Systematic review

Meta-analysis of clinical outcome after treatment for achalasia based on manometric subtypes

C. Andolfi[1] and P. M. Fisichella[2]

[1]Department of Surgery, University of Chicago Pritzker School of Medicine, Chicago, Illinois, and [2]Department of Surgery, Brigham and Women's Hospital and Boston VA Healthcare System, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to: Dr P. M. Fisichella, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School and Boston VA Healthcare System, 1400 VFW Parkway, West Roxbury, Massachusetts 02132, USA (e-mail: piero.fisichella@va.gov)

Background: **The introduction of high-resolution manometry and the Chicago classification has made it possible to diagnose achalasia and predict treatment response accurately. The aim of this study was to compare the effect of the different treatments available on symptomatic outcomes across all achalasia subtypes.**

Methods: **The study was conducted according to PRISMA and MOOSE guidelines. A literature search of PubMed and MEDLINE databases was undertaken to identify all relevant articles reporting clinical outcomes of patients with achalasia after botulinum toxin injection, pneumatic dilatation, laparoscopic Heller myotomy (LHM) and peroral endoscopic myotomy (POEM) based on manometric subtypes. Patients were grouped according to the Chicago classification and the success rate in treating symptoms was measured as the primary endpoint.**

Results: **Twenty studies (1575 patients) were selected, and data on botulinum toxin, pneumatic dilatation, LHM and POEM were extracted. Success rates for LHM in type I, II and III achalasia were 81, 92 and 71 per cent respectively. Those for POEM were 95, 97 and 93 per cent respectively. POEM was more likely to be successful than LHM for both type I (odds ratio (OR) 2·97, 95 per cent c.i. 1·09 to 8·03; $P = 0·032$) and type III (OR 3·50, 1·39 to 8·77; $P = 0·007$) achalasia. The likelihood of success of POEM and LHM for type II achalasia was similar.**

Conclusion: **Pneumatic dilatation had a lower but still acceptable success rate compared with POEM or LHM in patients with type II achalasia. POEM is an excellent treatment modality for type I and type III achalasia, although it did not show any superiority over LHM for type II achalasia.**

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Introduction

Achalasia is a motor disorder of the oesophagus characterized by aperistalsis and impaired relaxation of the lower oesophageal sphincter (LOS), which leads to chronic dysphagia, regurgitation and chest pain[1]. The introduction of high-resolution manometry (HRM) and the classification of achalasia into subtypes has made it possible to diagnose the disease and predict the response to treatment accurately[2,3]. According to the updated Chicago classification (version 3.0), achalasia is classified into three subtypes[4]. Type I is characterized by a median integrated relaxation pressure (IRP) exceeding 15 mmHg and 100 per cent failed peristalsis; type II by a median IRP over 15 mmHg, absence of normal peristalsis and panoesophageal pressurization with at least 20 per cent of swallows; and type III by a median IRP of more than 15 mmHg, absence of normal peristalsis and spastic contractions with at least 20 per cent of swallows. However, understanding of the pathophysiology of primary achalasia remains limited, with treatment options that do not provide definitive cure, only palliation by controlling symptoms using methods that decrease the resting pressure of the non-relaxing LOS. Such methods include botulinum toxin injection, pneumatic dilatation, laparoscopic Heller myotomy (LHM) and peroral endoscopic myotomy (POEM). Some studies have demonstrated that HRM subtypes of achalasia may be important predictors of clinical outcomes. However, these reports included a small number of patients. Furthermore, no comparison exists of the symptomatic outcomes for the different types of treatment available across all achalasia subtypes.

Hence, it remains uncertain whether symptomatic outcomes after the different treatments are similar for all subtypes. The authors hypothesized that different treatments had a varied effect on outcomes across achalasia subtypes. To examine this hypothesis, a meta-analysis was undertaken to compare outcomes in patients with each of the three manometric achalasia subtypes after treatment with botulinum toxin, pneumatic dilatation, LHM and POEM.

Methods

Search strategy

This review and analysis were carried out in accordance with PRISMA[5] and MOOSE[6] guidelines. A literature search of PubMed and MEDLINE databases was conducted to identify all relevant articles published between 2008 and 2018, describing clinical outcomes of patients with achalasia after treatment with botulinum toxin, pneumatic dilatation, LHM or POEM based on HRM subtypes. The string search was ('achalasia') AND ('Chicago classification') AND ('pneumatic dilation' OR 'Heller myotomy' OR 'Botulinum toxin' OR 'POEM'). The references of extracted articles and abstracts presented at conferences were also reviewed to identify additional pertinent studies.

Inclusion criteria were: studies published in the English language; studies that specifically diagnosed achalasia subtypes on HRM according to the Chicago classification; studies of patients treated with botulinum toxin, pneumatic dilatation, LHM or POEM; studies that explicitly described the clinical outcomes for each subtype; and studies that contained original data.

Exclusion criteria were: studies that did not clearly state the outcomes for each achalasia subtype; those with insufficient original data for the statistical analysis; articles that reported data included in other selected references; reviews; case reports; and commentary or opinion pieces.

