Peroral endoscopic myotomy versus pneumatic dilation in treatment-naive patients with achalasia: 5-year follow-up of a randomised controlled trial

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Summary

Background 2-year follow-up data from our randomised controlled trial showed that peroral endoscopic myotomy is associated with a significantly higher efficacy than pneumatic dilation as initial treatment of therapy-naive patients with achalasia. Here we report therapeutic success rates in patients treated with peroral endoscopic myotomy compared with pneumatic dilation at the 5-year follow-up.

Methods We did a multicentre, randomised controlled trial in six hospitals in the Netherlands, Germany, Italy, Hong Kong, and the USA. Adults aged 18–80 years with newly diagnosed symptomatic achalasia (based on an Eckardt score >3) were eligible for inclusion. Patients were randomly assigned (1:1) to peroral endoscopic myotomy or pneumatic dilation using web-based randomisation with a random block size of 8 and stratification according to site. Randomisation concealment for treatment type was double blind until official study enrolment. Treatment was unmasked because of the different technical approach of each procedure. Patients in the pneumatic dilation group were dilated with a single series of 30–35 mm balloons. The need for subsequent dilations in the pneumatic dilation group, and the need for dilation after initial treatment in the peroral endoscopic myotomy group, was considered treatment failure. The primary outcome was therapeutic success (Eckardt score ≤3 in the absence of severe treatment-related complications and no need for retreatment). Analysis of the primary outcome was by modified intention to treat, including all patients randomly assigned to a group, excluding those patients who did not receive treatment or were lost to follow-up. Safety was assessed in all included patients. This study is registered at the Dutch Trial Registry, NTR3593, and is completed.

Findings Between Sept 21, 2012, and July 20, 2015, 182 patients were assessed for eligibility, 133 of whom were included in the study and randomly assigned to peroral endoscopic myotomy (n=67) or pneumatic dilation (n=66). 5-year follow-up data were available for 62 patients in the peroral endoscopic myotomy group and 63 patients in the pneumatic dilation group. 50 (81%) patients in the peroral endoscopic myotomy group had treatment success at 5 years, compared with 25 (40%) in the pneumatic dilation group, an adjusted absolute difference of 41% (95% CI 25–57; p<0·0001). Reasons for failure were no initial effect of treatment (one patient in the peroral endoscopic myotomy group *vs* 12 patients in the pneumatic dilation group) and recurrent symptoms causing treatment failure (11 patients in the peroral endoscopic myotomy group [seven patients between 2 and 5 years] *vs* 25 patients in the pneumatic dilation group [nine patients between 2 and 5 years]); one patient in the pneumatic dilation group had treatment failure due to an adverse event. Proton-pump inhibitor use (mostly daily) was significantly higher after peroral endoscopic myotomy than after pneumatic dilation among patients still in clinical remission (23 [46%] of 50 patients *vs* three [13%] of 24 patients; p=0·008). 5-year follow-up endoscopy of patients still in clinical remission showed reflux oesophagitis in 14 (33%) of 42 patients in the peroral endoscopic myotomy group (12 [29%] grade A or B, two [5%] grade C or D) and two (13%) of 16 patients in the pneumatic dilation group (two [13%] grade A or B, none grade C or D; p=0·19). No intervention-related serious adverse events occurred between 2 and 5 years after treatment. The following non-intervention-related serious adverse events occurred between 2 and 5 years: a stroke (one [2%]) in the peroral endoscopic myotomy group; and death due to a melanoma (one [2%]) and dementia (one [2%]) in the pneumatic dilation group.

Interpretation Based on this study, peroral endoscopic myotomy should be proposed as an initial treatment option for patients with achalasia. Although our study has shown that peroral endoscopic myotomy has greater long-term efficacy with a low risk of major treatment-related complications, this should not lead to abandonment of pneumatic dilation from clinical practice. Ideally, all treatment options should be discussed with treatment-naive patients with achalasia and a shared decision should be made.

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Research in context

Evidence before this study

We searched PubMed for papers published in English between Jan 1, 1997, and July 31, 2012, using the search terms "achalasia", "pneumodilation", "peroral endoscopic myotomy", and "laparoscopic Heller myotomy". We restricted the search to reviews, clinical trials, large prospective studies, large retrospective studies, and case series. Treatment of achalasia is focused on disruption of the lower oesophageal sphincter by endoscopic pneumatic dilation or laparoscopic Heller myotomy. At the time this study was designed, pneumatic dilation was the most frequently used treatment, and is minimally invasive but with a variable long-term success rate of 50–85% depending on dilation strategy, patient selection, and balloon size. Studies on laparoscopic Heller myotomy showed good success rates of 70–90% after long-term follow-up; however, this technique is more invasive, has higher costs, and can be associated with severe complications. The 2011 European Achalasia trial, comparing pneumatic dilation with laparoscopic Heller myotomy in idiopathic achalasia showed a similar efficacy of both treatments (93% *vs* 90%) and became a landmark paper for achalasia management. However, one of the concerns in this trial was the multiple redilations that were allowed in the pneumatic dilation group, whereas only one laparoscopic intervention was permitted. Case series and prospective studies showed excellent safety and short-term efficacy rates (80–97%) of peroral endoscopic myotomy. However, data comparing peroral endoscopic myotomy with the current treatment options with longer follow-up to determine its true value are absent.

Added value of this study

To our knowledge, this is the first randomised controlled trial comparing the efficacy of peroral endoscopic myotomy with the standard treatment at the time for patients with achalasia, pneumatic dilation. After 5 years of follow-up, our data showed significantly more patients had treatment success after peroral endoscopic myotomy than after a single series of pneumatic dilation. The data confirmed that peroral endoscopic myotomy is a safe technique as no intervention-related serious adverse events were observed. The incidence of reflux symptoms and the use of proton-pump inhibitors was higher after peroral endoscopic myotomy than after pneumatic dilation. It seems appropriate to inform patients of this before treatment.

