JAMA | Original Investigation

Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia
A Randomized Clinical Trial

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IMPORTANCE Case series suggest favorable results of peroral endoscopic myotomy (POEM) for treatment of patients with achalasia. Data comparing POEM with pneumatic dilation, the standard treatment for patients with achalasia, are lacking.

OBJECTIVE To compare the effects of POEM vs pneumatic dilation as initial treatment of treatment-naive patients with achalasia.

DESIGN, SETTING, AND PARTICIPANTS This randomized multicenter clinical trial was conducted at 6 hospitals in the Netherlands, Germany, Italy, Hong Kong, and the United States. Adult patients with newly diagnosed achalasia and an Eckardt score greater than 3 who had not undergone previous treatment were included. The study was conducted between September 2012 and July 2015, the duration of follow-up was 2 years after the initial treatment, and the final date of follow-up was November 22, 2017.

INTERVENTIONS Randomization to receive POEM (n = 67) or pneumatic dilation with a 30-mm and a 35-mm balloon (n = 66), with stratification according to hospital.

MAIN OUTCOMES AND MEASURES The primary outcome was treatment success (defined as an Eckardt score ≤3 and the absence of severe complications or re-treatment) at the 2-year follow-up. A total of 14 secondary end points were examined among patients without treatment failure, including integrated relaxation pressure of the lower esophageal sphincter via high-resolution manometry, barium column height on timed barium esophagogram, and presence of reflux esophagitis.

RESULTS Of the 133 randomized patients, 130 (mean age, 48.6 years; 73 [56%] men) underwent treatment (64 in the POEM group and 66 in the pneumatic dilation group) and 126 (95%) completed the study. The primary outcome of treatment success occurred in 58 of 63 patients (92%) in the POEM group vs 34 of 63 (54%) in the pneumatic dilation group, a difference of 38% ([95% CI, 22%-52%]; $P < .001$). Of the 14 prespecified secondary end points, no significant difference between groups was demonstrated in 10 end points. There was no significant between-group difference in median integrated relaxation pressure (9.9 mm Hg in the POEM group vs 12.6 mm Hg in the pneumatic dilation group; difference, 2.7 mm Hg [95% CI, −2.1 to 7.5]; $P = .07$) or median barium column height (2.3 cm in the POEM group vs 0 cm in the pneumatic dilation group; difference, 2.3 cm [95% CI, 1.0-3.6]; $P = .05$). Reflux esophagitis occurred more often in the POEM group than in the pneumatic dilation group (22 of 54 [41%] vs 2 of 29 [7%]; difference, 34% [95% CI, 12%-49%]; $P = .002$). Two serious adverse events, including 1 perforation, occurred after pneumatic dilation, while no serious adverse events occurred after POEM.

CONCLUSIONS AND RELEVANCE Among treatment-naive patients with achalasia, treatment with POEM compared with pneumatic dilation resulted in a significantly higher treatment success rate at 2 years. These findings support consideration of POEM as an initial treatment option for patients with achalasia.

TRIAL REGISTRATION Netherlands Trial Register number: NTR3593

JAMA. 2019;322(2):134-144. doi:10.1001/jama.2019.8859

Visual Abstract

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Achalasia is an esophageal motility disorder characterized by absent peristalsis in the esophageal body and impaired relaxation of the lower esophageal sphincter (LES), which hampers esophageal emptying, that typically results in symptoms of dysphagia, regurgitation of food, chest pain, and weight loss.[1] Treatment for patients with achalasia involves medical, endoscopic, and surgical options. Endoscopic pneumatic dilation is the most commonly performed treatment worldwide for patients with achalasia. The procedure is minimally invasive and the long-term therapeutic rate of success, defined as a reduction of the Eckardt score to less than or equal to 3 and the absence of the need for retreatment, is 50% to 85%.[2-5] Approximately 1% to 3% of endoscopic pneumatic dilation procedures are complicated by a perforation.[2,6,7] Laparoscopic Heller myotomy combined with an antireflux procedure offers a more permanent solution for patients with achalasia, with success rates of 80% to 90%.[2,3,6] However, this technique is considerably more invasive and can be associated with severe complications, including transmural perforation (4%-10%), bleeding, or infection, and, therefore, is generally considered as treatment for patients who do not respond to pneumatic dilation.[6]

In 2009, peroral endoscopic myotomy (POEM) was introduced as an alternative treatment option for patients with achalasia.[8,9] The technique allows myotomy to be performed endoscopically.[8] Advantages of POEM include a lack of abdominal incisions, rapid recovery, possibility to create a longer proximal myotomy, and high efficacy.[8,10,11] Findings of case series have led to increased adoption of POEM.[8,9,12-15] However, data comparing POEM with the current treatment options in a randomized clinical trial are lacking. Because pneumatic dilation is considered the current standard of care for patients with achalasia, and some clinicians are questioning whether more invasive procedures than pneumatic dilation, such as POEM or laparoscopic Heller myotomy, should be contemplated as first-line treatment, a primary comparison between POEM and pneumatic dilation is relevant. Therefore, the aim of this study was to compare the effects of POEM vs pneumatic dilation as the initial treatment for treatment-naive patients with idiopathic achalasia.

Key Points

Question What is the effect of peroral endoscopic myotomy (POEM), compared with pneumatic dilation, on symptom severity and treatment outcomes among patients with treatment-naive achalasia?

Findings In this randomized clinical trial that included 133 treatment-naive adult patients with achalasia, the treatment success rate, defined as a reduction in the patient's Eckardt score to less than or equal to 3 and the absence of severe complications or need for re-treatment, after 2 years of follow-up was 58 of 63 patients (92%) in the POEM group and 34 of 63 (54%) in the pneumatic dilation group, which was a statistically significant difference.

Meaning These findings support the consideration of POEM as an initial treatment option for patients with achalasia.

Methods

Study Design

This was a multicenter randomized clinical trial. Patients seen in 6 hospitals with expertise in achalasia management in the Netherlands, Germany, Italy, Hong Kong, and the United States between September 2012 and July 2015 were included. The institutional review board of each hospital approved the study protocol (Supplement 1). Written informed consent was obtained from each patient before enrollment and randomization. Patients were followed up 3 months, 1 year, and 2 years after initial treatment. The primary end point was measured at the 2-year follow-up. A data and safety monitoring board reviewed the safety and efficacy of the treatment groups each time 20 consecutive patients were included. The statistical analysis plan is available in Supplement 2.

