ESOPHAGUS

Long-Term Outcomes of Peroral Endoscopic Myotomy vs Pneumatic Dilation After Prior Laparoscopic Heller Myotomy for Achalasia

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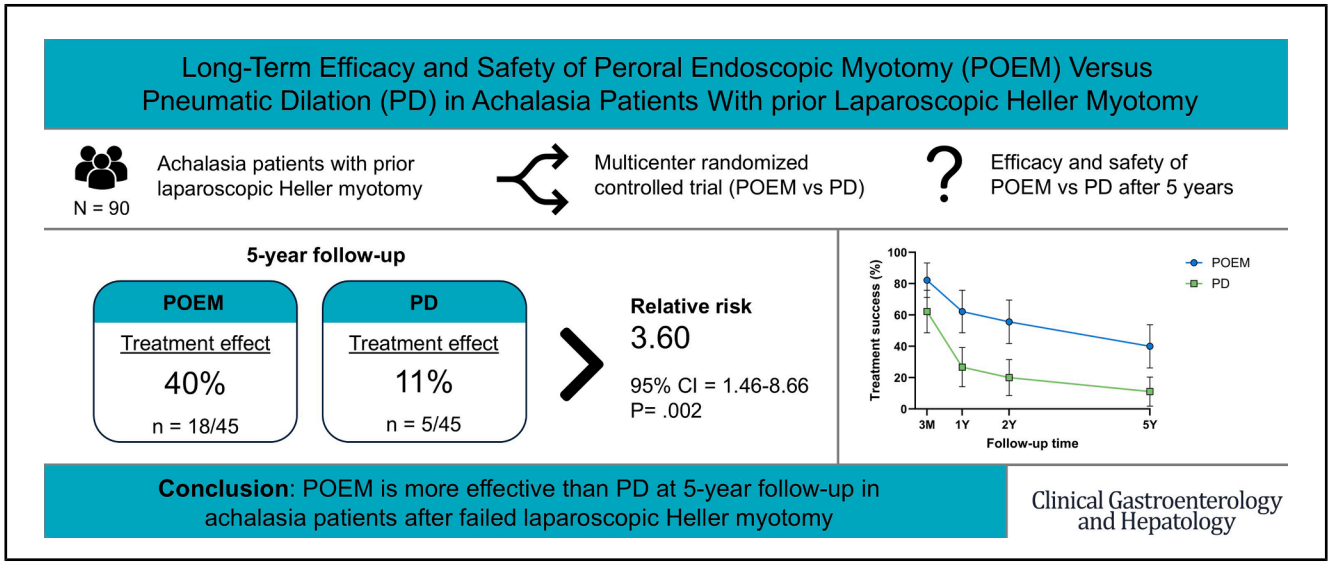

BACKGROUND & AIMS: **Peroral endoscopic myotomy (POEM) demonstrated higher efficacy at 1-year follow-up compared with pneumatic dilation (PD) in patients after failed laparoscopic Heller myotomy (LHM). The aim of this study was to evaluate the 5-year efficacy and safety of POEM compared with PD in patients with achalasia after failed LHM.**

METHODS: **This study reports the long-term follow-up results of a previously published multicenter randomized controlled trial performed in the Netherlands, Belgium, and Italy. Adult patients with achalasia confirmed by esophageal manometry were included when they had recurrent symptoms after LHM. Patients were randomized to PD 30 to 35 mm or POEM in a 1:1 ratio. The primary outcome was treatment success at 5-year follow-up, defined as Eckardt score ≤3**

Abbreviations used in this paper: Achalasia-DSQoL, Achalasia Disease-Specific Quality of Life; ASA, American Society of Anesthesiologists; CI, confidence interval; GerdQ, Gastroesophageal Reflux Disease Questionnaire; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; PD, pneumatic dilation; POEM, peroral endoscopic myotomy; PPI, proton pump inhibitor; SF-36, 36-Item Short-Form Health Survey.

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without retreatment. Patients who underwent additional dilation once up to 40 mm within 1 year after initial PD were not considered as treatment failure. Intention-to-treat analysis was applied for the primary outcome.

RESULTS: In total, 90 patients were included between January 2014 and June 2020 and randomized to PD (n = 45) or POEM (n = 45). At 5-year follow-up, treatment success was 11% after PD (n = 5/45) and 40% after POEM (n = 18/45) with a relative risk of 3.60 (95% confidence interval, 1.46–8.66; $P = .002$). Median time to treatment failure was 12 months for PD and 60 months for POEM ($P = .005$). Reflux esophagitis grade B to D was observed in 11% of the patients after POEM (n = 4/37) and in 9% after PD (n = 3/34) ($P = .548$). No procedure-related serious adverse events were reported between 1-year and 5-year follow-up.