Implications of all the available evidence

This study supports the use of peroral endoscopic myotomy as first-line treatment for patients with achalasia and makes it an option for routine clinical practice as well as pneumatic dilation and laparoscopic Heller myotomy. The incidence of reflux symptoms and reflux oesophagitis is a concern, and after treatment, patients might require lifelong use of proton-pump inhibitors.

Introduction

Achalasia is an oesophageal motor disorder characterised by dysphagia, regurgitation, chest pain, and weight loss. These symptoms are the result of a combination of absent peristalsis and impaired relaxation of the lower oesophageal sphincter.[1]

Currently there is no cure for achalasia. Treatment options focus on decreasing the resting pressure of the lower oesophageal sphincter, with the aim to improve emptying of the oesophagus and relief of symptoms. Available treatment options include pneumatic dilation, laparoscopic Heller myotomy, and peroral endoscopic myotomy.[2] Pneumatic dilation is a commonly used and widely accepted treatment technique for achalasia. It is a safe and minimally invasive procedure and is effective in the treatment of achalasia symptoms.[3] However, the need for redilation (in 15–50% of patients) to achieve a long-term effect is high.[4,5] By comparison, laparoscopic Heller myotomy is seen as a more permanent solution in achalasia treatment. A large trial comparing pneumatic dilation with laparoscopic Heller myotomy showed similar efficacy rates of both treatments (93% *vs* 90%), although it should be noted that multiple redilations were allowed in the group receiving pneumatic dilation, compared with a single laparoscopic intervention for the myotomy.[6] On the other hand, laparoscopic Heller myotomy is more invasive and is associated with more major complications, a longer hospital stay, and longer recovery time compared with pneumatic dilation.[3,7,8]

Peroral endoscopic myotomy was first performed in 2008 and was presented as a promising alternative treatment option for patients with achalasia. With this technique it is possible to perform a myotomy of the lower oesophageal sphincter and oesophageal body muscle endoscopically.[9] The absence of abdominal incision and a shorter recovery time are advantages of peroral endoscopic myotomy compared with laparoscopic Heller myotomy. The efficacy rate of laparoscopic Heller myotomy is 80–90% at 2 years.[6,10] The 2-year follow-up data of our randomised controlled trial in treatment-naive patients with achalasia showed a significantly higher treatment success of 92% (58 of 63 patients) with peroral endoscopic myotomy compared with 54% (34 of 63 patients) with pneumatic dilation ($p<0·001$), while safety data was similar in the two groups. However, reflux oesophagitis occurred significantly more often in the patients treated with peroral endoscopic myotomy than in the patients treated with pneumatic dilation (22 [41%] of 54 patients *vs* two [7%] of 29 patients; $p=0·002$).[4]

A single series of pneumatic dilation was considered as first-line treatment at the time this trial was designed. Since then, pneumatic dilation, peroral endoscopic myotomy, and laparoscopic Heller myotomy have all

become accepted as first-line treatment.[2,11] In the current Article, we aimed to evaluate the long-term efficacy and safety of peroral endoscopic myotomy compared with a single series of pneumatic dilation in treatment-naive patients.

Methods

Study design and participants

We did a multicentre, randomised controlled trial in treatment-naive patients with achalasia. Patients were enrolled in six hospitals with expertise in achalasia in the Netherlands, Germany, Italy, Hong Kong, and the USA. Adults aged 18–80 years with newly diagnosed symptomatic achalasia (Eckardt score >3) were eligible for inclusion. Diagnosis was based on high-resolution manometry findings as absent or abnormal oesophageal peristalsis with an integrated relaxation pressure of the lower oesophageal sphincter of at least 15 mm Hg.[12] Patients who were previously endoscopically or surgically treated or patients with an American Society of Anesthesiologists classification of III or higher were excluded. Detailed inclusion and exclusion criteria have been published previously[4] and are in the study protocol (appendix pp 11–27). Written informed consent was obtained before enrolment.

2-year results have been previously published in detail.[4] The last 5-year follow-up data were obtained by Jan 27, 2022. This study received institutional review board approval in each participating hospital (NL40053.018.12 v3.0).

Randomisation and masking

Patients meeting eligibility criteria were randomly assigned (1:1) to peroral endoscopic myotomy or pneumatic dilation using web-based randomisation with a random block size of 8 and stratification according to site. Enrolment of patients was done by study staff. Randomisation concealment for treatment type was double-blind until official study enrolment. Treatment was unmasked because the different technical approach of the two procedures meant that masking was not possible.

Procedures

Pneumatic dilation was done using a Rigiflex balloon (Boston Scientific, Natick, MA, USA). Under fluoroscopic guidance, the balloon was positioned at the oesophagogastric junction and dilated at a pressure of 5 pounds per square inch (PSI) for 1 min and 8 PSI for another 1 min. Patients in the pneumatic dilation group were initially dilated using a 30 mm balloon. Symptoms were evaluated 3 weeks after initial treatment. If the Eckardt score was greater than 3, a second pneumatic dilation with a 35 mm balloon was performed, and if the Eckardt score was less than or equal to 3, a high-resolution manometry was performed. If the integrated relaxation pressure was 10 mm Hg or higher, patients were also treated with a second pneumatic dilation using a 35 mm balloon.

Peroral endoscopic myotomy was performed while patients received general anaesthesia with endotracheal intubation in a supine position. The procedure itself was done as described by Inoue and colleagues.[9] An endoscopic knife was used to access the submucosa, create the submucosal tunnel, and divide the circular muscle layer in the distal oesophagus over a minimum length of 6 cm and 2–3 cm onto the cardia, including cutting the lower oesophageal sphincter according to the standards of surgical myotomy. Standard endoscopic clips were used for closure of the mucosal entry site. Patients were admitted to the hospital the day before or the day of the procedure and discharged the day after if the fluoroscopy showed no leakage or perforation. Full peroral endoscopic myotomy procedure details are in the appendix (p 9).

