, Lannettoni M D, Orringer M B, Marshall B. Esophagectomy for achalasia: Patient selection and clinical experience. Ann Thorac Surg 2001; 72: 854–8.
266 Glatz S M, Richardson J D. Esophagectomy for end stage achalasia. J Gastrointest Surg 2007; 11: 1134–7.
267 Tank A K, Kumar A, Babu T L, Singh R K, Saxena R, Kapoor V K. Resectional surgery in achalasia cardia. Int J Surg 2009; 7: 155–8.
268 Menezes M A, Andolfi C, Herbella F A, Patti M G. High-resolution manometry findings in patients with achalasia and massive dilated megaesophagus. Dis Esophagus 2017; 30: 1–4.

269 Miller D L, Allen M S, Trastek V F, Deschamps C, Pairolero P C. Esophageal resection for recurrent achalasia. Ann Thorac Surg 1995; 60: 922–6; discussion 5–6.
270 Eldaif S M, Mutrie C J, Rutledge W C *et al.* The risk of esophageal resection after esophagomyotomy for achalasia. Ann Thorac Surg 2009; 87: 1558–63; discussion 62-3.
271 Meyer A, Catto-Smith A, Crameri J *et al.* Achalasia: outcome in children. J Gastroenterol Hepatol 2017; 32: 395–400.
272 Askegard-Giesmann J R, Grams J M, Hanna A M, Iqbal C W, Teh S, Moir C R. Minimally invasive Heller's myotomy in children: safe and effective. J Pediatr Surg 2009; 44: 909–11.
273 Chen W F, Li Q L, Zhou P H *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.
274 Di Nardo G, Rossi P, Oliva S *et al.* Pneumatic balloon dilation in pediatric achalasia: efficacy and factors predicting outcome at a single tertiary pediatric gastroenterology center. Gastrointest Endosc 2012; 76: 927–32.
275 Mehra M, Bahar R J, Ament M E *et al.* Laparoscopic and thoracoscopic esophagomyotomy for children with achalasia. J Pediatr Gastroenterol Nutr 2001; 33: 466–71.
276 Ip K S, Cameron D J, Catto-Smith A G, Hardikar W. Botulinum toxin for achalasia in children. J Gastroenterol Hepatol 2000; 15: 1100–4.
277 Pastor A C, Mills J, Marcon M A, Himidan S, Kim P C. A single center 26-year experience with treatment of esophageal achalasia: is there an optimal method? J Pediatr Surg 2009; 44: 1349–54.
278 Lee C W, Kays D W, Chen M K, Islam S. Outcomes of treatment of childhood achalasia. J Pediatr Surg 2010; 45: 1173–7.
279 Petrosyan M, Khalafallah A M, Guzzetta P C, Sandler A D, Darbari A, Kane T D. Surgical management of esophageal achalasia: evolution of an institutional approach to minimally invasive repair. J Pediatr Surg 2016; 51: 1619–22.
280 Nabi Z, Ramchandani M, Reddy D N *et al.* Per oral endoscopic myotomy in children with achalasia cardia. J Neurogastroenterol Motil 2016; 22: 613–9.
281 Caldaro T, Familiari P, Romeo E F *et al.* Treatment of esophageal achalasia in children: today and tomorrow. J Pediatr Surg 2015; 50: 726–30.
282 Corda L, Pacilli M, Clarke S, Fell J M, Rawat D, Haddad M. Laparoscopic oesophageal cardiomyotomy without fundoplication in children with achalasia: a 10-year experience. Surg Endosc 2010; 24: 40–44.
283 Pacilli M, Davenport M. Results of laparoscopic Heller's myotomy for achalasia in children: a systematic review of the literature. J Laparoendosc Adv Surg Tech 2017; 27: 82–90.
284 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.
285 Hallal C, Kieling C O, Nunes D L *et al.* Diagnosis, misdiagnosis, and associated diseases of achalasia in children and adolescents: a twelve-year single center experience. Pediatr Surg Int 2012; 28: 1211–7.
286 Pastor D M, Eggers A D, Drabick J J, Loughran T P, Bayerl M G, Shope T R. Retroperitoneal diffuse large B-cell lymphoma presenting as pseudoachalasia. J Clin Oncol 2010; 28: e184–7.
287 Smits M, van Lennep M, Vrijlandt R *et al.* Pediatric achalasia in the Netherlands: incidence, clinical course, and quality of life. J Pediatr 2016; 169: 110–115.e3.
288 Dantas R O, Alves L M, Nascimento W V. Effect of bolus volume on proximal esophageal contractions of patients with Chagas' disease and patients with idiopathic achalasia. Dis Esophagus 2010; 23: 670–4.
289 Dalmazo J, Dantas R O. Esophageal contractions after wet and dry swallows in patients with esophagitis, Chagas' disease and idiopathic achalasia. Gastroenterol Res 2010; 3: 156–62.
290 Souza D H, Vaz Mda G, Fonseca C R, Luquetti A, Rezende Filho J, Oliveira E C. Current epidemiological profile of Chagasic megaesophagus in Central Brazil. Rev Soc Bras Med Trop 2013; 46: 316–21.