CONCLUSIONS: POEM is more effective than PD at 5-year follow-up in patients with achalasia after failed LHM. Clinical trial registry: Dutch Trial Registry (NL4361; NTR4501)

Keywords: Achalasia; Laparoscopic Heller Myotomy; Peroral Endoscopic Myotomy; Pneumatic Dilation; Treatment Outcome.

Achalasia is a primary esophageal motility disorder characterized by absent or abnormal esophageal peristalsis and the inability of the lower esophageal sphincter (LES) to relax.[1] This leads to esophageal stasis and subsequently triggers typical achalasia symptoms including dysphagia, regurgitation of undigested food, retrosternal pain, and weight loss.[2] Main treatment options comprise pneumatic dilation (PD), peroral endoscopic myotomy (POEM) and laparoscopic Heller myotomy with Dor fundoplication (LHM), all of which aim to reduce LES pressure and thereby enhance esophageal emptying.[3] The trial was registered at https://onderzoekmetmensen.nl/nl/trial/50756 (CCMO NL48223.018.14).

During POEM, a submucosal tunnel is created towards the LES followed by myotomy of both the LES and distal part of the esophageal muscle.[4] Since the publication of the first POEM series in 2010,[5] this procedure has become a widely adopted and effective treatment option for achalasia, with numerous studies consistently demonstrating high efficacy rates of around 80% at long-term follow-up.[6] PD continues to be a commonly used treatment option; however, a graded dilation protocol and repeated dilations are often required to maintain long-term treatment effect.[7,8] Previous studies have established that PD and POEM are effective in treatment-naive patients with achalasia, with success rates, defined by Eckardt score ≤ 3 without retreatment, of 66% to 90% and 95%, respectively, at 1-year follow-up, and 40% to 82% and 81% at 5-year follow-up.[9–11]

LHM is another effective long-term treatment option for achalasia. A randomized controlled trial comparing the effect of LHM and POEM showed 5-year success rates of 71% and 75%, respectively.[12] Despite the high success rates of LHM, 16% to 29% of the patients experienced persistent or recurrent symptoms after 5-year follow-up, necessitating further treatment.[11,12] PD or POEM is recommended as rescue therapy in case of persistent or recurrent symptoms after LHM, and in some cases, redo LHM may be performed.[3]

We previously published 1-year follow-up outcomes of our multicenter randomized controlled trial comparing effects of PD and POEM in patients with achalasia and persistent or recurrent symptoms after LHM, showing PD was effective in only 26.7% of patients, whereas POEM demonstrated a success rate of 62.2%.[13] Follow-up of these patients was continued, and we now describe the 5-year efficacy and safety of POEM compared with PD in patients with achalasia and persistent or recurrent symptoms following LHM.

Methods

Study Design

This multicenter, international, randomized controlled trial was performed in 3 academic centers with achalasia expertise (Netherlands, Belgium, and Italy). The current study reports the long-term follow-up results, whereas the 1-year outcomes were published previously.[13] Patients with achalasia and persistent or recurrent symptoms after LHM were included in the study between January 2014 and June 2020. Findings from 1-year follow-up have been previously published.[13] This study reports the 5-year follow-up results after treatment. The last 5-year follow-up visit was at May 2025. The Institutional Medical Ethics Board approved the study in each participating center (NL48223.018.14). Registration can be found in the Dutch Trial Registry (NL4361; NTR4501). A Data Safety Monitoring Board was established to monitor safety and evaluate efficacy after every 20 included patients. An additional internal quality audit authorized the study in May 2017. Written informed consent was obtained from all patients before enrollment and randomization. All

authors had access to the study data and reviewed and approved the final manuscript.

Patient Selection

Patients between 18 and 80 years old and diagnosed with manometrically proven achalasia were included in the study when they had persistent or recurrent achalasia symptoms after LHM. Recurrence of symptoms was defined as an Eckardt score above 3 together with significant stasis (≥2 cm) observed on timed barium esophagram 5 minutes after barium contrast administration.

Exclusion criteria comprised prior POEM or having undergone PD after LHM, and previous gastric or esophageal surgery other than LHM. Additional inclusion and exclusion criteria are reported in our previous report[13] and provided in Supplementary Table 1.

Randomization and Blinding

Patients were randomized by study staff using a web-based online program that assigned patients to undergo either PD or POEM. Randomization was done in a 1:1 ratio and was stratified for each participating center. Blinding the treatment was not possible because of the different technical nature of the procedures and follow-up care.

Procedures

The protocol used in this trial was similar to the 3 major preceding achalasia trials and a meta-analysis.[7,9,14] Patients followed a liquid diet 3 days before PD, followed by an overnight fast. PD was performed by experienced endoscopist according to a graded dilation protocol starting with a 30-mm balloon, followed by a 35-mm balloon after 1 to 3 weeks. After positioning the Rigiflex balloon at the level of the esophagogastric junction using fluoroscopic guidance, 1-minute dilation at a pressure of 5 PSI was performed followed by dilation with 8 PSI for another minute. An additional dilation with a 40-mm balloon was allowed in case of persistent symptoms or symptom recurrence within 3 months after the first dilation. When symptoms reoccurred between 3 months and 1 year, a graded dilation protocol was performed with a 35-mm balloon followed by a 40-mm balloon. Patients were discharged on the same day with a prescription for a proton pump inhibitor (PPI) that had to be taken for 2 weeks after each dilation.