Patients and Eligibility Criteria

Adult patients aged 18 to 80 years were eligible for enrollment if they were newly diagnosed with symptomatic achalasia, had an Eckardt symptom score greater than 3, and had an American Society of Anesthesiologists classification of I to II (range, I-VI; I indicates a healthy patient; II indicates a mild systemic disease).[16] 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).[17] Diagnosis of achalasia was based on high-resolution manometry (HRM) findings and defined as absent peristalsis with impaired relaxation of the LES reflected by an integrated relaxation pressure (IRP) of at least 15 mm Hg.[18] Patients were excluded if they had previous endoscopic or surgical treatment for achalasia, except botulinum toxin injections received more than 3 months before inclusion. Detailed eligibility criteria are provided in Supplement 1.

Randomization and Masking

Web-based randomization assigned patients to undergo POEM or pneumatic dilation in a 1:1 ratio with a random block size of 8 and with stratification according to hospital. Study staff enrolled the patients. Randomization concealment for the type of treatment was maintained for both patients and study staff until official study enrollment. Blinding for treatment was not possible because of the different technical approach of each procedure.

Interventions

Pneumatic Dilation

Pneumatic dilation was performed by experienced endoscopists who had each performed more than 20 pneumatic dilation procedures. Under fluoroscopic guidance, a Rigiflex balloon (Boston Scientific) was positioned at the esophagogastric junction and dilated at a pressure of 5 psi for 1 minute,

followed by dilation with 8 psi for another minute. Initial pneumatic dilation was performed using a 30-mm balloon. Symptoms were evaluated 3 weeks after the procedure, and if the Eckardt score was greater than 3, a subsequent pneumatic dilation with a 35-mm balloon was scheduled (eFigure 1 in Supplement 3). Patients with an Eckardt score less than or equal to 3 underwent an HRM and, if the IRP was at least 10 mm Hg, a second pneumatic dilation with a 35-mm balloon was scheduled (eFigure 1 in Supplement 3). All patients randomized to receive pneumatic dilation underwent 1 or 2 pneumatic dilations within 6 to 8 weeks after randomization. Follow-up started after the first pneumatic dilation was performed, but assessment of the secondary end points was performed after the last pneumatic dilation. Patients were instructed to adhere to a liquid diet for 3 days before the procedure and to ingest only clear liquids the day before the procedure. The patients were instructed not to ingest any food or liquids by mouth for 8 hours before the procedure. After each pneumatic dilation, a proton pump inhibitor (PPI; once daily for 2 weeks) was prescribed.

Peroral Endoscopic Myotomy

POEM is an advanced endoscopic procedure and was performed by expert endoscopists who had each performed more than 20 POEM procedures. POEM was performed while the patient received general anesthesia with endotracheal intubation and was in the supine position. The patient's mouth, throat, and esophagus were rinsed with saline and chlorhexidine. The POEM procedure was then performed as described by Inoue et al.[8] Detailed information on the full procedure is described in eAppendix 1 in Supplement 3. Patients were admitted to the hospital the day before or the day of the procedure (depending on the travel distance of each patient) and discharged the day after. Patients undergoing POEM were instructed to adhere to the same diet as patients undergoing pneumatic dilation before the procedure. On the day of the procedure, antibiotics (metronidazole plus cefazoline) and a double-dose PPI were administered to the patient intravenously. The day after the procedure, patients were discharged after fluoroscopy was performed to rule out leakage or perforation. At discharge, patients were advised to adhere to a liquid diet for 1 day followed by a soft diet for 2 weeks and were prescribed a PPI (once daily for 2 weeks).

Outcomes

The primary outcome was treatment success at the 2-year follow-up, defined by an Eckardt score less than or equal to 3 and the absence of severe treatment-related complications or the need for endoscopic or surgical re-treatment. 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 assessed at baseline and 3 months, 1 year, and 2 years after initial treatment and included the following: Eckardt score, basal LES pressure and IRP based on HRM findings, esophageal stasis and diameter evaluated by timed barium esophagogram, complication rate, the rate of endoscopic or surgical re-treatment, presence of reflux esophagitis based on endoscopy findings, esophageal acid exposure, reflux symptoms, PPI use, and general health-related (physical and mental aspects) and achalasia-related quality of life.

Reflux symptoms were analyzed with the Gastroesophageal Reflux Disease Questionnaire (GERDQ) and quality of life was assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and achalasia-specific quality-of-life (achalasia-DSQoL) questionnaire.[19-21] The GERDQ score ranged from 0 to 18, in which a score of at least 8 was highly suggestive for GERD.[19] The SF-36 measured general quality of life by scoring mental and physical aspects, which ranged from 0 to 100, with higher scores indicating a better quality of life.[20] The achalasia-DSQoL measured quality of life related to achalasia and scores ranged from 10 to 33, in which lower scores indicated a better quality of life.[21] After treatment, an IRP less than 15 mm Hg, measured via HRM, and a barium column less than 5 cm and/or greater than 50% improvement of stasis on timed barium esophagogram indicated a successful treatment.[22-25] Presence of any grade of reflux esophagitis after treatment was considered clinically relevant. Complications were classified as serious adverse events (severe) or adverse events (mild) (detailed classification criteria are provided in eAppendix 2 in Supplement 3).

Clinical Assessment and Follow-up

At baseline, medical history was obtained and physical examination and routine laboratory tests were performed (eFigure 1 in Supplement 3). Patients completed the GERDQ, SF-36, and achalasia-DSQoL questionnaires. HRM was performed to diagnose achalasia and to differentiate patients into achalasia subtypes.[18] Upper endoscopy and a timed barium esophagogram were performed to quantify esophageal stasis by measuring barium column height at 5 minutes on radiographic images after ingesting 200 mL of low-density barium sulfate suspension during a time window of 30 to 60 seconds.[26]

Symptoms and questionnaires were assessed and HRM and timed barium esophagogram were performed 3 months, 1 year, and 2 years after treatment (eFigure 1 in Supplement 3). Esophageal 24-hour pH-impedance monitoring was performed after PPI cessation for at least 7 days at the 1-year follow-up to evaluate esophageal acid exposure (percentage pH <4). Upper endoscopy was performed at the 1-year and 2-year follow-up visits. For the 2-year follow-up, patients who were taking PPIs did not have to discontinue PPI use. Severity of reflux esophagitis was scored according to the Los Angeles classification, with no reflux esophagitis to mild esophagitis classified as grade A to B and severe esophagitis as grade C to D.[27] Grade A was defined as at least 1 mucosal break with a length of less than or equal to 5 mm that did not extend between the tops of 2 mucosal folds, B as at least 1 mucosal break with a length greater than 5 mm that did not extend between the tops of 2 mucosal folds, C as at least 1 mucosal break that was continuous between the tops of 2 or more mucosal folds and involving less than 75% of the esophageal circumference, and D as at least 1 mucosal break that is continuous between the tops of 2 or more mucosal folds and involving a least 75% of the esophageal circumference.[27] After treatment,

PPI was started for patients who experienced reflux symptoms independent of follow-up time or when reflux esophagitis was observed during upper endoscopy.