291 Pinazo M J, Lacima G, Elizalde J I *et al.* Characterization of digestive involvement in patients with chronic T. cruzi infection in Barcelona, Spain. PLoS Negl Trop Dis 2014; 8: e3105.
292 Hirano I. Pathophysiology of achalasia. Curr Gastroenterol Rep 1999; 1: 198–202.
293 Herbella F A, Oliveira D R, Del Grande J C. Are idiopathic and Chagasic achalasia two different diseases? Dig Dis Sci 2004; 49: 353–60.
294 Hirano I, Tatum R P, Shi G, Sang Q, Joehl R J, Kahrilas P J. Manometric heterogeneity in patients with idiopathic achalasia. Gastroenterology 2001; 120: 789–98.
295 Abrahao L J, Jr, de Oliveira Lemme E M. Esophageal body motility in achalasia and Chagas' disease. Dis Esophagus 2011; 24: 312–7.
296 Csendes A, Strauszer T, Uribe P. Alterations in normal esophageal motility in patients with Chagas' disease. Digest Dis Sci 1975; 20: 437–42.
297 Dantas R O. Idiopathic achalasia and Chagasic megaesophagus. J Clin Epidemiol 1988; 10: 13–5.
298 Dantas R O, Deghaide N H, Donadi E A. Esophageal motility of patients with Chagas' disease and idiopathic achalasia. Dig Dis Sci 2001; 46: 1200–6.
299 Meneghelli U G, Peria F M, Darezzo F M *et al.* Clinical, radiographic, and manometric evolution of esophageal involvement by Chagas' disease. Dysphagia 2005; 20: 40–45.
300 Pinotti H W, Felix V N, Zilberstein B, Cecconello I. Surgical complications of Chagas' disease: megaesophagus, achalasia of the pylorus, and cholelithiasis. World J Surg 1991; 15: 198–204.
301 Martins P, Morais B B, Cunha-Melo J R. Postoperative complications in the treatment of chagasic megaesophagus. Int Surg 1993; 78: 99–102.
302 Felix V N, Sakai P, Cecconello I, Pinotti H W. Esophageal endoscopic aspects after forceful dilation of the gastric cardia in patients with achalasia of Chagas' disease. Dis Esophagus 2000; 13: 91–95.
303 Pinotti H W, Sakai P, Ishioka S. Cardiomyotomy and fundoplication for esophageal achalasia. Jpn J Surg 1983; 13: 399–403.
304 Nakano S M S, Faintuch J, Cecconello I, JMd Rocha, Gama-Rodrigues J J. Quality of life of patients operated for advanced Chagas' megaesophagus. Arq Bras Cir Dig 2005; 18: 129–32.
305 Herbella F, Del Grande J, Lourenço L, Mansur N, Haddad C. Resultados tardios da operação de Heller associada à fundoplicatura no tratamento do megaesôfago: análise de 83 casos. Rev Assoc Med Bras 1999; 45: 317–22.
306 Pinotti H W, Cecconello I, da Rocha J M, Zilberstein B. Resection for achalasia of the esophagus. Hepatogastroenterology 1991; 38: 470–3.
307 Pantanali C A, Herbella F A, Henry M A, Mattos Farah J F, Patti M G. Laparoscopic Heller myotomy and fundoplication in patients with Chagas' disease achalasia and massively dilated esophagus. Am Surg 2013; 79: 72–5.
308 Crema E, Ribeiro L B, Terra J A, Jr, Silva A A. Laparoscopic transhiatal subtotal esophagectomy for the treatment of advanced megaesophagus. Ann Thorac Surg 2005; 80: 1196–201.
309 DePaula A L, Hashiba K, Ferreira E A, de Paula R A, Grecco E. Laparoscopic transhiatal esophagectomy with esophagogastroplasty. Surg Laparosc Endosc 1995; 5: 1–5.
310 Serra H O, Felix V N, Cecconello I, Pinotti H W. Reapplication of myotomy and fundoplication in the surgical treatment of recurrent dysphagia after incomplete myotomy. Rev Hosp Clin Fac Med Sao Paulo 1998; 53: 129–33.
311 Ponciano H, Cecconello I, Alves L, Ferreira B D, Gama-Rodrigues J. Cardioplasty and Roux-en-Y partial gastrectomy (Serra-Dória procedure) for reoperation of achalasia. Arq Gastroenterol 2004; 41: 155–61.
312 Alves A P, de Oliveira P G, de Oliveira J M, de Mesquita D M, Dos Santos J H. Long-term results of the modified Thal procedure in patients with chagasic megaesophagus. World J Surg 2014; 38: 1425–30.
313 Ferraz A A, da Nobrega Junior B G, Mathias C A, Bacelar T S, Lima F E, Ferraz E M. Late results on the surgical treatment of Chagasic megaesophagus with the Thal-Hatafuku procedure. J Am Coll Surg 2001; 193: 493–8.