Patients in whom initial pneumatic dilation was unsuccessful were re-treated with a 40 mm balloon, and, if symptoms persisted, were offered peroral endoscopic myotomy. Retreatment for patients in whom initial peroral endoscopic myotomy was unsuccessful consisted of pneumatic dilation, starting with a 30 mm balloon, followed by a 35 mm balloon and 40 mm balloon if necessary. Follow-up after retreatment was continued according to protocol following initial treatment.

See Online for appendix

Visits were scheduled at 3 months, and at 1, 2, and 5 years after initial treatment. The following measurements were performed at all visits: Eckardt score and questionnaires (achalasia-specific quality of life [achalasia-DSQoL], Medical Outcomes Study 36-item Short Form Health Survey [SF-36], and Gastroesophageal Reflux Disease Questionnaire [GERDQ]); high-resolution manometry parameters; timed barium oesophagogram; and upper endoscopy. At the 1-year follow-up, 24 h pH impedance monitoring was performed in addition to the other measurements.

Outcomes

The primary outcome was treatment success (defined as an Eckardt score ≤3 in the absence of severe treatment-related complications or the need for retreatment). Time to treatment success was measured from the date of initial treatment, or the first treatment session for patients in the pneumatic dilation group, until the last follow-up visit or the end of the study.

Secondary outcomes were high-resolution manometry parameters (integrated relaxation pressure of the lower oesophageal sphincter), oesophageal stasis (barium column height) and diameter on timed barium oesophagogram, presence of reflux oesophagitis during endoscopy, proton-pump inhibitor use, presence of reflux symptoms, achalasia-related quality of life and general quality of life. The complete treatment and study follow-up algorithm can be found in the study protocol (appendix pp 11–27).[4] Primary and secondary outcomes

were assessed at 3 months, and at 1, 2, and 5 years after initial treatment; here we report the results of the 5-year follow-up.

The Eckardt symptom score assesses the severity of achalasia symptoms by combining the sum of symptom frequency scores for dysphagia, regurgitation, and chest pain (range for each symptom, 0–3: 0 indicates absent; 1, occasionally; 2, daily; 3, at each meal) and a weight loss score (range 0–3: 0 indicates no weight loss; 1, <5 kg of weight loss; 2, 5–10 kg of weight loss; 3, >10 kg of weight loss), resulting in a range of 0 (the lowest severity of symptoms) to 12 (the highest severity of symptoms).[13]

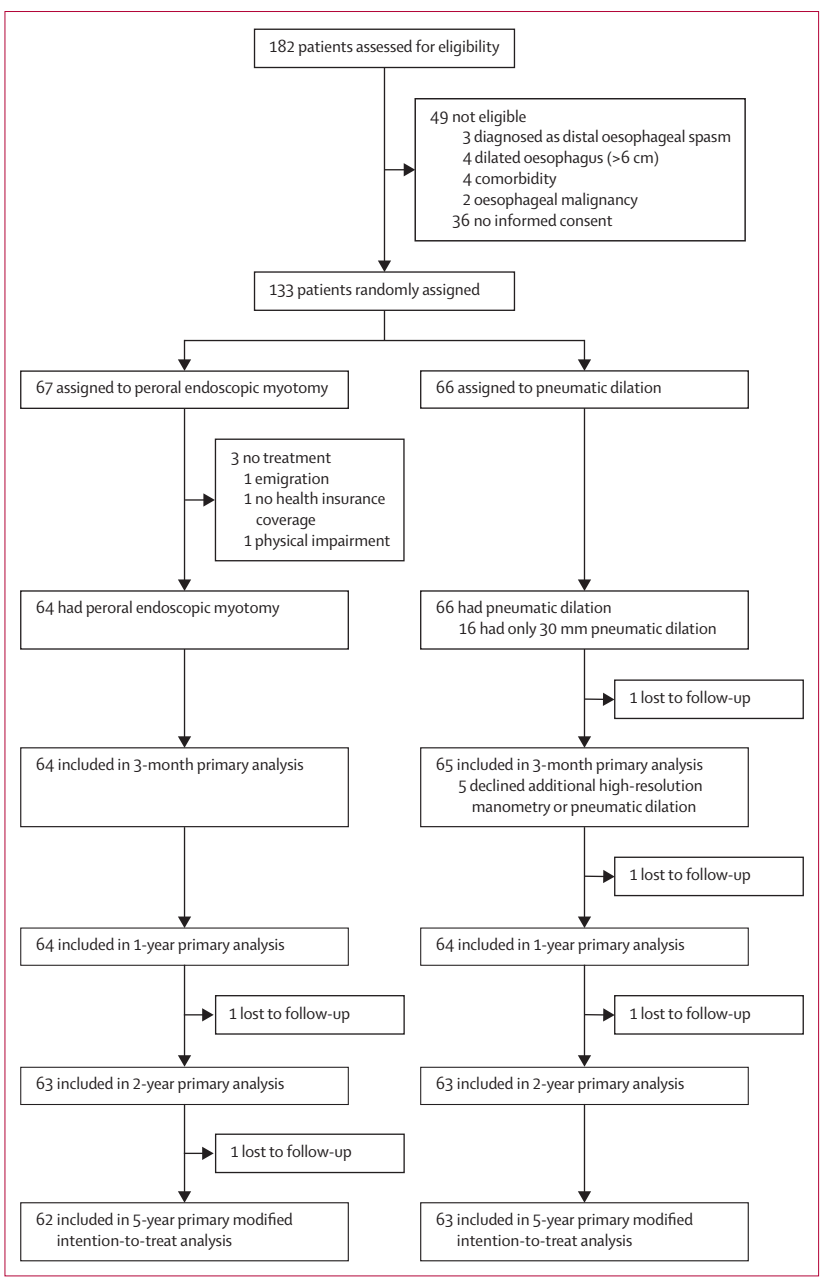

Figure 1: **Trial profile**

Reflux symptoms were analysed by the GERDQ. A score of 8 or higher is highly suggestive for gastro-oesophageal reflux disease. Achalasia-related quality of life was measured using the achalasia-DSQoL questionnaire and the SF-36 was used to analyse general quality of life.[14–16] Scores on the achalasia-DSQoL ranged from 10 to 33, with a lower score indicating a better quality of life.[15] Scores on the SF-36 ranged from 0 to 100, with a higher score indicating a better quality of life.[16]

Adverse events were defined as any unwanted event that occurred following the study treatment, secondary to the study treatment or unrelated to study treatment during follow-up in all patients included in the study. Classification of adverse events is shown in the appendix (p 9).