One author extracted the data from the included studies and the other author checked the extracted data. Disagreements were resolved by discussion. The following data were extracted from each article: first author; year of publication; publication type; previous treatments; number of patients treated with each procedure and achalasia subtype; treatment successes and failures for each subtype and type

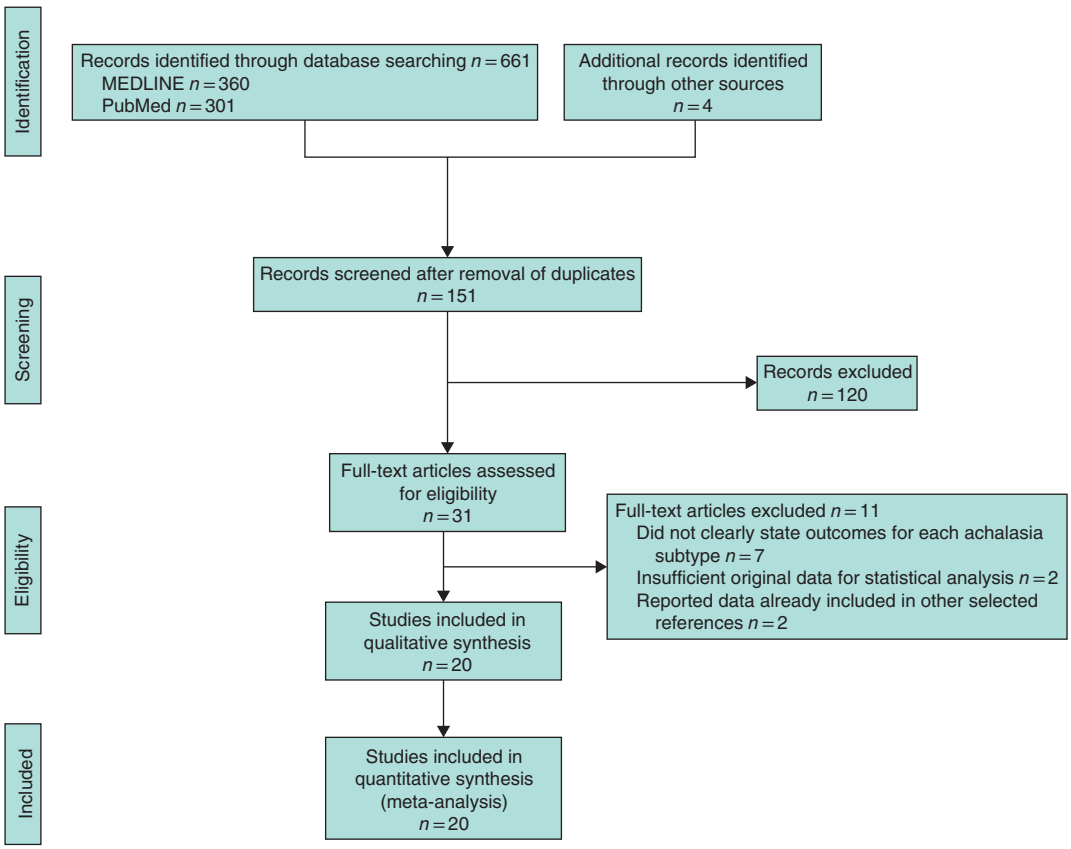

Fig. 1 PRISMA flow diagram showing selection of articles for review

Table 1 Results obtained with botulinum toxin and pneumatic dilatation

Reference	Study design	*n*	Follow-up (months)*	Previous treatment	Success rate by achalasia subtype		
					I	II	III
Botulinum toxin							
Pandolfino *et al.*[3]	RC	18	20	None	0 of 2	6 of 7	2 of 9
Min *et al.*[8]	RC	33	6(3)	None	2 of 13	9 of 18	0 of 2
Lee *et al.*[9]	RC	7	30(11)	None	1 of 5	1 of 2	–
Pneumatic dilatation							
Pandolfino *et al.*[3]	RC	45	20	None	3 of 8	19 of 26	0 of 11
Pratap *et al.*[10]	PC	45	6(0)	None	14 of 22	18 of 20	1 of 3
Min *et al.*[8]	RC	25	6(3)	None	3 of 8	13 of 15	0 of 2
Rohof *et al.*[11]	RCT	85	43(9)	None	18 of 22	53 of 53	4 of 10
Yamashita *et al.*[12]	PC	25	12(0)	None	5 of 6	12 of 15	2 of 4
Lee *et al.*[13]	PC	11	24(7)	None	5 of 7	3 of 4	–
Hosaka *et al.*[14]	PC	21	25	None	10 of 13	7 of 7	0 of 1
Park *et al.*[15]	RC	51	16(8)	n.a.	11 of 17	26 of 26	5 of 8
Lee *et al.*[9]	RC	35	30(11)	None	10 of 17	11 of 14	2 of 4
Meng *et al.*[16]	RC	40	30(14)	None	9 of 14	18 of 22	2 of 4
Müller *et al.*[17]	RC	102	48(31)	None	22 of 46	22 of 50	1 of 6

*Values are mean(s.d.). RC, retrospective cohort; PC, prospective cohort; n.a., not available.