Re-treatment After Unsuccessful Treatments

Patients in whom initial pneumatic dilation was unsuccessful underwent re-treatment with pneumatic dilation with a 40-mm balloon, and, if symptoms persisted, they were offered POEM (Supplement 1). Re-treatment for patients in whom initial POEM was unsuccessful consisted of pneumatic dilation, starting with a 30-mm balloon and followed by a 35-mm balloon and 40-mm balloon if necessary (Supplement 1). Follow-up after re-treatment was continued according to protocol following initial treatment.

Statistical Methods

Based on assumed success rates of 90% for POEM[12,14,15] and 70% for pneumatic dilation[2-5] after 2 years, a difference of at least 20% in success rates between the treatments was hypothesized for the purpose of sample size calculations. With 62 patients per treatment group (124 patients in total), the study would have 80% power to detect the described difference in success rate, with a 2-sided α of .05. To account for an estimated 5% loss to follow-up, the aim was to enroll 130 patients. The data and safety monitoring board was assigned to advise on early termination of the study because of unacceptable occurrence of serious adverse events (SAEs), defined as an incidence of SAEs greater than 10% per treatment group, or because of futility.

Primary analysis of the primary and secondary outcomes was conducted at the 2-year follow-up and included all patients, except patients who did not undergo treatment after randomization or who were lost to follow-up. Patients were analyzed according to their randomization group. In cases of unsuccessful treatment, patients were excluded from further analysis of the secondary outcomes. The per-protocol analysis included patients who received treatment according to the study protocol and was only performed for the primary outcome. Missing data for the primary outcome were addressed by performing a post hoc sensitivity analysis using multiple imputation with 5 iterations.

Post hoc analyses were performed for adjustment of the primary outcome by center and interaction with achalasia subtype. Additionally, primary and secondary outcomes at 3-month and 1-year follow-ups and efficacy of re-treatment with pneumatic dilation after treatment failure were assessed post hoc.

Continuous data are presented as mean (SD) or median (interquartile range [IQR]), according to distribution. Categorical data are presented as percentages. Continuous data were compared using unpaired *t* or Mann-Whitney tests and categorical data were analyzed using χ^2 or Fisher exact tests. Absolute differences of comparative results were calculated by subtracting percentages, means, or medians of the groups and calculating the 95% CIs of the difference. Linear mixed models for repeated measures during follow-up were used to analyze the effect of treatment type on continuous secondary outcome parameters with fixed effects for time and treatment. A random intercept was set for each patient to capture the correlation among measurements within the same patient. Pneumatic dilation was used as the reference and nonparametric data were first log transformed. Success rates in the treatment groups were analyzed by comparing percentages using χ^2 and post hoc logistic regression. To adjust for the heterogeneity of centers on the primary outcome, a post hoc analysis was performed using mixed-effect logistic regression with center as a random intercept. To study the interaction of achalasia subtype on treatment in relation to primary outcome, a post hoc subgroup analysis was performed using logistic regression, including interaction variables, with pneumatic dilation and subtype II achalasia as references. *P* values less than .05 were considered statistically significant. All reported *P* values are 2-tailed. Findings for the secondary end points are considered exploratory because adjustment for multiple comparisons was performed post hoc using the Holm-Bonferroni method. Statistical analysis was performed using IBM SPSS Statistics 24 (IBM Corporation) and R software, version 3.4.0.

Results

Enrollment and Patient Characteristics

Between September 2012 and July 2015, 133 patients with achalasia were randomized, of whom 67 were randomly assigned to receive POEM and 66 were assigned to receive pneumatic dilation (**Table 1**). Three patients randomized to receive POEM never underwent treatment (**Figure 1**). The final date of follow-up was November 22, 2017.

A total of 130 patients were included in the analyses (64 in the POEM group and 66 in the pneumatic dilation group; age range, 18-80 years; mean age, 48.6 years; 73 [56%] men; Figure 1). Four patients were lost to follow-up during the study. In the pneumatic dilation group, 50 patients underwent 2 dilations and 16 patients only underwent pneumatic dilation with a 30-mm balloon. The single pneumatic dilation was performed in 10 patients according to the protocol, but 6 patients refused to undergo an additional HRM because of complete symptom relief. These patients were not excluded from follow-up. Median (IQR) follow-up time for the POEM group was 24 (24-24) months compared with 24.5 (24-25) months in the pneumatic dilation group. Baseline characteristics were similar between groups (Table 1).

Primary Outcome

Analysis of the primary outcome showed higher treatment success at the 2-year follow-up in the POEM group (58 of 63 patients [92%]) than in the pneumatic dilation group (34 of 63 patients [54%]) (absolute difference, 38% [95% CI, 22%-52%]; *P* < .001; risk ratio, 1.71 [95% CI, 1.34-2.17]; **Table 2**). In the pneumatic dilation group, 1 patient had an unsuccessful treatment related to an SAE, which involved a perforation that occurred during pneumatic dilation with a 30-mm balloon (Table 2 and **Figure 2**). The other patients who had unsuccessful initial treatment were all symptomatic

Table 1. Baseline Characteristics of Patients in a Study of the Effect of Peroral Endoscopic Myotomy (POEM) vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes in Patients With Achalasia