Statistical analysis

To calculate the sample size, a difference in success rates between peroral endoscopic myotomy and pneumatic dilation of 20% was hypothesised: 90% for peroral endoscopic myotomy[9,17] and 70% for pneumatic dilation[6,18,19] after 2 years. The sample size required to achieve 80% power, with a predefined significance level of 0·05, was estimated at 62 participants per treatment group. Considering a maximum dropout rate of 5%, 130 patients needed to be randomly assigned. Analysis of the primary outcome was by modified intention to treat, including all patients randomly assigned except those who did not undergo treatment after random assignment or were lost to follow-up. A strict intention-to-treat analysis was also done. Safety was assessed in all patients included in the study.

A post-hoc sensitivity analysis of the primary outcome was done using the last observation carried forward. A post-hoc analysis was done evaluating the effect of the 40 mm dilation on treatment success. A post-hoc subgroup analysis excluding patients with type III achalasia was done evaluating primary and secondary outcomes. Another post-hoc analysis was done evaluating the Eckardt score and individual questions of the Eckardt score during the course of the trial.

Friedman test for trends in repeated secondary outcome measurements was used. Secondary outcomes were also analysed using all treated patients (treatment success and treatment failure). Descriptive statistics were presented as mean (SD) or median (IQR) for continuous variables according to distribution and as number and percentage for categorical data. Analysis was performed using the unpaired *t* or Mann-Whitney tests and categorical data were analysed using χ^2 or Fisher exact tests. p values less than 0·05 were considered statistically significant. Logistic regression was used to determine prognostic factors in post-hoc analysis, significant variables were used to perform a multiple logistic regression analysis. SPSS statistics (version 26) was used for statistical analysis. This study is registered at the Dutch Trial Registry, NTR3593, and is completed.

Role of the funding source
The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 21, 2012, and July 20, 2015, 182 patients were assessed for eligibility, 133 of whom were included in the study and randomly assigned to peroral endoscopic myotomy (n=67) or pneumatic dilation (n=66; figure 1). Three patients in the peroral endoscopic myotomy group did not receive treatment; 50 patients in the pneumatic dilation group had two dilations and 16 patients had pneumatic dilation with only a 30 mm balloon (figure 1). Five patients in the pneumatic dilation group refused to undergo an additional high-resolution manometry because of complete symptom relief. Ten patients had a single pneumatic dilation according to the protocol. Baseline characteristics of the 130 patients who received treatment were similar in both groups (table 1). At 5 years, follow-up data were available in 125 patients (figure 1).

At the 5-year follow-up, more patients had treatment success after peroral endoscopic myotomy (50 [81%] of 62) than after pneumatic dilation (25 [40%] of 63), representing a significant unadjusted absolute difference of 41% (95% CI 25–57; p<0·0001; table 2). Reasons for treatment failure are shown in table 2. Seven patients in the peroral endoscopic myotomy group and nine in the pneumatic dilation group had symptom recurrence between 2 and 5 years. The intention-to-treat analysis showed a treatment success rate in the peroral endoscopic myotomy group of 75% (50 of 67 patients) versus 38% (25 of 66 patients) in the pneumatic dilation group, and an unadjusted absolute difference of 37% (95% CI 21–52; p<0·0001).

The median time from initial random assignment to treatment was 15 days (IQR 9–29) in the peroral endoscopic myotomy group compared with 22 days (8–40) in the pneumatic dilation group (p=0·30). After peroral endoscopic myotomy, the median time to treatment failure or loss to follow-up was 60 months (IQR 60–60) compared with 24 months (6–60) after pneumatic dilation (figure 2).

By the 5-year follow-up, eight (13%) of 62 patients in the peroral endoscopic myotomy group were retreated; seven (11%) received additional pneumatic dilations and in one (2%) patient a laparoscopic Heller myotomy was done. Of all 63 patients in the pneumatic dilation group, 30 (48%) were retreated after treatment failure; 26 (41%) patients received additional pneumatic dilations, nine (14%) patients underwent peroral endoscopic myotomy after additional pneumatic dilations, three (8%) patients underwent peroral endoscopic myotomy without additional pneumatic dilations, and in one (2%) patient laparoscopic Heller myotomy was done.

At 5-year follow-up, patients in the peroral endoscopic myotomy group who had not undergone retreatment 5 years after initial treatment did not significantly differ in median integrated relaxation pressure, barium column height at 5 min, or Eckardt score compared with the pneumatic dilation group (table 3).