A liquid diet 3 days before treatment followed by an overnight fast was also advised for patients undergoing POEM. POEM was performed by experienced interventional endoscopists under general anesthesia with endotracheal intubation. The protocol was followed as previously described by Ponds et al.[10] Patients were admitted for 1 night and were discharged when they were clinically stable and esophageal leakage was ruled out by routine esophagram. PPIs were prescribed for at least 2 weeks after treatment, and a soft diet was advised for 2 weeks.

What You Need to Know

Background

Although achalasia treatment is highly effective, some patients develop persistent or recurrent symptoms, necessitating further treatment. After failed laparoscopic Heller myotomy, peroral endoscopic myotomy (POEM) or pneumatic dilation (PD) is recommended.

Findings

In patients with achalasia and persistent or recurrent symptoms after laparoscopic Heller myotomy, POEM is more effective compared with PD, achieving 5-year success rates of 40% and 11%, respectively.

Implications for patient care

After failed laparoscopic Heller myotomy, POEM shows higher efficacy, but PD remains an alternative option. Careful patient selection and clearly informing patients about expected treatment outcomes are essential.

Follow-Up

Patients were contacted 3 weeks after PD (35-mm balloon) to assess achalasia symptoms using the Eckardt score and determine whether further dilation with a 40-mm balloon was necessary. All patients undergoing PD and POEM were contacted at 3 months, 1 year, 2 years, and 5 years after treatment. Questionnaires were completed during all follow-up visits and consisted of the Eckardt score, Gastroesophageal Reflux Disease Questionnaire (GerdQ), Achalasia Disease-Specific Quality of Life Questionnaire (achalasia-DSQoL) and 36-Item Short-Form Health Survey (SF-36). High-resolution manometry, timed barium esophagram, and upper gastrointestinal endoscopy were carried out on specific follow-up moments as can be seen in Supplementary Table 2 and Supplementary Figure 1.

During high-resolution manometry, a catheter is transnasally positioned into the esophagus beyond the esophagogastric junction. After baseline measurement of 30 seconds, 10 wet swallows of 5 mL of water were given with 30-second intervals. The contraction pattern and pressure of the LES were assessed (basal LES pressure and integrated relaxation pressure [IRP]). Timed barium esophagram consisted of radiographic images 1, 2, and 5 minutes after drinking 100 to 200 mL of barium contrast. The maximal width of the distal

esophagus and the column height at each time point were measured. Reflux esophagitis was assessed during upper gastrointestinal endoscopy and was graded according to the Los Angeles classification.[15] PPIs were not temporarily stopped prior to upper gastrointestinal endoscopy.

Outcome Measures

Primary outcome was treatment success at 5-year follow-up defined as Eckardt score $\leq$3 without retreatment. Patients who underwent PD were allowed to undergo 1 additional dilation up to a 40-mm balloon within 1 year after the first PD. This included 40-mm balloon dilation within the first 3 months or 35- to 40-mm balloon dilation between 3 months and 1 year after the first PD. Any additional PD or other treatment such as POEM after PD was seen as treatment failure. Patients with recurrence after POEM were offered PD and were classified as treatment failure. Follow-up was continued after retreatment according to the study protocol.

Secondary outcomes included the Eckardt score, reflux symptoms assessed by GerdQ, quality of life assessed by achalasia-DSQoL questionnaire and SF-36, column height after 5 minutes and maximal width of the distal esophagus on timed barium esophagram, basal LES pressure and IRP on high-resolution manometry, the presence of reflux esophagitis observed during upper gastrointestinal endoscopy, and PPI use. Other baseline variables included age, sex, body mass index, American Society of Anesthesiologists (ASA) score, type of achalasia according to the Chicago classification version 3.0,[16] (Supplementary Table 3) and the number of patients who underwent PD prior to LHM. After treatment failure, patients remained in the study for follow-up, and the number and success of any subsequent retreatment were reported.

For the Eckardt score, the severity of symptoms, including dysphagia, regurgitation, retrosternal pain, and weight loss, was assessed on a scale from 0 to 3, based on the frequency of their occurrence. The total Eckardt score ranged from 0 to 12, with higher scores indicating a greater burden of achalasia symptoms[17] (Supplementary Table 4). Other questionnaires included GerdQ, achalasia-DSQoL, and SF-36 (Supplementary Table 5).