Characteristic	No. (%)	
	POEM (n = 64)	Pneumatic dilation (n = 66)
Center (location)		
Amsterdam UMC (the Netherlands)	38 (59)	36 (55)
Evangelische Krankenhaus (Düsseldorf, Germany)	8 (12.5)	10 (15)
Agostino Gemelli University Hospital (Rome, Italy)	8 (12.5)	9 (13)
Prince of Wales Hospital (Hong Kong, China)	7 (11)	9 (14)
Helios Klinikum Krefeld (Düsseldorf, Germany)	2 (3)	1 (2)
Northwestern Memorial Hospital (Chicago, Illinois)	1 (2)	1 (2)
Sex		
Male	33 (52)	40 (61)
Female	31 (48)	26 (39)
Age, median (IQR), y	47 (37-56)	50 (32-62)
Weight, mean (SD), kg	71.5 (16.1)	69.6 (13.9)
BMI, mean (SD)	23.2 (3.7)	23.4 (4.1)
Achalasia subtype[a]		
I	10 (16)	21 (32)
II	42 (65)	39 (59)
III	12 (19)	6 (9)
Eckardt score, median (IQR)[b]	8 (6-9)	7 (6-9)
Basal lower esophageal sphincter pressure, median (IQR), mm Hg	31 (25-45)	32.8 (24-45)
Integrated relaxation pressure, median (IQR), mm Hg	26.4 (20.2-34.9)	28.5 (20.4-37.3)
Barium column, median (IQR), 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, median (IQR)[c]	25 (22-27)	24 (22-26)
GERDQ score, median (IQR)[d]	8 (6-11)	8 (6-10)
SF-36 score, median (IQR)[e]		
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)

Abbreviations: Achalasia-DSQoL, achalasia-specific quality-of-life; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GERDQ, gastroesophageal reflux disease questionnaire; IQR, interquartile range; SF-36, 36-Item Short-Form Health Survey.

[a] Achalasia subtypes were based on observations from high-resolution manometry. Type I indicates 100% failed peristalsis; type II, 100% failed peristalsis and panesophageal pressurization in ≥20% of swallows; type III, no normal peristalsis and premature/spastic contractions in ≥20% of swallows.

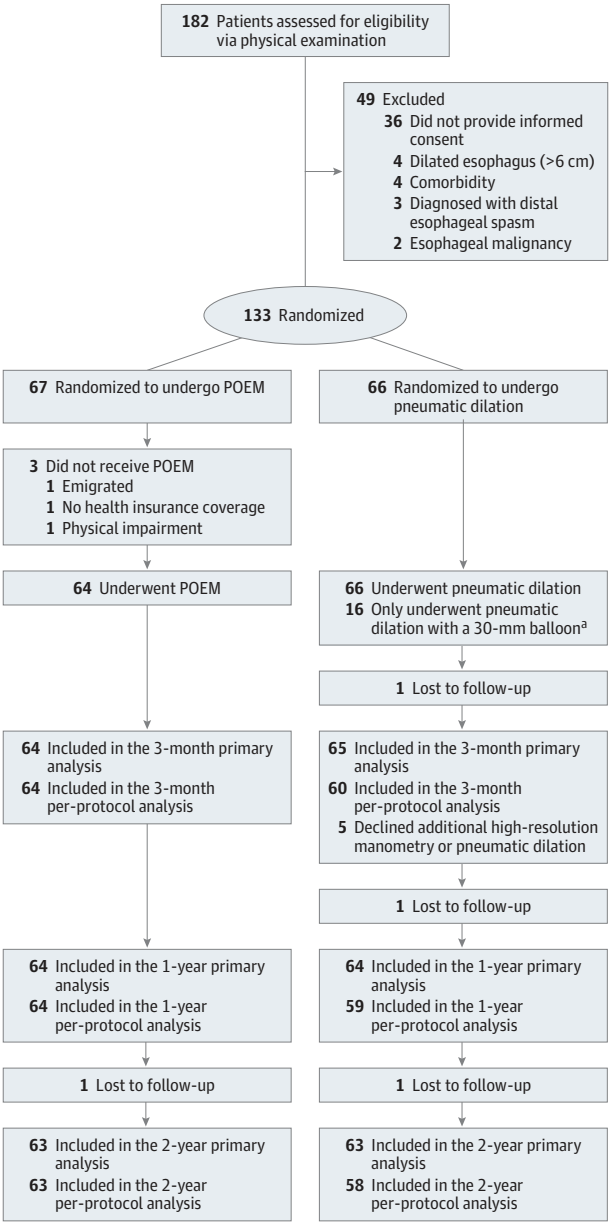
[b] Eckardt score ranges from 0-12, with a higher score indicating more severe symptoms.

[c] Achalasia-DSQoL score ranges from 10-33, with a lower score indicating a better quality of life.

[d] GERDQ score ranges from 0-18, with a score ≥8 being highly suggestive of the presence of GERD.

[e] SF-36 score consisted of a Physical Component Summary score and Mental Component Summary score, which each ranged from 0-100, with higher scores indicating better quality of life.

Figure 1. Enrollment, Randomization, and Follow-up of Patients in a Study of the Effect of Peroral Endoscopic Myotomy (POEM) vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes in Patients With Achalasia



[a] These patients only underwent a pneumodilation with a 30-mm balloon because adequate symptom control (Eckardt score ≤3) was achieved after a single pneumatic dilation procedure, confirmed by an IRP less than 10 mm Hg during high-resolution manometry. Of the 16 patients, 6 patients refused to undergo the additional high-resolution manometry.

after treatment (ie, Eckardt score >3; median [IQR] score after treatment, 4 [4-5.3]) and required re-treatment (Figure 2). Four of the 29 patients (14%) in whom pneumatic dilation was not successful underwent pneumatic dilation with a 30-mm balloon only. Two of these patients were not treated according to the protocol because they refused additional HRM.