Table 2 Results obtained with laparoscopic Heller myotomy and peroral endoscopic myotomy

Reference	Design	*n*	Follow-up (months)*	Previous treatment	Success rate by achalasia subtype		
					I	II	III
Laparoscopic Heller myotomy							
Pandolfino *et al.*[3]	RC	20	20	None	4 of 6	13 of 13	0 of 1
Salvador *et al.*[18]	RC	246	31(11)	None	82 of 96	121 of 127	16 of 23
Rohof *et al.*[11]	RCT	91	43(9)	None	19 of 22	57 of 61	7 of 8
Lee *et al.*[13]	PC	11	24(7)	None	2 of 4	6 of 7	–
Hosaka *et al.*[14]	PC	13	25	None	4 of 4	7 of 7	2 of 2
Kumbhari *et al.*[19]	RC	26	21·5(4)	19 PD or BT	–	–	21 of 26
Hamer *et al.*[20]	RC	95	36	14 PD	22 of 32	33 of 50	4 of 13
Lee *et al.*[9]	RC	9	30(11)	None	5 of 7	2 of 2	–
Crespin *et al.*[21]	RC	72	26(9)	n.a.	12 of 13	53 of 54	5 of 5
Peroral endoscopic myotomy							
Kumbhari *et al.*[19]	RC	49	8·6(1·7)	15 PD or BT 4 LHM	–	–	48 of 49
Hungness *et al.*[22]	RC	103	30(11)	34 PD or BT	24 of 25	54 of 58	18 of 20
Worrell *et al.*[23]	RC	34	3(0)	18 PD or BT	8 of 8	21 of 21	5 of 5
Meng *et al.*[16]	RC	32	25(11)	None	5 of 5	17 of 18	8 of 9
Kim *et al.*[24]	RC	83	16(3)	18 PD 12 BT 2 PD and BT	47 of 48	24 of 24	10 of 11
Zhang and Linghu[25]	RC	32	27(8)	1 BT	–	–	29 of 32
Martinek *et al.*[26]	PC	116	24(0)	21 PD 11 LHM 3 BT	15 of 18	87 of 88	10 of 10

*Values are mean(s.d.). RC, retrospective cohort; PC, prospective cohort; PD, pneumatic dilatation; BT, botulinum toxin; n.a., not available; LHM, laparoscopic Heller myotomy.

of procedure; data on postoperative gastro-oesophageal reflux disease (GORD) where available; and follow-up interval. The primary endpoint of the study was symptomatic outcome, which was treated as a dichotomous variable (success or failure). The secondary aim was to define the incidence of postoperative GORD. An analysis was therefore undertaken to determine how the authors defined clinical success or failure, and how they defined and assessed postoperative GORD.

Statistical analysis

Statistical analysis was performed using MedCalc® software (MedCalc, Ostend, Belgium). Clinical patient data