All adverse events reported by the patient or observed by the investigators between initial treatment and last follow-up visit were documented, regardless of their relationship to the randomized treatment. The definition of (serious) adverse events are provided in Supplementary Table 6. The Data Safety Monitoring Board was informed about all adverse events.

Statistical Analysis

Treatment success after LHM were assumed to be 58% for PD and 85% for POEM, based on long-term outcomes reported in previous studies and specified in our previous report[13] and the study protocol (page 16). According to the sample size calculation, 43 patients per group were needed to detect a difference in treatment success with a power of 80% and a 2-sided significance level of 5%. To account for an anticipated 5% loss to follow-up, 90 patients were enrolled.

All statistical analyses were conducted using SPSS Statistics version 28.0. For nonparametric data, median values with interquartile range were reported and Mann-Whitney U test was used to compare differences between POEM and PD at a single time point, as well as between treatment success and treatment failure. For normally distributed data, mean values with standard deviation were reported, and independent t-test was applied. Categorical variables were compared using the χ^2 test or Fisher exact test.

All patients were included in the intention-to-treat analysis in the treatment group to which they were initially assigned, regardless of whether the treatment was performed or the follow-up status. In this analysis, patients lost to follow-up were considered as treatment failures. In the per-protocol analysis, outcomes were analyzed based on the treatment patients actually received, and those lost to follow-up were excluded from the analysis. For intention-to-treat analysis and per-protocol analyses, absolute differences and risk ratios were reported. A Kaplan-Meier curve was generated, and the log-rank test was applied to compare the effect of POEM and PD over time.

Secondary outcomes at 5-year follow-up were reported for patients who did not undergo retreatment after the randomized treatment (any additional dilation up to 40 mm within 1 year after initial PD was not considered as retreatment). For these secondary outcomes, violin plots were created to illustrate the distribution of the outcomes. To compare secondary outcomes at baseline, 1-year, and 5-year follow-up, the Friedman test was applied, followed by Wilcoxon signed-rank test for post-hoc analysis to determine where differences were present between follow-up time points.

Statistical significance level of 2-sided P values below .05 was set as the threshold for significance. For repeated measurements, a Bonferroni-Holm correction was applied to the Wilcoxon signed-rank test, adjusting the significance threshold top-values of .017, .025, and .05, corresponding to the ordered Wilcoxon signed-rank test P values from smallest to largest.

Results

Patient Selection and Characteristics

In total, 90 patients with achalasia and persistent or recurrent symptoms after LHM were randomized, of which 45 underwent POEM and 45 underwent PD.

POEM was not successful in 2 patients due to submucosal fibrosis, and these patients subsequently underwent PD. In 1 patient, POEM was not performed because the patient chose to refrain from treatment after randomization. During the 5-year follow-up, 2 patients in the POEM group died, and 1 patient was lost to follow-up. In the PD group, 3 patients died, and 4 were lost to follow-up. Overall, 45 patients were included in the intention-to-treat analysis for both groups. The per-protocol analysis included 39 patients for POEM and 40 patients for PD at 5-year follow-up (Figure 1; Supplementary Table 7).

The median age of the patients who underwent POEM was 53 years, and 60% were female (n = 27/45). For patients who underwent PD, the median age was 52 years, and 64% were female (n = 29/45). All patients had persistent or recurrent symptoms after LHM, and PD prior to LHM was performed in 57.8% of the patients in the POEM group (n = 26/45) and in 53.3% of the patients in the PD group (n = 24/45). All baseline characteristics were statistically similar except for baseline GerdQ score (median 8 vs 10 for POEM and PD, respectively; $P = .003$) and SF-36 mental component score (median 70 vs 53 for POEM and PD, respectively;