Table 2. Primary Outcome of Overall Treatment Success in Patients With Achalasia at 2 Years, 1 Year, and 3 Months of Follow-up After Peroral Endoscopic Myotomy (POEM) or Pneumatic Dilation

	POEM		Pneumatic Dilation		Unadjusted Absolute Difference, % (95% CI)[a]	Unadjusted Risk Ratio (95% CI)	*P* Value[b]
	No. (%)	SD	No. (%)	SD			
2-y Follow-up (primary end point)	**(n = 63)**		**(n = 63)**				
Overall treatment success	58 (92)	3.4	34 (54)	6.3	38 (22 to 52)	1.71 (1.34 to 2.17)	<.001
Reasons for failure[c]							
Eckardt score >3	5 (8)	3.4	28 (44)	6.2	36 (20 to 50)		<.001
Re-treatment	5 (8)	3.4	26 (41)	10.5	33 (17 to 47)		<.001
Treatment-related SAEs	0	0	1 (1.6)	1.6	1.6 (−5 to 10)		>.99
3-mo Follow-up (secondary end point)	**(n = 64)**		**(n = 65)**				
Overall treatment success	63 (98)	1.8	52 (80)	5	18 (7 to 30)	1.23 (1.09 to 1.40)	.001
Reasons for failure[c]							
Eckardt score >3	1 (2)	1.8	12 (18)	4.8	16 (5 to 29)		.002
Re-treatment	1 (2)	1.8	11 (17)	4.7	15 (4 to 27)		.004
Treatment-related SAEs	0	0	1 (2)	1.7	2 (−5 to 9)		>.99
1-y Follow-up (secondary end point)	**(n = 64)**		**(n = 64)**				
Overall treatment success	61 (95)	2.7	42 (66)	5.9	31 (17 to 45)	1.45 (1.21 to 1.75)	<.001
Reasons for failure[c]							
Eckardt score >3	3 (5)	2.7	21 (33)	5.9	28 (14 to 42)		<.001
Re-treatment	3 (5)	2.7	19 (30)	5.7	25 (11 to 38)		<.001
Treatment-related SAEs	0	0	1 (1.6)	1.6	2 (−5 to 9)		>.99

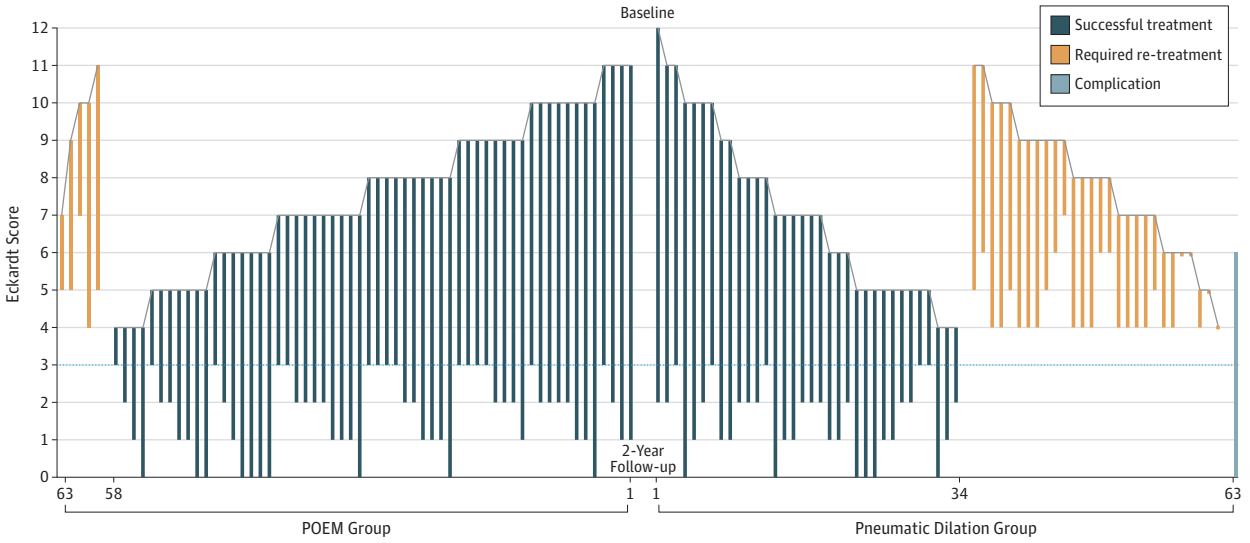
Abbreviation: SAEs, serious adverse events.

[a] Absolute difference between percentages.

[b] Success rates were analyzed by comparing percentages using χ^2 test.

[c] The reasons for failure were not mutually exclusive.

Figure 2. Eckardt Score at Baseline and the 2-Year Follow-up of Patients With Achalasia After Peroral Endoscopic Myotomy (POEM) or Pneumatic Dilation



Each vertical line represents an individual patient. Patients who achieved an Eckardt score of ≤3 (vertical line ends at or below the dashed horizontal line) had adequate symptom control and were considered successfully treated. One patient had a severe complication (a perforation) during pneumatic dilation and was considered a direct treatment failure, but still had an Eckardt score of 0 after treatment.

Secondary Outcome

Reflux Esophagitis, PPI Use, and Reflux Symptoms

At the 2-year follow-up, 54 of 58 patients (93%) in the POEM group and 29 of 34 (85%) in the pneumatic dilation group underwent endoscopy (P = .28). Reflux esophagitis was observed significantly more frequently in patients treated with POEM than with pneumatic dilation (22 of 54 patients [41%] in the POEM group, of whom 19 [35%] were assigned grade A-B and 3 [6%] were assigned grade C, vs 2 of 29 [7%] in the pneumatic dilation group, all of whom were assigned grade A; absolute difference, 34% [95% CI, 12%-49%]; P = .002). Reflux symptoms and daily use of PPI were significantly more frequent

Table 3. Secondary Outcomes at 2 Years of Follow-up After Peroral Endoscopic Myotomy in (POEM) or Pneumatic Dilation