When considering all patients, including those receiving unscheduled retreatments due to symptom

	Peroral endoscopic myotomy (n=64)	Pneumatic dilation (n=66)
Centre		
Amsterdam University Medical Center, Amsterdam, Netherlands	38 (59%)	36 (55%)
Evangelische Krankenhaus, Düsseldorf, Germany	8 (13%)	10 (15%)
Agostino Gemelli University Hospital, Rome, Italy	8 (13%)	9 (14%)
Prince of Wales Hospital, Hong Kong Special Administrative Region, China	7 (11%)	9 (14%)
Helios Klinikum Krefeld, Düsseldorf, Germany	2 (3%)	1 (2%)
Northwestern Memorial Hospital, Chicago, IL, USA	1 (2%)	1 (2%)
Sex		
Male	33 (52%)	40 (61%)
Female	31 (48%)	26 (39%)
Age, years	47 (37–56)	50 (32–62)
Bodyweight, kg	71·5 (16·1)	69·6 (13·9)
BMI, kg/m²	23·2 (3·7)	23·4 (4·1)
Achalasia subtype*		
I	10 (16%)	21 (32%)
II	42 (66%)	39 (59%)
III	12 (19%)	6 (9%)
Eckardt score†	8 (6–9)	7 (6–9)
Integrated relaxation pressure, mm Hg	26·4 (20·2–34·9)	28·5 (20·4–37·3)
Barium column, cm		
Height	7·2 (4·5–9·2)	6·7 (3·0–10·1)
Diameter	3·5 (2·7–4·5)	3·3 (2·8–4·3)
Achalasia-DSQoL score‡	25 (22–27)	24 (22–26)
GERDQ score§	8 (6–11)	8 (6–10)
SF-36 score¶		
Physical component summary score	46·3 (39·9–49·9)	45·6 (38·7–50·9)
Mental component summary score	45·7 (35·6–54·6)	45·2 (36·8–53·5)

Data are n (%), median (IQR), or mean (SD). Achalasia-DSQoL=achalasia-specific quality of life. GERDQ=Gastroesophageal Reflux Disease Questionnaire. SF-36=Medical Outcomes Study 36-item Short Form Health Survey. *Achalasia subtype I=100% failed peristalsis; subtype II=100% failed peristalsis and panoesophageal pressurisation ≥20% of swallows; subtype III=no normal peristalsis and premature or spastic contractions ≥20% of swallows. †Eckardt score measures achalasia symptoms, range 0–12, highest score indicates most pronounced symptoms. ‡Achalasia-DSQoL measures quality of life related to achalasia, range 10–33, lower score indicates a better quality of life. §GERDQ measures gastro-oesophageal reflux disease, range 0–18, score ≥8 is highly suggestive for presence of GERD. ¶SF-36 measures general quality of life consisting of physical component scale, range 0–100, and mental component scale, range 0–100, higher score indicates a better quality of life.

Table 1: **Baseline characteristics of patients who received treatment**

	Peroral endoscopic myotomy	Pneumatic dilation	Unadjusted absolute difference (95% CI)	Unadjusted risk ratio (95% CI)	p value
Outcome at 5 years					
Overall treatment success	50/62 (81%)	25/63 (40%)	41% (25–57)	2·03 (1·46–2·82)	<0·0001
Recurrent symptoms (Eckardt score >3)	11/62 (18%)	25/63 (40%)	..	..	..
Initial treatment failure	1/62 (2%)	12/63 (19%)	..	..	..
Adverse event	0	1/63 (2%)	..	..	..
Outcome at 2 years					
Overall treatment success	58/63 (92%)	34/63 (54%)	38% (24–52)	1·71 (1·34–2·17)	<0·0001
Recurrent symptoms (Eckardt score >3)	4/63 (6%)	16/63 (25%)	..	..	..
Initial treatment failure	1/63 (2%)	12/63 (19%)	..	..	..
Adverse event	0	1/63 (2%)	..	..	..
Outcome at 1 year					
Overall treatment success	61/64 (95%)	42/64 (66%)	31% (17–45)	1·45 (1·21–1·75)	<0·0001
Recurrent symptoms (Eckardt score >3)	2/64 (3%)	9/64 (14%)	..	..	..
Initial treatment failure	1/64 (2%)	12/64 (19%)	..	..	..
Adverse event	0	1/64 (2%)	..	..	..
Outcome at 3 months					
Overall treatment success	63/64 (98%)	52/65 (80%)	18% (7–30)	1·23 (1·09–1·40)	0·0008
Initial treatment failure	1/64 (2%)	12/65 (18%)	..	..	..
Adverse event	0	1/65 (2%)	..	..	..

Table 2: **Primary outcome of overall treatment success**

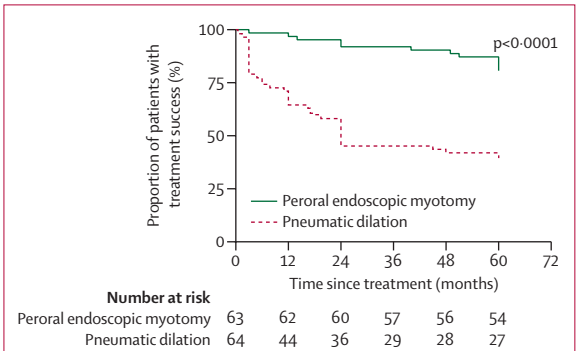

Figure 2: **Log-rank survival curves for the proportion of patients with treatment success**

recurrence (62 in the peroral endoscopic myotomy group and 63 in the pneumatic dilation group), no significant difference at 5-year follow-up between the peroral endoscopic myotomy group and pneumatic dilation group was seen in median integrated relaxation pressure (12·1 mm Hg [IQR 9·1–17·0] *vs* 11·8 mm Hg [9·0–16·7]; p=0·83), Eckardt score (2 [IQR 1–3] *vs* 2 [1–3]; p=0·24), or barium column height at 5 min (3·0 cm [IQR 0·0–4·6] *vs* 2·0 cm [0·0–4·0]; p=0·28). However, at 5-year follow-up after treatment with peroral endoscopic myotomy, the oesophagus was significantly wider than after pneumatic dilation (3·0 cm [IQR 2·3–3·7] *vs* 2·3 cm [1·5–2·8]; p=0·0041).