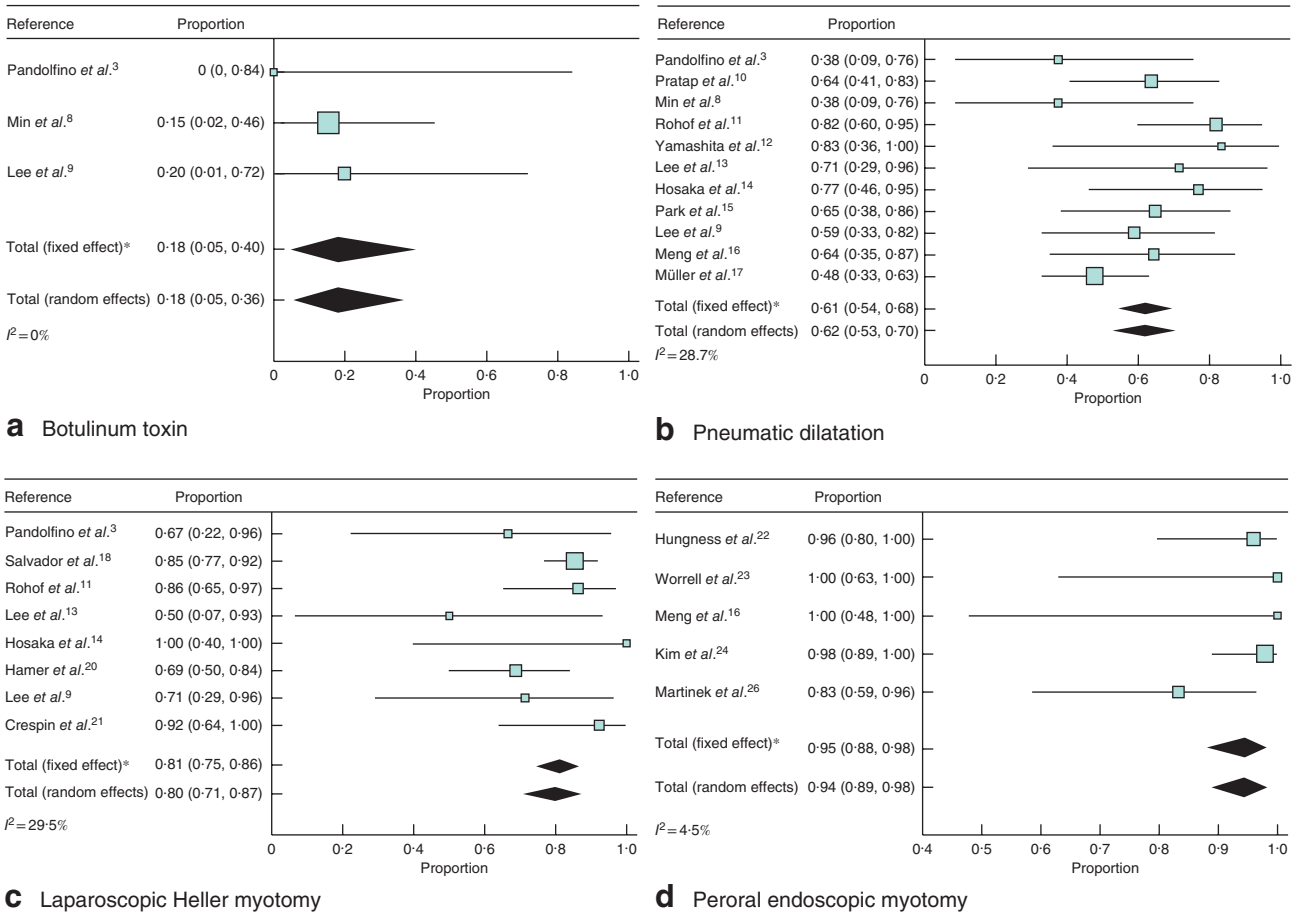

Fig. 2 Success rates for type I achalasia. **a** Botulinum toxin, **b** pneumatic dilatation, **c** laparoscopic Heller myotomy and **d** peroral endoscopic myotomy. Proportions are shown with 95 per cent confidence intervals. *Pooling method adopted, based on I^2 value

from individual studies were analysed to obtain summary statistics, including number of patients with improved symptoms, mean follow-up, and number of patients who had previous treatments. Continuous data are reported as mean(s.d.). All median (range) values were converted to mean(s.d.) according to the method of Hozo and colleagues[7]. Postoperative success rates were calculated as the proportion of events among the number of patients available for follow-up, and 95 per cent confidence intervals were then calculated for a single proportion. Heterogeneity among studies was assessed by means of the I statistic, which describes the percentage of total variation attributable to between-study heterogeneity as opposed to random error or chance. I^2 values of 0–50, 51–74 and 75 per cent or more were considered to indicate a low, moderate and high degree of heterogeneity respectively. In the presence of substantial heterogeneity (I^2 over 50 per cent), a random-effects model was used as a pooling method; otherwise, a fixed-effect model was adopted. As is standard in meta-analyses combining multiple studies, summary statistics were treated as independent observations that were analysed using standard methods for independent data. All calculations with details for each included study can be found in *Appendix S1* (supporting information).

Results

Twenty articles were included in the review (1575 patients) (*Fig. 1*)[3,8–26]. Three studies reported data on botulinum toxin (58 patients), 11 on pneumatic dilatation (485 patients), nine on LHM (583 patients) and seven on POEM (449 patients) (*Tables 1* and *2*). Mean(s.d.) follow-up was longer among studies on LHM (botulinum toxin, 17(3) months; pneumatic dilatation, 24(11) months; LHM, 31(8) months; POEM, 18(4) months; $P = 0{\cdot}023$). Patients in the botulinum toxin and pneumatic dilatation groups had received no previous treatments. The proportion of