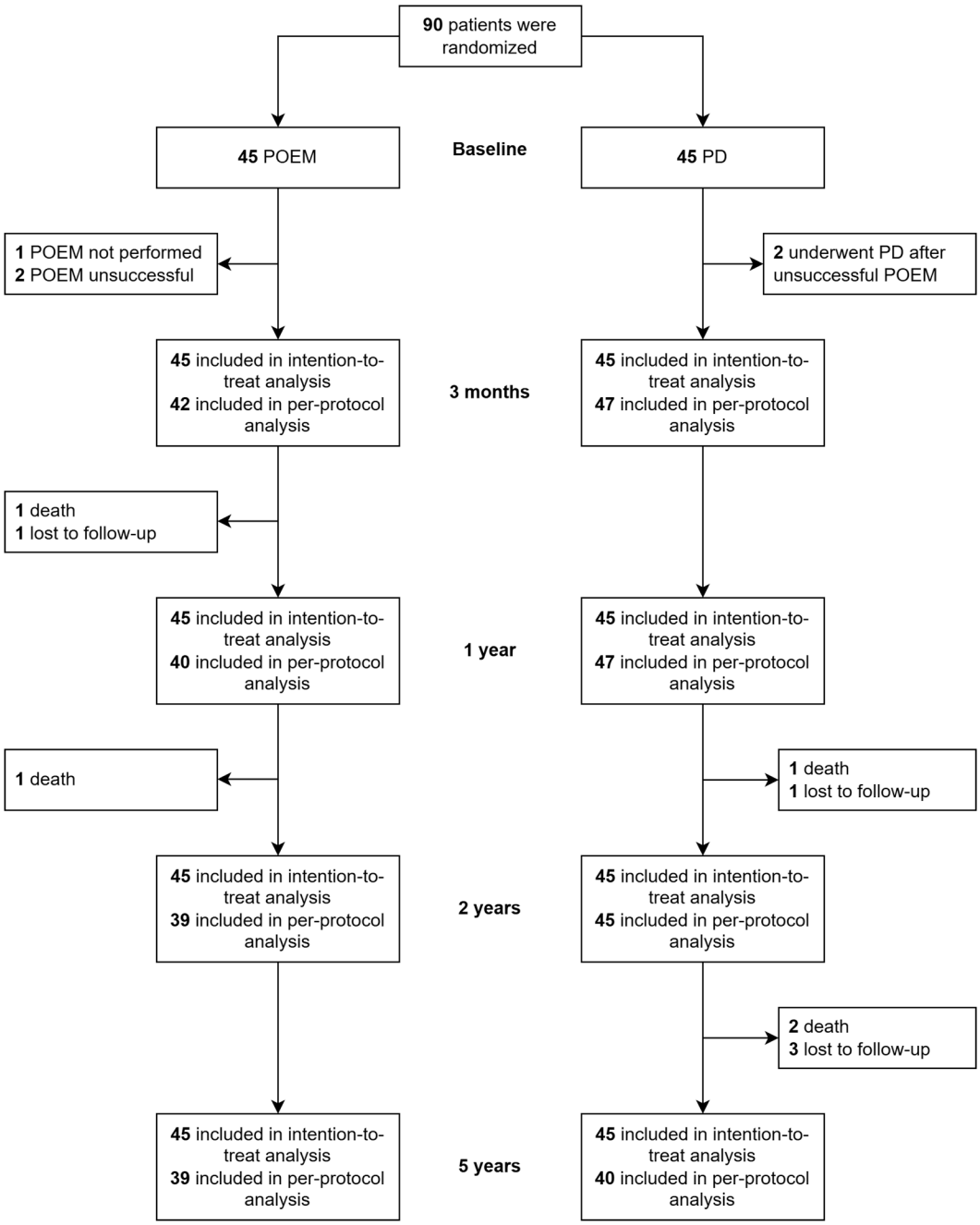

Figure 1. Flow chart.

$P = .046$) (Table 1). Waist obliteration was obtained in all patients undergoing PD.

Primary Outcome

At 5-year follow-up, treatment success was significantly higher after POEM (n = 18/45; 40%) compared with PD (n = 5/45; 11%) with an absolute difference of 29% (95% confidence interval [CI], 12%–46%) and a relative risk of 3.6 (95% CI 1.5–8.7; $P = .002$) (Table 2). Treatment success for both procedures across all follow-up time points is presented in Table 2 and Figure 2.

Per-protocol analysis demonstrated treatment success rates of 46% for POEM (n = 18/39) and 13% for PD (n = 5/40) with an absolute difference of 34% (95% CI, 15%–52%) and a relative risk of 3.7 (95% CI, 1.5–9.0; $P < .001$). Survival analysis indicated that POEM was associated with a significantly higher treatment success compared with PD ($P = .005$). The median time to treatment failure was 12 months for PD, whereas POEM showed a longer median time to failure of 60 months (Figure 3).

Univariate analysis of factors associated with treatment success showed that male patients were more likely to experience treatment success (n = 13/23; 57%)

Table 1. Patient Characteristics

	POEM (n = 45)	PD (n = 45)	*P* value
Age, *y*	53 (24)	52 (27)	.884
Sex			.664
Female	27 (60.0)	29 (64.4)	
Male	18 (40.0)	16 (35.6)	
Body-mass index, kg/m^2	24.0 (4.1)	24.8 (4.3)	.376
ASA score			.114
I	27 (60.0)	21 (46.7)	
II	13 (28.9)	22 (48.9)	
III	5 (11.1)	2 (4.4)	
Type of achalasia[a]			.796
Type 1	9 (20.0)	10 (22.2)	
Type 2	15 (33.3)	15 (33.3)	
Type 3	4 (8.9)	3 (6.7)	
Not specified	17 (37.8)	17 (37.8)	
Pneumatic dilation prior to LHM	26 (57.8)	24 (53.3)	.416
Time between LHM and randomized treatment, *y*	2 (8)	2 (9)	.931
Baseline outcomes			
Questionnaires			
Eckardt score	6 (2)	6 (2)	.559
GerdQ score	8 (4)	10 (4)	.003
Achalasia-DSQoL	25 (5)	26 (5)	.117
SF-36			
Mental component score	70 (31)	53 (48)	.046
Physical component score	55 (35)	58 (36)	.625
High resolution manometry			
IRP, *mm Hg*	14.9 (10.4)	21.0 (16.0)	.128
Basal LES pressure, *mm Hg*	20.0 (19.5)	21.7 (18.7)	.628
Timed barium esophagram			
Maximum diameter, *cm*	3.5 (1.9)	3.3 (1.3)	.760
Column height 5 min, *cm*	3.5 (3.1)	4.0 (2.8)	.579
Reflux esophagitis			.223
None	42 (93.3)	42 (93.3)	
Grade A	1 (2.2)	3 (6.7)	
Grade B	0 (0.0)	0 (0.0)	
Grade C	2 (4.4)	0 (0.0)	
Grade D	0 (0.0)	0 (0.0)	