	Median (IQR)		Unadjusted Absolute Difference (95% CI)	*P* Value[f,g]	β (95% CI)[h]	*P* Value[g]
	POEM (n = 58)	Pneumatic Dilation (n = 34)				
Eckardt score[a]	2 (1 to 3)	2 (1 to 2)	0 (−1 to 1)	.47 (.97)		
Integrated relaxation pressure, mmHg	9.9 (7 to 14)	12.6 (7.4 to 19)	2.7 (−2.1 to 7.5)	.07 (.56)	−0.09 (−0.21 to 0.04)	.19 (.76)
Basal LES pressure, mm Hg	13.6 (9 to 19.5)	20.5 (8.4 to 32)	6.9 (−7.5 to 21.3)	.58 (.58)	−0.13 (−0.26 to −0.01)	.04 (.23)
Barium column height, cm	2.3 (0 to 3.7)	0 (0 to 2.5)	2.3 (1 to 3.6)	.05 (.45)	0.60 (−0.28 to 1.49)	.18 (.90)
Barium column diameter, cm	2.6 (2.1 to 3.5)	2 (1.5 to 2.9)	0.6 (0.3 to 0.9)	.01 (.11)	0.10 (0.03 to 0.16)	.004 (.03)
Achalasia DSQoL score[b]	14 (12 to 17)	14 (11 to 17)	0 (−3 to 3)	.52 (.96)	0.02 (−0.03 to 0.06)	.45 (.99)
GERDQ score[c]	7 (6 to 8)	6 (6 to 8)	1 (0 to 2)	.003 (.04)	0.06 (0.01 to 0.11)	.02 (.16)
GERDQ score ≥8, % (SD)	40 (6.4)	27 (7.6)	13 (−7 to 32)	.20 (.98)		
SF-36 score[d]						
Physical Component Summary score	54.1 (50.9 to 57.9)	53.8 (46.1 to 57.6)	0.3 (−4.3 to 4.9)	.49 (>.99)	0.002 (−0.03 to 0.03)	.88 (.88)
Mental Component Summary score	54 (50.3 to 57.2)	52.9 (48.3 to 56)	1.1 (−1.6 to 3.8)	.49 (>.99)	0.01 (−0.02 to 0.04)	.57 (.97)
Endoscopic reflux esophagitis[e]	(n = 54)	(n = 29)				
No. (%)	22 (41)	2 (7)	34 (12 to 49)	.002 (.03)		
SD	6.5	4.7				
Grade, No. (%)						
A	17 (31)	2 (7)				
B	2 (4)	0				
C	3 (6)	0				
D	0	0				
PPI use, No (%)	24 (41)	7 (21)	20 (1 to 38)	.004 (.04)		
SD	6.5	7				
Reflux esophagitis, No. (%)	10 (42)	0				
No reflux esophagitis, No. (%)	14 (58)	7 (100)				

Abbreviations: Achalasia-DSQoL, achalasia-specific quality-of-life questionnaire; GERDQ, gastroesophageal reflux disease questionnaire; IQR, interquartile range; LES, lower esophageal sphincter; PPI, proton pump inhibitor; SF-36, 36-item Short-Form Health Survey.

[a] Eckardt score ranges from 0-12, with a higher score indicating more severe symptoms.

[b] Achalasia-DSQoL score ranges from 10-33, with a lower score indicating a better quality of life.

[c] GERDQ score ranges from 0-18, with a score ≥8 being highly suggestive of the presence of GERD.

[d] SF-36 score consisted of a Physical Component Summary score and Mental Component Summary score, which each ranged from 0-100, with higher scores indicating better quality of life.

[e] Severity of reflux esophagitis according to the Los Angeles classification. Grade A indicates mild esophagitis and ≥1 mucosal break with a length of ≤5 mm not extending between the tops of 2 mucosal folds; B, mild esophagitis and ≥1 mucosal break with a length of >5 mm not extending between the tops of 2 mucosal folds; C, severe esophagitis and ≥1 mucosal break continuous between tops of 2 or more mucosal folds involving <75% of the esophageal circumference; D, severe esophagitis and ≥1 mucosal break continuous between tops of 2 or more mucosal folds involving ≥75% of the esophageal circumference.

[f] Continuous data were analyzed using Mann-Whitney and categorical data χ^2 tests.

[g] *P* value adjusted for multiple comparison shown in parentheses.

[h] β coefficient represents the difference in outcome of continuous secondary end points between treatment groups, adjusted for repeated measurements within patients over time and measured by linear mixed models with pneumatic dilation as the reference treatment.

in patients treated with POEM (**Table 3**). The median (IQR) percentage of time with esophageal pH less than 4 during pH-impedance measurement at the 1-year follow-up was not significantly different between the POEM group (7.0% [1.1%-21.3%] vs the pneumatic dilation group (3.0% [1.0%-10.2%]) (absolute difference, 4% [95% CI, 0%-8.2%]; *P* = .95).

Eckardt Score, HRM, Timed Barium Esophagogram, and Quality of Life

The primary analysis showed no significant difference in Eckardt score, IRP and basal LES pressure based on HRM findings, barium column height and diameter during timed barium esophagogram, or quality of life at the 2-year follow-up after post hoc adjustment for multiple comparisons (Table 3). Additional linear mixed-model analysis showed that, adjusted for repeated measures over time, the esophageal diameter of patients who underwent POEM was 0.1 cm wider than patients who underwent pneumatic dilation (Table 3). No significant difference in outcomes of the other secondary end points was observed between the treatment groups over time.

Re-treatment

POEM was unsuccessful in 5 of 63 patients (8%), who then underwent re-treatment with pneumatic dilation (Figure 2).

Re-treatment was successful in 4 of the 5 patients (80%) (eTable 1 in Supplement 3). Treatment with pneumatic dilation was unsuccessful in 29 of 63 patients (46%) (Figure 2). Additional treatment with pneumatic dilation was performed in 23 of the 29 patients (79%; 3 declined, 2 received POEM, and 1 received laparoscopic Heller myotomy; eTable 1 in Supplement 3). Recurrent symptoms were observed in 9 of the 23 patients (39%), who then underwent POEM. The total number of treatments performed was 75 in the POEM group and 162 in the pneumatic dilation group ($P < .001$). The post hoc analysis, which evaluated the association between an additional pneumatic dilation with a 40-mm balloon and treatment success of pneumatic dilation, showed an improved success rate of pneumatic dilation (48 of 63 patients [76%]), but it was still less than the success rate for POEM (58 of 63 patients [92%]) (absolute difference, 16% [95% CI, 2%-30%]; $P = .008$; eTable 1 in Supplement 3).

Complications and Adverse Events

In total, 7 SAEs occurred during the study, of which 2 were related to pneumatic dilation and the other 5 occurred independent of a study intervention. One of the SAEs related to pneumatic dilation was a perforation after dilatation with a 30-mm balloon, requiring endoscopic closure, antibiotics, and 13 days of hospitalization. This patient was considered to have an unsuccessful treatment. Another patient was admitted to the hospital for 1 night after undergoing pneumatic dilation because of severe chest pain without signs of perforation. The patient continued the study and was considered to have a successful treatment. Detailed information on SAEs independent of the study interventions is provided in eAppendix 3 in Supplement 3. Adverse events were more common after POEM (42 of 63 patients [67%]) vs pneumatic dilation (14 of 63 [22%]). Adverse events in the POEM group were related to reflux esophagitis (n = 29), reflux symptoms (n = 8), Candida esophagitis (n = 2), ulcer at the esophagogastric junction that healed after PPI treatment (n = 2), and periprocedural mucosal tear that was managed conservatively and healed at endoscopy performed 1 week later (n = 1). In the pneumatic dilation group, reported adverse events were reflux esophagitis (n = 7), reflux symptoms (n = 7), Candida esophagitis (n = 1), and belching/dyspepsia (n = 1).