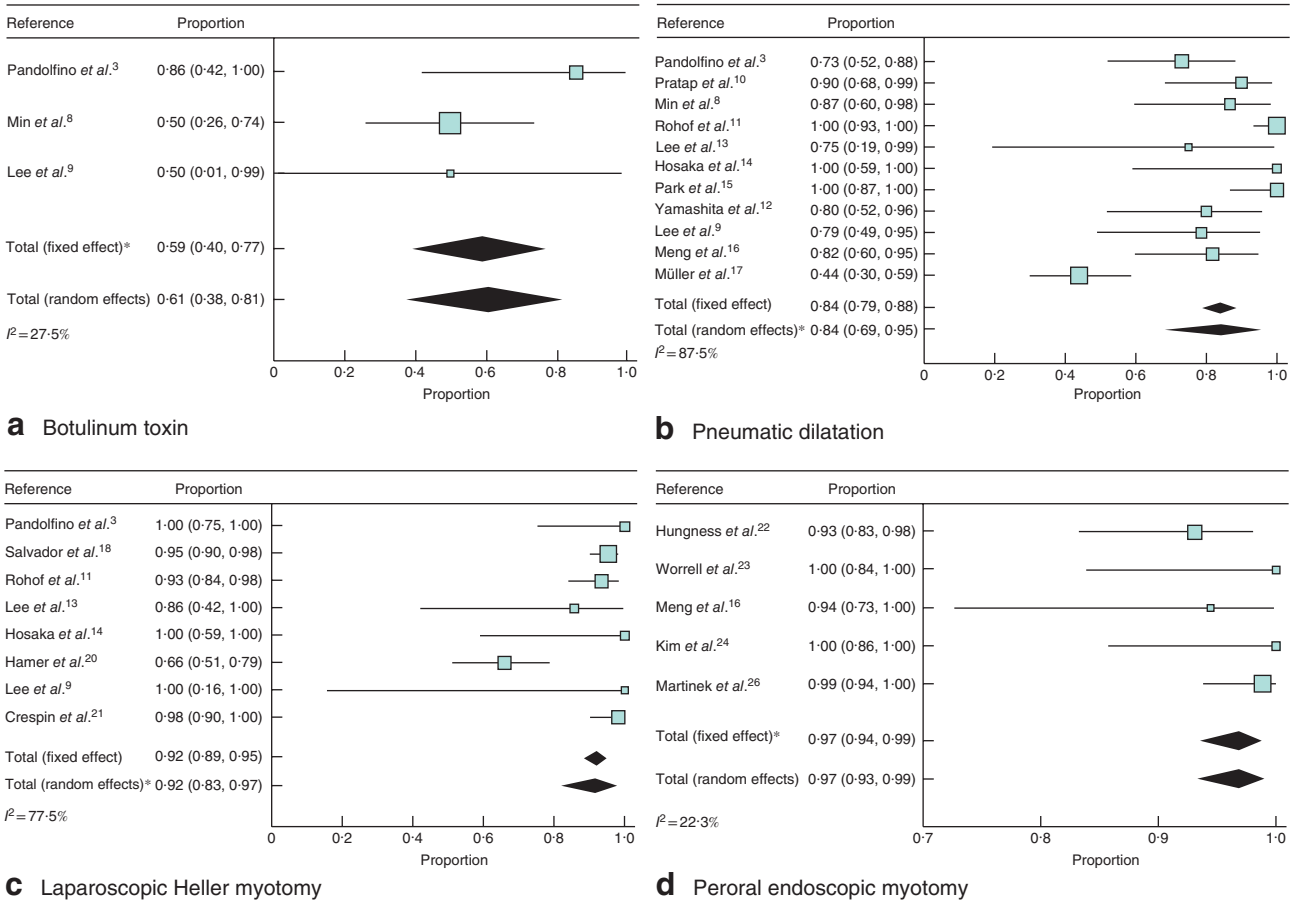

Fig. 3 Success rates for type II achalasia. **a** Botulinum toxin, **b** pneumatic dilatation, **c** laparoscopic Heller myotomy and **d** peroral endoscopic myotomy. Proportions are shown with 95 per cent confidence intervals. *Pooling method adopted, based on I^2 value

patients who received previous treatment was higher in the POEM group than in LHM group (31 and 6 per cent respectively; $P < 0{\cdot}001$).

Treatment success was defined differently among the studies. Yamashita and colleagues[12] used a composite score based on severity of dysphagia and chest pain. Each symptom was given a score between 0 and 2 (0, almost no symptoms; 1, occasional symptoms; 2, daily symptoms). The authors defined clinical remission as having total scores (0–4) of less than 2 and each symptom scored as less than 1. Salvador and co-workers[18] calculated the scores for dysphagia, regurgitation and chest pain by combining the severity of each symptom (0, none; 2, mild; 4, moderate; 6, severe) with its frequency (0, never; 1, occasionally; 2, once a month; 3, every week; 4, twice a week; 5, daily). They then calculated the symptom score as the sum of the dysphagia and regurgitation scores, considering the chest pain score separately, and defined treatment failure as a postoperative symptom score exceeding the tenth percentile of the preoperative score. Pratap and colleagues[10], Pandolfino and co-workers[3], Hosaka *et al.*[14] and Crespin and colleagues[21] defined clinical success as symptomatic relief not requiring further treatment at the last follow-up. Hamer and co-workers[20] used a modified Eckardt score that considered dysphagia, chest pain and regurgitation. A score from 0 to 3 was given to each symptom and a total score of 3 or less defined success. The remaining studies[8,9,11,13,15–17,19,22–26] used the Eckardt score, and a score of 3 or less was used to define clinical remission.

Based on calculation of weighted summary proportions across all studies, the success rate for type I achalasia was 18 per cent for botulinum toxin, 61 per cent for pneumatic dilatation, 81 per cent for LHM and 95 per cent for POEM (*Fig. 2*). The odds of success of POEM for type I achalasia were found to be 2·97 times the odds of success of LHM (odds ratio (OR) 2·97, 95 per cent c.i. 1·09