NOTE. Data are presented as number (%), median (interquartile range), or mean (standard deviation).
ASA, American Society of Anesthesiologists; Achalasia-DSQoL, Achalasia Disease-Specific Quality of Life; GerdQ, Gastroesophageal Reflux Disease Questionnaire; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; PD, pneumatic dilatation; POEM, peroral endoscopic myotomy; SF-36, 36-Item Short-Form Health Survey.
[a]Based on Chicago classification version 3.0.[16]

Table 2. Treatment Success Across All Follow-Up Time Points After POEM and PD

	POEM	PD	Unadjusted absolute difference (95% CI)	Unadjusted relative risk (95% CI)	*P* value
3 mo					
Treatment success – ITT[a]	37 (82.2)	28 (62.2)	20.0 (2.0–38.0)	1.32 (1.01–1.72)	.034
Treatment success – PP[b]	36 (85.7)	28 (59.6)	26.1 (8.6–43.7)	1.44 (1.10–1.88)	.006
1 y					
Treatment success – ITT[a]	28 (62.2)	12 (26.7)	35.6 (16.4–54.7)	2.33 (1.37–3.99)	<.001
Treatment success – PP[b]	28 (70.0)	13 (27.7)	42.3 (23.2–61.5)	2.53 (1.53–4.19)	<.001
2 y					
Treatment success – ITT[a]	25 (55.6)	9 (20.0)	35.6 (16.9–54.2)	2.78 (1.47–5.27)	<.001
Treatment success – PP[b]	25 (64.1)	9 (20.0)	44.1 (25.0–63.2)	3.21 (1.71–6.02)	<.001
5 y					
Treatment success – ITT[a]	18 (40.0)	5 (11.1)	28.9 (11.9–45.9)	3.60 (1.46–8.86)	.002
Treatment success – PP[b]	18 (46.2)	5 (12.5)	33.7 (15.0–52.3)	3.69 (1.52–8.97)	<.001

NOTE. Data are presented as number (%) unless otherwise indicated.
CI, confidence interval; ITT, intention-to-treat analysis; PD, pneumatic dilatation; POEM, peroral endoscopic myotomy; PP, per-protocol analysis.
[a]POEM, n = 45; PD, n = 45.
[b]3 months: POEM, n = 42; PD, n = 47. 1 year: POEM, n = 40; PD, n = 47. 2 years: POEM, n = 39; PD, n = 45. 5 years: POEM, n = 39; PD, n = 40.

compared with those with treatment failure (n = 21/67; 31%) ($P = .032$). Age, type of achalasia, and PD prior to LHM were not associated with treatment success, nor were baseline outcomes of Eckardt score, IRP on high-resolution manometry, and column height after 5 minutes on timed barium esophagram (Supplementary Table 8).

Secondary Outcomes

The Eckardt score at 5-year follow-up did not significantly differ between patients who underwent POEM and those who underwent PD without retreatment (median score of 3 for both groups; $P = .722$). No significant differences were observed in reflux symptoms (GerdQ score) and quality of life (Achalasia-DSQoL and SF-36 score) between the groups at 5-year follow-up. Although patients who underwent POEM more frequently used PPIs, this difference was not statistically significant (64% vs 36%; $P = .078$).

At 5-year follow-up, among patients who had not undergone retreatment after their randomized treatment, high-resolution manometry was performed in 29 patients (n = 29/47; 62%) and timed barium esophagram in 40 patients (n = 40/47; 85%). The median IRP was 9.7 mm Hg after POEM and 14.0 mm Hg after PD without reaching statistical significance ($P = .085$). Column height on timed barium esophagram, measured 5 minutes after drinking barium contrast, had median values of 2.8 cm and 4.0 cm in patients who underwent POEM and PD, respectively ($P = .074$).