	Peroral endoscopic myotomy (n=50)	Pneumatic dilation (n=24)	p value
Eckardt score	2 (1–3)	1 (1–2)	0·52
Eckardt subscore dysphagia	2 (1–3)	1 (0–1)	0·35
Eckardt subscore pain	0 (1–1)	0 (0–1)	0·81
Eckardt subscore regurgitation	0 (0–1)	0 (0–1)	0·025
Eckardt subscore weight loss	0 (0–1)	0 (0–0)	1·00
Integrated relaxation pressure, mm Hg	11·3 (8·3–15·5)	14·0 (11·3–21·3)	0·085
Barium column at 5 min, cm			
Height	2·8 (0·0–4·2)	0·0 (0·0–4·1)	0·28
Diameter	2·8 (2·3–3·7)	1·9 (1·5–2·5)	0·0009
Reflux oesophagitis*	..	..	0·19
None	28 (67%)	14 (88%)	..
Grade A or B	12 (29%)	2 (13%)	..
Grade C or D	2 (5%)	0	..
Proton-pump inhibitor use	23 (46%)	3 (13%)	0·0082
GERDQ score†	7 (6–9)	6 (6–7)	0·0081
GERDQ score ≥8†	24 (49%)	4 (17%)	0·0076
Achalasia-DSQoL score	15 (13–18)	13 (11–17)	0·066
SF-36 score			
Physical component summary score	51·1 (46·3–56·6)	49·2 (41·3–54·8)	0·36
Mental component summary score	53·6 (47·8–57·9)	52·4 (46·4–55·5)	0·25

Data are median (IQR) or n (%) unless otherwise specified. Achalasia-DSQoL=achalasia-specific quality-of-life. GERDQ=Gastroesophageal Reflux Disease Questionnaire. SF-36=Medical Outcomes Study 36-item Short-Form Health Survey. *Denominators are the numbers of patients who had upper endoscopy at 5 years: peroral endoscopic myotomy group n=42 and pneumatic dilation group n=16. †One patient in the peroral endoscopic myotomy group had a missing GERDQ score; therefore, n=49.

Table 3: **Secondary outcomes at 5-year follow-up of patients still in clinical remission**

Upper endoscopy was done in 58 (78%) of 74 patients who were still in clinical remission 5 years after treatment (42 in the peroral endoscopic myotomy group and 16 in the pneumatic dilation group). 5-year follow-up endoscopy showed high degrees of reflux oesophagitis in patients treated with peroral endoscopic myotomy and no retreatment, and less so after treatment with pneumatic dilation without retreatment, although this difference was not significant (table 3). The use of proton-pump inhibitors was significantly higher after peroral endoscopic myotomy compared with pneumatic dilation at 5-year follow-up (table 3). Details regarding the use of proton-pump inhibitors in relation to oesophagitis are in the appendix (p 5).

At 5-year follow-up, the incidence of reflux symptoms, defined as a GERDQ score of 8 or more, was also significantly higher in patients treated with peroral endoscopic myotomy than in those treated with

pneumatic dilation (table 3). Among patients using proton-pump inhibitors, 12 (24%) of 49 patients treated with peroral endoscopic myotomy reported a GERDQ score of 8 or more compared with one (4%) 23 in the pneumatic dilation group (p=0·16). A Barrett's segment (<2 cm, intestinal metaplasia) was found in one (2%) patient treated with peroral endoscopic myotomy during endoscopy 5 years after initial treatment.

The median achalasia-DSQoL score was similar at 5 years after treatment with peroral endoscopic myotomy and pneumatic dilation (table 3). There was no significant difference between the groups in median physical component summary score or median mental component summary score general quality of life subscales using the SF-36 questionnaire (table 3).

Details of adverse events that occurred at the time of the trial have been published previously.[4] Between 2 and 5 years after treatment, no patients in either group had intervention-related serious adverse events.

Between 2 and 5 years after treatment, one (2%) patient in the peroral endoscopic myotomy group and two (4%) in the pneumatic dilation group had serious adverse events that were considered not to be related to the intervention. One (2%) patient in the pneumatic dilation group died due to a melanoma. One (2%) patient in the pneumatic dilation group was diagnosed with dementia and 5-year follow-up for this patient is missing; however, this patient's treatment was already considered to have failed. One (2%) patient treated with peroral endoscopic myotomy had a stroke and this patient was able to continue planned follow-up.

The post-hoc sensitivity analysis of the primary outcome using last observation carried forward showed a high treatment success rate after peroral endoscopic myotomy (52 [81%] of 64) compared with pneumatic dilation (28 [42%] of 66; unadjusted absolute difference 39% [95% CI 24–54]; p<0·0001). Post-hoc analysis evaluating the effect of additional pneumatic dilations up to a 40 mm balloon if they were not marked as treatment failure showed an improved treatment success rate (27 [43%] of 63) in the pneumatic dilation group; however, this was still significantly lower than in the peroral endoscopic myotomy group (50 [81%] of 62; unadjusted absolute difference 38% [95% CI 22–53]; p<0·0001; appendix p 2).

Additional analysis showed a significantly higher rate of treatment failure in the peroral endoscopic myotomy group in patients younger than 40 years at the time of randomisation compared with patients aged 40 years or older (eight [44%] of 18 *vs* four [9%] of 44; p=0·0033). In the pneumatic dilation group, no significant difference in treatment success was seen comparing patients younger and older than 40 years at the time of randomisation (16 [73%] of 22 *vs* 22 [54%] of 41; p=0·21). In addition, achalasia subtype, gender, barium column height, Eckardt score, and integrated relaxation pressure at baseline were not found to be prognostic factors of treatment success in either treatment group (data not shown).

We did an additional analysis excluding patients with achalasia type III. In this analysis, more patients in the peroral endoscopic myotomy group had treatment success compared with the pneumatic dilation group (43 [84%] of 51 *vs* 22 [40%] of 55; unadjusted absolute difference 44% [95% CI 28–62]; p<0·0001). Secondary outcomes in this subgroup are shown in the appendix (p 3).