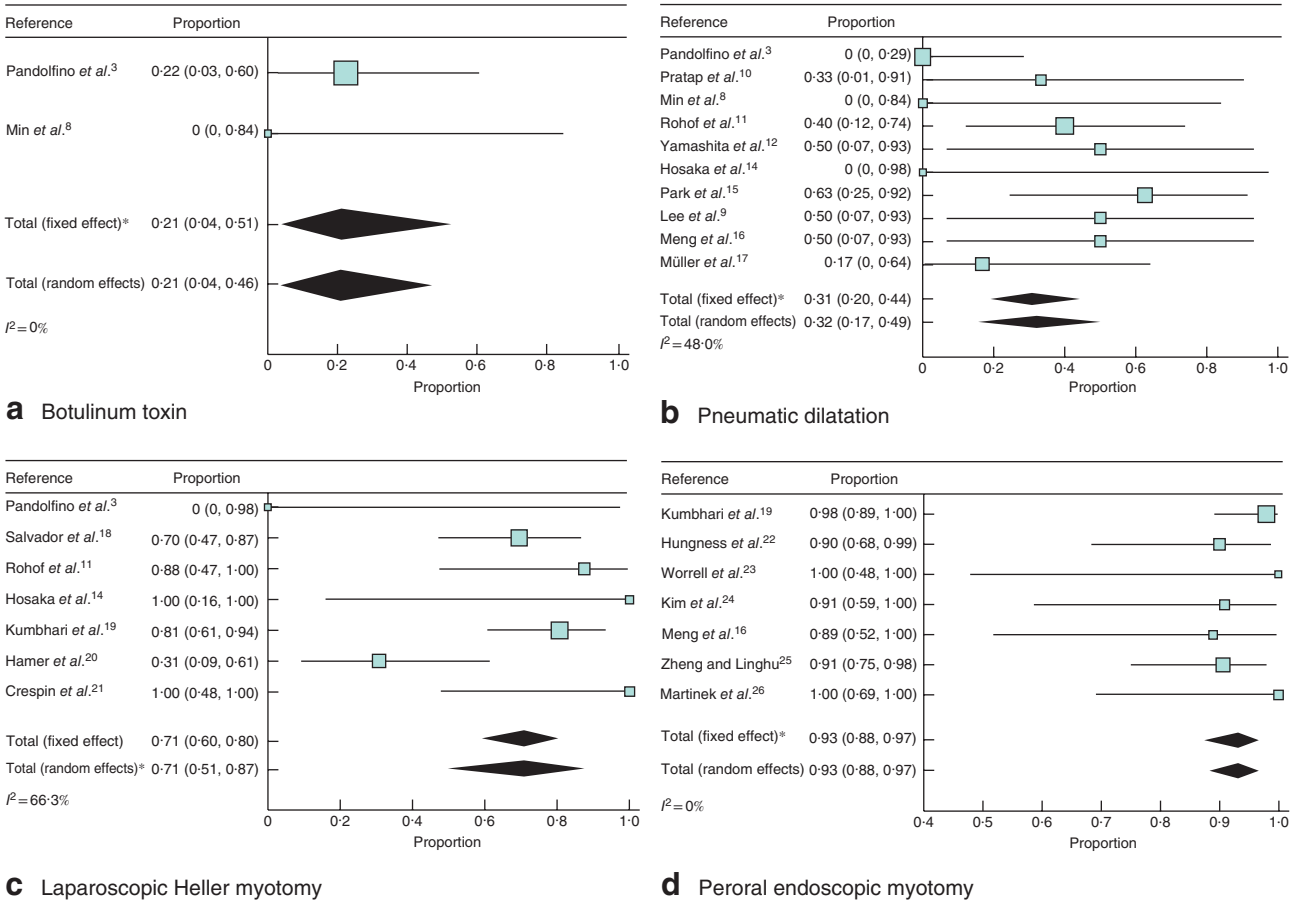

Fig. 4 Success rates for type III achalasia. **a** Botulinum toxin, **b** pneumatic dilatation, **c** laparoscopic Heller myotomy and **d** peroral endoscopic myotomy. Proportions are shown with 95 per cent confidence intervals. *Pooling method adopted, based on I^2 value

to 8·03; $P = 0·032$). Therapeutic success for type II achalasia was achieved in 59 per cent in the botulinum toxin group, 84 per cent in the pneumatic dilatation group, 92 per cent in the LHM group and 97 per cent in the POEM group (*Fig. 3*). There was no difference in odds of success between POEM and LHM for type II achalasia (OR 1·31, 0·48 to 3·55; $P = 0·591$). Therapeutic success for type III achalasia was achieved in 21 per cent of patients in the botulinum toxin group, 31 per cent in the pneumatic dilatation group, 71 per cent in the LHM group and 93 per cent in the POEM group (*Fig. 4*). POEM was significantly more likely to be successful for type III achalasia than LHM (OR 3·50, 1·39 to 8·77; $P = 0·007$). Four of the seven groups that performed POEM accomplished a longer myotomy for patients with type III achalasia. Kim and colleagues[24], Hungness and co-workers[22], Worrell *et al.*[23] and Kumbhari and co-workers[19] reported a mean myotomy length of 9·3, 15·8, 16 and 16 cm respectively. Conversely, five[11,18–21] of the seven studies that described outcomes of LHM for type III achalasia reported shorter myotomy lengths, ranging from a minimum of 6 cm to a maximum of 9 cm.

Within the various treatment groups, only four studies[11,12,22,25] reported objective data on treatment response, and three[13,19,21] documented specific data on treatment failures and reinterventions (*Table S1*, supporting information).