Upper gastrointestinal endoscopy at 5-year follow-up was performed in 37 patients after POEM and 34 patients after PD. Reflux esophagitis was observed in 35% of the patients after POEM (n = 13/37; 9 grade A, 1 grade B, 3 grade C) and 18% after PD (n = 6/34; 3 grade

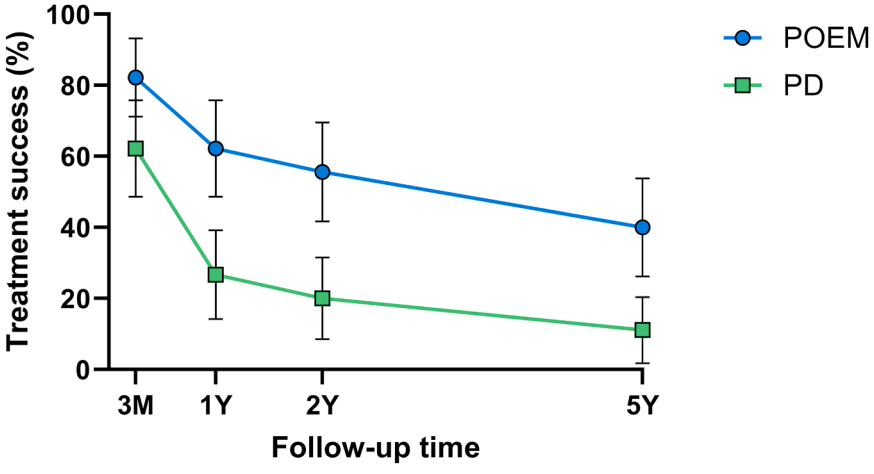

Figure 2. Treatment success across all follow-up time points after POEM and PD (intention-to-treat analysis). Treatment success was defined as total Eckardt score ≤3 without retreatment.

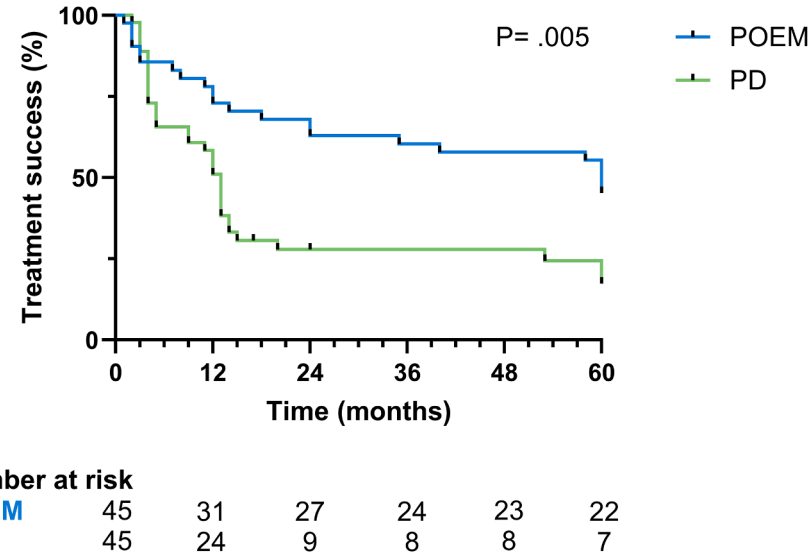

Figure 3. Survival curves of treatment success showing a statistical significant difference between POEM and PD. Treatment success was defined as total Eckardt score ≤3 without retreatment.

A, 2 grade B, 1 grade C), although the difference between the 2 groups was not statistically significant ($P = .096$) (Supplementary Figure 2). When excluding reflux esophagitis grade A, the percentages were 11% after POEM (n = 4/37) and 9% after PD (n = 3/34) ($P = .548$). Furthermore, excluding patients who had undergone retreatment after their randomized treatment, reflux esophagitis grade B to D was observed in 13% of the patients after POEM (n = 4/31) and 8% after PD (n = 1/12) ($P = .569$) (Table 3). No cases of peptic strictures or Barrett esophagus were identified.

Table 3. Secondary Outcomes at 5-Year Follow-Up in Patients Without Retreatment

	POEM	PD	*P* value
Questionnaires			
Eckardt score	3 (2)	3 (3)	.722
GerdQ score	9 (4.5)	9 (5)	.571
Achalasia-DSQoL	20 (8)	19 (7)	.676
SF-36			
Physical component score	74 (46)	72 (46)	.716
Mental component score	78 (60)	78 (62)	.910
PPI use	21 (63.6)	5 (35.7)	.078
High resolution manometry			
IRP, *mm Hg*	9.7 (8.5)	14.0 (13.5)	.085
Basal LES pressure, *mm Hg*	15.3 (8.1)	24.0 (15.5)	.234
Timed barium esophagram			
Maximum diameter, *cm*	3.3 (1.9)	4.0 (2.2)	.422
Column height 5 min, *cm*	2.8 (4.0)	4.0 (5.8)	.074
Reflux esophagitis			.618
None	20 (64.5)	10 (83.3)	
Grade A	7 (22.6)	1 (8.3)	
Grade B	1 (3.2)	0 (0.0)	
Grade C	3 (9.7)	1 (8.3)	
Grade D	0 (0.0)	0 (0.0)	

NOTE. Data are presented as number (%) or median (IQR).
NOTE. Questionnaires: POEM, n = 33; PD, n = 14. High resolution manometry: POEM, n = 20; PD, n = 9. Timed barium esophagram: POEM, n = 28; PD, n = 12. Upper gastrointestinal endoscopy: POEM, n = 31; PD, n = 12.