Sensitivity and Per-Protocol Analyses

Post hoc sensitivity analysis of the primary outcome using multiple imputation for missing data revealed a higher success rate for POEM (58 of 64 patients [91%]) compared with pneumatic dilation (35 of 66 [53%]) at the 2-year follow-up (absolute difference, 38% [95% CI, 21%-51%]; $P < .001$; risk ratio, 1.71 [95% CI, 1.34-2.18]). The per-protocol analysis of treatment success at the 2-year follow-up showed a higher success rate for POEM (58 of 63 [92%]) compared with pneumatic dilation (31 of 58 [53%]) (absolute difference, 39% [95% CI, 22%-53%]; $P < .001$; risk ratio, 1.72 [95% CI, 1.34-2.21]; eTable 2 in Supplement 3). Post hoc per-protocol analysis of treatment success at 3 months and 1 year also revealed a higher success rate with POEM vs pneumatic dilation (eTable 2 in Supplement 3).

Post Hoc Outcomes

Post hoc analysis of the primary outcome at 3 months and 1 year showed a higher success rate of POEM compared with pneumatic dilation (Table 2). Secondary end points were also evaluated 3 months and 1 year after initial treatment. No significant differences were observed in Eckardt score, IRP and basal LES pressure based on HRM findings, barium column height and diameter during timed barium esophagogram, or quality of life after post hoc adjustment for multiple comparisons (eTable 3 in Supplement 3). Endoscopy at the 1-year follow-up was completed in 59 of 61 patients (97%) in the POEM group and 36 of 42 (85%) in the pneumatic dilation group ($P = .66$). Endoscopy was performed after PPI cessation for at least 7 days and reflux esophagitis was found in significantly more patients in the POEM group (29 of 59 patients [49%], of whom 41% were assigned grade A-B and 8% were assigned grade C-D) vs the pneumatic dilation group (4 of 36 [11%], all of whom were assigned grade A-B) (absolute difference, 38% [95% CI, 17%-53%]; $P < .001$; eTable 3 in Supplement 3). Reflux symptoms and PPI use showed no statistically significant difference between treatment groups (eTable 3 in Supplement 3).

Adjusting the primary outcome for the different centers revealed an odds ratio of 12.3 ([95% CI, 4.2-37.3]; $P < .001$) for treatment success, in favor of POEM. This was comparable to the unadjusted odds ratio of 9.89 ([95% CI, 3.5-28]; $P < .001$).

The interactions between treatment, achalasia subtype, and the primary outcome were not statistically significant, with P values ranging from .23 to .35. In eTable 4 in Supplement 3, adjusted odds ratios are presented and show that the effect of POEM and pneumatic dilation on treatment outcome was not related to achalasia subtypes.

Discussion

In this randomized clinical trial that compared POEM with pneumatic dilation as the initial treatment for treatment-naive patients with achalasia, POEM resulted in a significantly higher treatment success rate at 2 years. However, development of reflux esophagitis was more frequent after POEM than after pneumatic dilation, and POEM was associated with increased PPI use.

To our knowledge, this is the first randomized clinical trial that evaluated the use of POEM as an initial treatment for achalasia. The efficacy of POEM in this study was similar to the results reported in uncontrolled prospective and retrospective studies, which showed therapeutic success rates of 80% to 97% after 12 months or more.[12-15] The definition of success in these studies was an Eckardt score less than or equal to 3, the need for re-treatment, or both. Some studies have suggested that the recurrence rate after POEM could further increase with time.[9,28] However, most of the prospective studies were not restricted to treatment-naive patients with achalasia, which makes direct comparison difficult. In previous studies involving laparoscopic Heller myotomy, efficacy at 5 years decreased to 80% to 85%.[3,5] Outcome data for POEM with such a long follow-up is not available, but it can be anticipated that

POEM most likely will perform similarly to laparoscopic Heller myotomy because 1-year and 2-year follow-up data reveal similar success rates.[2,6] Randomized clinical trials comparing POEM to laparoscopic Heller myotomy are necessary to answer that question. The observed success rate of 92% at 2 years in this trial should be considered as a medium-term outcome and follow-up data at 5 years will help to provide information about the duration of the treatment effect.

The data confirmed that POEM was a technique with a low risk of major complications because SAEs were not observed in the POEM group. For pneumatic dilation, the rate of perforations was 1.5% despite the use of the smallest (30-mm) balloon for the initial pneumatic dilation. This finding was within the reported range of complication rates of previous studies.[2,6,7] Although POEM is more invasive and requires more technical endoscopic skills, the risk of severe complications was not higher than with pneumatic dilation, especially when performed by experienced endoscopists.[6,7,29]

Treatment success of pneumatic dilation ranged from 54% to 80% during the study, which is on the lower end compared with other studies in which success ranged from 50% to 85%.[2-5,30] One reason for this discrepancy could be the pneumatic dilation protocol that was followed in the current study. Patients were considered to have unsuccessful treatment after 1 or 2 pneumatic dilation procedures with a 35-mm or smaller balloon. Other studies included an additional pneumatic dilation with a 40-mm balloon in cases of clinical recurrence or extra dilation series with 2 or 3 pneumatic dilations.[2-5] Some evidence suggests that repeated dilation is accepted and reflects daily clinical practice.[3-5] However, patients will experience persistent or recurrent symptoms after previous pneumatic dilations as failed treatment. Pursuing another series of pneumatic dilations would be a second treatment. Furthermore, each time a pneumatic dilation is performed there is a perforation risk and multiple pneumatic dilation sessions form a potential bias in the comparison to 1 treatment intervention. Therefore, the effect of just 1 series of pneumatic dilations was compared with the effect of POEM. However, 23 of the 29 patients in the pneumatic dilation group whose treatment was unsuccessful in this study subsequently underwent pneumatic dilation with a 35-mm balloon, a 40-mm balloon, or both. Of these 23 patients, 9 (39%) still had persistent symptoms and underwent POEM. The additional pneumatic dilation increased the treatment success rate of pneumatic dilation to 76%, but this was still lower than the 92% success rate of POEM. Follow-up after re-treatment was less than 6 to 12 months in most patients, which cannot imply successful treatment. Previous data suggest that if symptoms do not improve after a pneumatic dilation series with a 30-mm and/or 35-mm balloon, it is unlikely that symptoms will improve after pneumatic dilation with a 40-mm balloon.[6,31] The minimal expected effect observed after additional pneumatic dilation with a 40-mm balloon was another reason not to include subsequent dilation sessions in the protocol. The 2011 trial by Boeckxstaens et al[2] differed from the current trial in that the former had a more aggressive dilation protocol and excluded patents with serious dilation complications after pneumatic dilation from further analysis. If that trial used the same definition of treatment success as the current study, the success rate of pneumatic dilation would be lower and comparable to the success rate of this study.