Ten[12,16,18–20,22–26] of the 20 studies determined the incidence of postoperative GORD. Data were inconsistent owing to differences in methods of assessment of pathological reflux. In addition, the presence of GORD across all subtypes was seldom recorded. Four studies[12,23–25], assessed GORD based on the presence of oesophagitis on endoscopy, two[16,22] reported the result of a questionnaire and calculated the GerdQ score based on symptoms, two[18,26] undertook pH monitoring systematically, and two[19,20] used the need for proton pump inhibitors (PPIs) as a surrogate for symptomatic GORD. Yamashita and

colleagues[12] and Meng *et al.*[16] reported GORD in 6 and 10 per cent of patients respectively after pneumatic dilatation. Three studies[18–20] reported data on GORD after LHM. Among these, Kumbhari and co-workers[19] and Hamer *et al.*[20] reported an incidence of postoperative reflux of 46 and 13 per cent respectively. However, both groups used the administration of PPIs as a surrogate for symptomatic reflux. Based on postoperative pH monitoring, Salvador and colleagues[18] documented GORD in only 9 per cent of patients after LHM. Seven studies[16,19,22–26] reported data on GORD after POEM. Worrell and colleagues[23], Kim and co-workers[24] and Zhang and Linghu[25] detected oesophagitis in 55, 22 and 19 per cent of patients respectively. Kim and colleagues[24] also undertook a subset analysis, which identified reflux in 17 per cent of patients with type I, 33 per cent with type II and 18 per cent with type III achalasia. Meng and co-workers[16] and Hungness *et al.*[22] registered a GerdQ score of more than 7 in 19 and 28 per cent of patients respectively. About half of the patients in the Hungness cohort underwent oesophagogastroduodenoscopy (OGD) and pH monitoring (if OGD did not show oesophagitis Los Angeles classification grade B or worse). Evidence of reflux was found in 40 per cent of patients: 40 per cent for type I, 37 per cent for type II and 33 per cent for type III achalasia. Kumbhari and colleagues[19] reported the use of PPIs in 39 per cent of patients after POEM. Martinek *et al.*[26] performed systematic pH monitoring 3 months after POEM and detected an overall pathological reflux rate of 42 per cent.

Discussion

The selection of therapies for achalasia has remained a topic of debate in clinical practice. For many years, the selection of treatment strategy was based primarily on the experiences of the experts or the willingness of the patients. However, patients' responses to various therapies differ among individuals and recurrence can still occur after interventions. Physicians have therefore sought to identify prognostic factors that can be used to select the most appropriate, or personalized, therapy for specific individuals. So far, older age, male sex and postoperative LOS exceeding 10 mmHg have been linked to a favourable prognosis[27–29]. Since the application of HRM and the Chicago classification, different manometric subtypes have also been proposed as potential prognostic factors[30,31]. By investigating the relationships between manometric subtypes and the outcomes of different therapies (botulinum toxin, pneumatic dilatation, LHM and POEM), this study aimed to identify which subtype would best respond to a specific treatment and gauge its prognostic value.

Patients with type II achalasia showed the best postoperative response, regardless of the treatment modality. This supports the generally accepted view that patients with type II achalasia are more likely to achieve treatment success than those with type I and III.

Botulinum toxin was by far the treatment modality with the worse outcomes (18 per cent for type I, 59 per cent for type II and 21 per cent for type III). Botulinum toxin injection results in temporary blockade of the acetylcholine-releasing neurones responsible for smooth muscle contractility. However, about half of patients need further injections at intervals of 6–24 months[32]. Multiple injections may induce a chronic inflammatory fibrotic reaction in the oesophageal wall, obliterating the muscle–submucosal plane and increasing the risk of perforation during LHM[27–31,33]. For these reasons, in 2013 the American College of Gastroenterology (ACG)[33] restricted the use of botulinum toxin to patients in whom pneumatic dilatation and LHM were contraindicated. The present results are in keeping with the ACG recommendation to use botulinum toxin only for patients in whom other treatments are not suitable.

Pneumatic dilatation remains a good treatment for type II achalasia, with a success rate of 84 per cent. In an RCT comparing pneumatic dilatation with LHM, Moonen and colleagues[34] reported similar outcomes after 5 years (82 *versus* 84 per cent in relieving dysphagia). However, 25 per cent of patients required multiple dilatations to treat recurrent dysphagia. Conversely, the present results showed that pneumatic dilatation is not as good for treatment of type I or III achalasia (success rate 61 and 31 per cent respectively) and confirmed that these patients (probably those who might need multiple dilatations) should be considered for other treatment options.