Discussion

Our findings suggest that peroral endoscopic myotomy has a significantly greater long-term therapeutic success than a single series of pneumatic dilations. Peroral endoscopic myotomy was associated with significantly greater use of proton-pump inhibitors and clinically relevant reflux symptoms compared with pneumatic dilation at 5-year follow-up. Quality of life was similar in both groups.

In this study, the success rate of 40% after pneumatic dilation treatment at 5-year follow-up is low compared with the success rates found in other trials, which varied from 50% to 85%.[18,19] One reason to explain this difference is the pneumatic dilation protocol followed in this study. Treatment was classified as having failed if symptoms persisted or recurred after one or two dilations with a 30–35 mm balloon or a 30 mm followed by a 35 mm balloon. Other studies used more extensive pneumatic dilation protocols, including dilation with a 40 mm balloon in cases of clinical recurrence or permitting repeated dilations during follow-up. Indeed, it could be argued that repeated pneumatic dilation should be acceptable as it reflects common clinical practice and, in guidelines published in 2020,[20] the need for infrequent redilations is usually not considered as treatment failure.[2,11,18,19] However, repeated pneumatic dilation could also be considered as a new treatment, representing an added burden for patients and a repeated risk of perforation. Therefore, a priori, in this trial we sought to compare the effect of peroral endoscopic myotomy with a single pneumatic dilation series.

The greater incidence of reflux oesophagitis after peroral endoscopic myotomy is generally considered a concern. At 2-year follow-up, 22 (41%) of 54 patients treated with peroral endoscopic myotomy had reflux oesophagitis compared with two (7%) of 29 patients after treatment with pneumatic dilation. 5 years after treatment, 14 (33%) of 42 patients in the peroral endoscopic myotomy group and two (13%) of 16 in the pneumatic dilation group showed reflux oesophagitis (p=0·19). It should be noted that the number of successfully treated patients who underwent endoscopy was small in the pneumatic dilation group (16 patients); therefore, it is very likely that the lack of significance reflects the low sample size. Additionally, proton-pump inhibitors were not stopped during endoscopy, which might have influenced the incidence of reflux oesophagitis. The consequence of severe reflux

after peroral endoscopic myotomy are not yet known and are a concern. The use of proton-pump inhibitors was significantly greater after peroral endoscopic myotomy than after pneumatic dilation at 5 years. In patients using proton-pump inhibitors, more patients in the peroral endoscopic myotomy group than in the pneumatic dilation group reported a GERDQ score of 8 or more, although the difference was not significant. Indeed, many patients treated with peroral endoscopic myotomy will depend on chronic use of a proton-pump inhibitor and it seems appropriate to inform patients of this before treatment.

5-year success rates for laparoscopic Heller myotomy seen in previous studies (80–85%)[18] are similar to those we observed for peroral endoscopic myotomy. In line with this, another trial directly comparing laparoscopic Heller myotomy and peroral endoscopic myotomy did not show a significant difference in treatment success at 2-year follow-up.[10] Of note, this trial did also include patients who were previously treated endoscopically (with pneumatic dilation or botulinum toxin injections). The fact that patients who had previously had dilation were included might also explain the lower success rate of peroral endoscopic myotomy at 2 years compared with our trial (83% *vs* 92%). In the trial by Werner and colleagues, the additional analysis excluding patients who had previously had dilation showed a treatment success rate of 89% after peroral endoscopic myotomy.[10]

Although type III achalasia has been associated with a greater risk of treatment failure for both pneumatic dilation and peroral endoscopic myotomy, this was not confirmed by our data.[16] Most likely, the number of patients with type III achalasia in our trial was too small to show a difference.

Our study found a significantly higher treatment failure after peroral endoscopic myotomy in patients younger than 40 years than in patients aged 40 years and older. This finding is similar to previous observations that an older age is associated with greater treatment success in most but not all studies.[21]

Although our study has shown that peroral endoscopic myotomy has greater long-term efficacy than pneumatic dilation, with a low risk of major treatment-related complications, this should not lead to abandonment of pneumatic dilation from clinical practice. Pneumatic dilation is less time-consuming, easier to learn, and is less likely to result in reflux oesophagitis or reflux symptoms compared with peroral endoscopic myotomy. Other reasons to prefer pneumatic dilation to peroral endoscopic myotomy are the need for general anaesthesia with peroral endoscopic myotomy and a potentially prolonged hospital stay after peroral endoscopic myotomy. Ideally, all treatment options should be discussed with treatment-naive patients with achalasia and a shared decision should be made based on patients' characteristics, such as achalasia subtype, age, comorbidity, and the patient's preference.

Some limitations to this study must be acknowledged. First, this trial had an unblinded design. Blinding of the trial would have required all patients allocated to pneumatic dilation to undergo general anaesthesia and admission similar to patients allocated to peroral endoscopic myotomy. Patients allocated to peroral endoscopic myotomy would need to undergo a sham pneumatic dilation 2 weeks after initial treatment. This was considered unethical and logistically highly complex. Second, it is difficult to evaluate the secondary outcomes in this study. If only the successfully treated patients were considered for evaluation there would be a selection bias. Alternatively, if all patients included in the study were used to evaluate the secondary outcomes, there would be a bias due to the high number of cross-over treatments. This might explain why no difference was seen between the groups in parameters of high-resolution manometry, barium column height, and quality of life. Finally, no 24 h pH-impedance monitoring was done 5 years after initial treatment to reduce patient discomfort.

The strengths of this trial include the large number of patients included given the low prevalence of the disease, the use of objective measurements to evaluate treatment success and manometric features, the long-term follow-up, and the small proportion of patients (4%) who were lost to follow-up 5 years after treatment.