The major disadvantage of POEM is the high incidence of reflux esophagitis. In this study, 49% of the patients had reflux esophagitis at the 1-year follow-up, and 8% had a severe grade. Endoscopy after 1 year was performed while PPI use in patients was discontinued, revealing the high incidence of this complication. Endoscopy after 2 years was performed while PPI use in patients receiving acid suppression was continued, which resulted in lower rates of esophagitis. Not all patients with reflux esophagitis had reflux symptoms. The frequent occurrence of reflux disease after POEM was previously described in a multicenter case controlled study of 282 patients in which endoscopic or pH-metric evidence of reflux disease after POEM was found in 58% of the patients, including endoscopic esophagitis in 23%.[10,15] Furthermore, a 2016 study by Jones et al[32] showed that the results of pH-metry after POEM did not correlate with the severity of reflux symptoms. Werner et al reported that 9 of 29 patients (31%) with a good clinical outcome and no reflux esophagitis at short-term endoscopy 3 to 6 months after undergoing POEM developed mild reflux esophagitis at later follow-up.[28] These studies illustrate the high risk of reflux esophagitis after POEM and underline the need for PPI use and endoscopic follow-up, because patients are often asymptomatic. However, the substantial prevalence of reflux esophagitis is not exclusively a problem associated with POEM. Randomized clinical trials showed that 20% of patients treated with laparoscopic Heller myotomy developed reflux esophagitis, and both retrospective and prospective long-term follow-up (5-20 years) studies reported use of antireflux medication in 39% to 65% of patients, and Barrett epithelium in 13% of these patients.[2,3,33-35] Thus, although an endoscopic or laparoscopic myotomy is highly effective for managing achalasia, it disrupts the antireflux barrier and causes significant reflux esophagitis.

The higher medium-term efficacy of POEM demonstrated by this study does not imply that pneumatic dilation should be abandoned. POEM is more time-consuming, significantly more invasive, and more likely to cause reflux esophagitis. Thus, it seems reasonable to offer both options to treatment-naive patients with achalasia and counsel them to select treatment based on the patient's characteristics, personal preference, comorbidity, and disease subtype.

The strengths of this randomized clinical trial were the substantial number of patients included, the use of objective measures to analyze treatment success and esophageal function, the use of adequately trained endoscopists to perform the procedures, and the stratification of the randomization by center. Furthermore, this was the first study, to our knowledge, in which POEM was compared with an alternative achalasia treatment in a randomized trial.

Limitations

This study had several limitations. First, a strict intention-to-treat analysis was not performed. Patients who were randomized but never underwent treatment or who were lost to

follow-up after initial treatment were excluded for the primary analysis. The number of patients excluded was small and, combined with the large treatment effect, it seems unlikely that this would affect the main conclusions. A sensitivity analysis of the primary outcome, accounting for loss to follow-up, further confirmed this. Second, the start time for follow-up was treatment initiation rather than randomization. Because of the dilation series in the pneumatic dilation group, follow-up time slightly differed between the treatment groups (24 months for the POEM group vs 24.5 months for the pneumatic dilation group). The reason for evaluation after the last performed dilation in the pneumatic dilation group was to compare a complete dilation series to a single POEM procedure. Because there was a minor difference in follow-up time, it seems unlikely that study conclusions were affected by this. Third, primary and secondary outcomes were assessed at the 2-year follow-up. Consequently, no conclusions can be drawn for longer-term treatment success of POEM, especially because achalasia is a lifelong chronic disease. Fourth, like most endoscopic or surgical studies that evaluate new interventional techniques, this trial had an unblinded design. A blinded trial would have required that patients in the pneumatic dilation group underwent general anesthesia and hospital admission and patients assigned to POEM would have had to undergo a sham pneumatic dilation.

Conclusions

Among treatment-naive patients with achalasia, treatment with POEM compared to pneumatic dilation resulted in a significantly higher treatment success rate at 2 years. These findings support consideration of POEM as an initial treatment option for patients with achalasia.

ARTICLE INFORMATION

Accepted for Publication: June 7, 2019.

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Obtained funding: Fockens, Bredenoord.
Administrative, technical, or material support: Ponds, Fockens, Lei, Beyna, Frieling, Chiu, Wu, Familiari, Kahrilas, Pandolfino, Bredenoord.
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Conflict of Interest Disclosures: Dr Fockens reported receiving personal fees from Cook Endoscopy, Olympus, Ethicon Endosurgery, and Fujifilm, consulting for Medtronic, and receiving research support from Boston Scientific and Ovesco outside the submitted work. Dr Beyna reported receiving grants, personal fees, and nonfinancial support from Olympus, and Boston Scientific, personal fees and nonfinancial support from Medtronic, personal fees from Falk Foundation, and grants and nonfinancial support from Erbe USA outside the submitted work. Dr Wu reported receiving personal fees from AstraZeneca, Takeda, Reckitt Benckiser, and Menarini outside the submitted work. Dr Costamagna reported receiving personal fees and nonfinancial support from Olympus, grants from Boston Scientific, and grants and nonfinancial support from Cook Medical outside the submitted work. Dr Kahrilas reported receiving grants from the National Institutes of Health during the conduct of the study. Dr Pandolfino reported receiving personal fees from Medtronic, Diversatek, Torax, Ironwood, and Takeda and a grant from Impleo outside the submitted work. Dr Bredenoord reported receiving grants and personal fees from Norgine, grants and personal fees from Laborie, personal fees from Medtronic, personal fees from Diversatek, grants from Nutricia, personal fees from Regeneron, personal fees from Celgene, grants and personal fees from Bayer, and personal fees from DrFalk outside the submitted work and grants from Fonds NutsOhra and ESGE Research during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was made possible with financial support from Fonds NutsOhra (FNO grant 1202-022) and an ESGE Research Grant.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 4.

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