In the present study, POEM exhibited excellent results for all achalasia subtypes (95 per cent for type I, 97 per cent for type II and 93 per cent for type III), and was significantly more likely be successful than LHM in treating type I and type III (OR 2·97 and 3·50 respectively). There was no statistical difference in odds of success between POEM and LHM for type II achalasia. In a meta-analysis, Schlottmann and colleagues[35] showed a non-significant improvement in dysphagia after POEM compared with LHM (93·5 *versus* 91·0 per cent). Although the present results were similar to those of Schlottmann and colleagues[35], the meta-analysis presented here showed a difference in the value of POEM for each achalasia subtype. Most importantly, the analysis showed that POEM could definitely be used as first-line treatment for type III (spastic) achalasia, for which results of other treatments have traditionally been mediocre or poor (71 per cent with LHM, 31 per cent with pneumatic

dilatation and 21 per cent with botulinum toxin). Furthermore, extrapolating the excellent results of POEM for type III achalasia, this treatment could even be considered for other spastic oesophageal motility disorders. In support of this are the results of a multicentre study[36] of the efficacy of POEM for spastic oesophageal disorders, which was excluded from the present review as it reported data from patients already considered in the analysis. Khashab and colleagues[36] showed that 68 of the 73 patients (93 per cent) who underwent POEM (54 with spastic achalasia, 10 with jackhammer oesophagus and 9 with diffuse oesophageal spasm) had a positive clinical response and the average myotomy length was 16 cm. More specifically, the success rates were 100 per cent for patients with diffuse oesophageal spasm, 96 per cent for patients with type III achalasia and 70 per cent for those with jackhammer oesophagus. The better ability of POEM to extend the myotomy proximally into the spastic thoracic oesophagus can most probably account for its good outcomes, as highlighted by the present finding that the myotomy in those with POEM for type III achalasia was longer than that achieved by LHM. However, considering that the symptoms of achalasia tend to deteriorate over time after treatment, longer follow-up is needed to better assess its superiority over LHM. In addition, in some LHM studies (Salvador and colleagues[18], Rohof *et al.*[11]) the reported data related to patients who were operated upon before the Chicago classification was established. The HRM charts of these patients were reviewed retrospectively for study purposes only, but the surgeon was unaware of the achalasia subtype at the time of the operation, and the myotomy length was standardized. Conversely, all studies on POEM reported that the operator was aware of the subtype before the procedure, allowing a tailored approach for patients with type III achalasia.

Nonetheless, the higher incidence of abnormal postoperative reflux on ambulatory pH monitoring with POEM (47·5 *versus* 11·1 per cent in patients with achalasia, regardless of subtype)[35] suggests that LHM should be always considered when discussing the available treatment options with the patient. Of note, Salvador and colleagues[18] and Martinek *et al.*[26] undertook systematic postoperative pH monitoring for LHM and POEM respectively. It is noteworthy that the incidence of postoperative objective reflux was 9 per cent in the LHM group compared with 42 per cent for the POEM group.

This study has several limitations. Only one RCT[11] was available for inclusion in the analysis. The remaining studies were retrospective or prospective cohort studies that could have been affected by selection, observer and reporting bias. In addition, patients in the POEM group had a significantly higher rate of previous treatments and shorter follow-up than those in the LHM group, which may have influenced the results. Furthermore, treatment success was defined differently among studies, making any comparison challenging. Ultimately, it was not possible to take into account the incidence of postoperative GORD because it was reported in only half of the studies, its assessment varied widely and, with some exceptions, it was not categorized across all subtypes.

The present results indicate that treatment for achalasia could be more personalized than a standard approach, as a patient with a specific achalasia subtype could now be offered a treatment that achieves the best result. Pneumatic dilatation led to a lower but still acceptable rate of remission compared with LHM or POEM in patients with type II achalasia. Botulinum toxin injection had the lowest remission rates among all subtypes. POEM was found to be an excellent treatment modality for type I achalasia and also for type III, a subtype that has traditionally been resistant to most forms of treatment. POEM did not show any superiority over LHM for type II achalasia. Unfortunately, the studies selected for this meta-analysis did not report substantial data on postoperative GORD, as this was assessed inconsistently. Nevertheless, the high incidence of postoperative GORD must always be balanced against the likelihood of therapeutic success.

Disclosure

The authors declare no conflict of interest.

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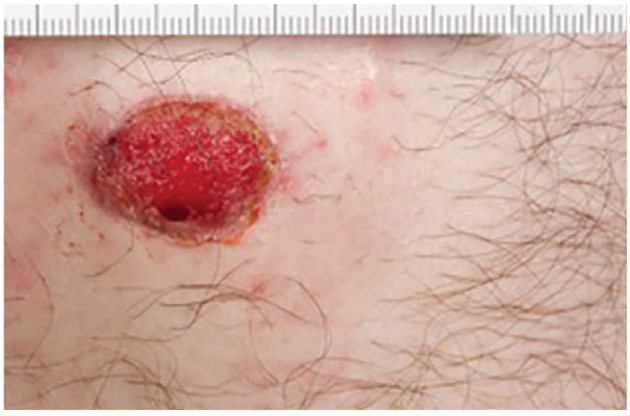
Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.

Snapshot quiz

Snapshot Quiz 19/5

Question: What is this abdominal lesion in a 78-year-old man having surveillance for colorectal malignancy?



The answer to the above question can be found on p. 435 of this issue of *BJS*.

Parkin E[1,2], Johnston R[1,3], Selvasekar C[1,2]: [1]Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, [2]Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, and [3]University of Glasgow School of Life Sciences, Wolfson Medical School, Glasgow, UK (e-mail: edward.parkin@christie.nhs.uk).

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