Our findings suggest that peroral endoscopic myotomy results in a significantly greater long-term treatment success than a single series pneumatic dilation (30–35 mm) in treatment-naive patients with achalasia. The incidence of reflux symptoms and proton-pump inhibitor use remains high 5 years after peroral endoscopic myotomy. Based on this study, peroral endoscopic myotomy should be proposed as an initial treatment option for patients with achalasia.

Contributors

TK and AJB accessed and verified the data. FAP, PFo, PWYC, PJK, JEP, AJPMS, and AJB contributed to the concept and design. TK, FAP, BAJB, PFo, AL, RABON, TB, JK, TF, PWYC, JCYW, VWYW, GC, PF, JEP, AJPMS, HN, and AJB contributed to acquisition, analysis, or interpretation of data. TK, FAP, RABON, and AJB drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. TK and FAP did the statistical analysis. PFo and AJB obtained funding. FAP, PFo, AL, TB, TF, PWYC, JCYW, PFa, PJK, JEP, and AJB provided administrative, technical, or material support. FAP, PFo, TB, GC, PFa, PJK, AJPMS, and AJB provided supervision. All authors had access to the study data and reviewed and approved the final manuscript. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

PFo received consultancy fees from Olympus and Cook Endoscopy. HN declares the following financial relationships with a commercial interest: consulting for Boston Scientific, Olympus, Medtronic, Cook, and Microtech; and grant or research support from Pentax and Erbe. TB declares the following financial relationships with a commercial interest: consulting for Olympus and Erbe. TF received speaker or consulting fees from Dr Wilmar Schwab, Sanofi-Aventis Deutschland, Takeda Pharma Vertriebs, Falk Foundation, Medizinisches Forum, Forum Medizinische Fortbildung, Promedia Medizintechnik A Ahnfeldt,

MEDICE Arzneimittel Pütter, ABOCA Group, Reckitt Benckiser Deutschland, Bayer Vital. PWYC declares the following financial relationships with a commercial interest: board membership for Cornerstone Robotics; advisory committees or review panels for EndoVision and EndoMaster; and consulting for Boston Scientific. GC reported the following financial relationships with a commercial interest: advisory committees or review panels for Olympus and Cook Endoscopy; and grant or research support from Boston Scientific. JEP received research funding from National Institutes of Health National Institute of Diabetes and Digestive and Kidney Disease, and declares the following financial relationships with a commercial interest: consulting for Medtronic, ethicon, diversatek, Ironwood, Phathom, and Neurogastrx; patent held or filed (FLIP-AI) for Medtronic; and speaking and teaching for Medtronic and ethicon. AJB received research funding from Nutricia, Dr Falk Pharma, Thelial, Side Sleep Technologies and Bayer and received speaker or consulting fees from Laborie, Medtronic, Dr Falk Pharma, Alimentiv, Sanofi/Regeneron, and AstraZeneca. All other authors declare no competing interests.

Data sharing

Data will be shared with third parties after written request to the corresponding author describing intention and full affiliation of the requesting organisation. If the request is approved and a data access agreement is signed only de-identified data will be shared. Data are available with publication.

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References

1 Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. *Lancet* 2014; **383:** 83–93.
2 Oude Nijhuis RAB, Zaninotto G, Roman S, et al. European guidelines on achalasia: United European Gastroenterology and European Society of Neurogastroenterology and Motility recommendations. *United European Gastroenterol J* 2020; **8:** 13–33.
3 Lynch KL, Pandolfino JE, Howden CW, Kahrilas PJ. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic review of the literature. *Am J Gastroenterol* 2012; **107:** 1817–25.
4 Ponds FA, Fockens P, Lei A, et al. Effect of peroral endoscopic myotomy *vs* pneumatic dilation on symptom severity and treatment outcomes among treatment-naive patients with achalasia: a randomized clinical trial. *JAMA* 2019; **322:** 134–44.
5 Pandolfino JE, Gawron AJ. Achalasia: a systematic review. *JAMA* 2015; **313:** 1841–52.
6 Boeckxstaens GE, Annese V, des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011; **364:** 1807–16.
7 Wang HM, Tai WC, Chuah SK, et al. Comparison of treatment outcomes of endoscope-guided pneumatic dilation and laparoscopic Heller myotomy. *Kaohsiung J Med Sci* 2015; **31:** 639–43.
8 Campos GM, Vittinghoff E, Rabl C, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 2009; **249:** 45–57.
9 Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42:** 265–71.
10 Werner YB, Hakanson B, Martinek J, et al. Endoscopic or surgical myotomy in patients with idiopathic achalasia. *N Engl J Med* 2019; **381:** 2219–29.
11 Weusten BLAM, Barret M, Bredenoord AJ, et al. Endoscopic management of gastrointestinal motility disorders—part 1: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2020; **52:** 498–515.
12 Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil* 2015; **27:** 160–74.
13 Eckardt VF. Clinical presentations and complications of achalasia. *Gastrointest Endosc Clin N Am* 2001; **11:** 281–92.
14 Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009; **30:** 1030–38.
15 Frankhuisen R, Heijkoop R, van Herwaarden MA, et al. Validation of a disease-specific quality-of-life questionnaire in a large sample of Dutch achalasia patients. *Dis Esophagus* 2008; **21:** 544–50.
16 Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; **305:** 160–64.
17 Familiari P, Gigante G, Marchese M, et al. Peroral endoscopic myotomy for esophageal achalasia: outcomes of the first 100 patients with short-term follow-up. *Ann Surg* 2016; **263:** 82–87.
18 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:** 732–39.
19 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.
20 Weusten BLAM, Barret M, Bredenoord AJ, et al. Endoscopic management of gastrointestinal motility disorders—part 1: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2020; **52:** 498–515.
21 Oude Nijhuis RAB, Prins LI, Mostafavi N, van Etten-Jamaludin FS, Smout AJPM, Bredenoord AJ. Factors associated with achalasia treatment outcomes: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2020; **18:** 1442–53.