Results of secondary outcomes at all follow-up time points in patients without retreatment after their initial randomized treatment are presented in Supplementary Table 9 and Supplementary Figures 3–5. In patients who underwent POEM without retreatment, Eckardt and achalasia-DSQoL score were improved at 1-year and 5-year follow-up compared with baseline, but no difference was seen between 1-year and 5-year scores. The same trend was seen in SF-36 results for both physical and mental component score; however, the difference between 5-year scores and baseline scores did not reach statistical significance. Reflux symptoms, as measured by GerdQ scores, worsened between 1-year and 5-year follow-up both for PD and POEM, but did not differ from baseline scores (Supplementary Table 10). For patients who underwent PD without retreatment, a similar trend was observed in Eckardt and achalasia-DSQoL scores, with a significant difference between 1-year and 5-year follow-up compared with baseline, but no difference between 1-year and 5-year results. In these patients, no significant difference was seen in SF-36 results, and GerdQ scores were only significantly lower at 1-year follow-up compared with baseline (Supplementary Table 11).

Adverse Events

Intraprocedural and postprocedural adverse events (within 1 month after treatment) are presented in Supplementary Table 12. Details of (serious) adverse events within 1-year follow-up have been published previously.[13] After 1-year follow-up, 2 serious adverse events occurred in the POEM group, neither of which were related to the treatment. In the PD group, 8 serious adverse events occurred after 1 year, all of which were also not related to the treatment. Adverse events occurred in 26% and 15% of the patients who underwent POEM and PD, respectively (n = 11/42 and n = 7/47).

Additional details on all (serious) adverse events throughout the study are provided in Supplementary Table 13.

Retreatment

In the PD group, 21 patients underwent further dilation with a 40-mm balloon within 3 months after initial PD, and 4 patients underwent dilation with a 35-mm and a 40-mm balloon between 3 months and 1 year after initial PD. A total of 26 patients underwent additional retreatment more than 1 year after randomized PD, of whom 23 underwent POEM and 3 underwent PD. Among the 14 patients who underwent retreatment with POEM within 1 year after PD, nearly all patients had treatment failure at 2-year follow-up. Of the 9 patients who underwent retreatment with POEM between 1 year and 2 years after PD, 89% (n = 8/9) achieved treatment success at 2-year follow-up, and 56% (n = 5/9) maintained treatment success at 5-year follow-up. Of all 23 patients who underwent POEM after PD, 6 subsequently required PD again due to treatment failure. Of these, 5 did not experience symptom relief, and 1 patient was lost to follow-up.

In the group randomized to and treated with POEM, 6 patients underwent retreatment with PD, yielding limited success at 2-year and 5-year follow-up (both n = 1/6; 17%) (Supplementary Figure 6).

Discussion

This multicenter randomized controlled trial demonstrated that POEM yielded greater long-term efficacy than PD in patients with achalasia and persistent or recurrent symptoms after LHM. Treatment failure was most commonly observed within the first year after treatment, after which there was a more gradual decline in treatment effect over time up to 5 years. Both procedures were found to be safe without major differences in procedure-related adverse events between the 2 groups.

Although POEM showed higher treatment success rates compared with PD, defined as Eckardt score $\leq$3 without retreatment, its efficacy after previous LHM is lower compared with treatment-naive patients with achalasia undergoing POEM. At 5-year follow-up, patients undergoing POEM in this study had treatment success of 40%, and patients undergoing PD had treatment success of 11%. A previous randomized controlled trial with treatment-naive patients with achalasia found treatment success rates of 81% and 40% to 82% for POEM and PD, respectively, at 5-year follow-up.[9,11] Thus, treatment success for POEM in this study was only one-half of that what was observed in treatment-naive patients, and for PD, this was even one-quarter of the treatment success rate observed in patients without prior LHM. Another study reporting 5-year follow-up results on the effects of POEM compared with LHM reported that POEM was effective in 75% of the patients after 5 years. Notably, about one-quarter of the patients who underwent POEM had previously been treated with PD before study enrollment.[12] The lower treatment success observed in our study may, at least in part, be attributed to disease severity and the complex clinical course, as patients had persistent or recurrent symptoms after prior LHM. This is in line with previous observations that patients with achalasia who have failed previous myotomy pose a larger challenge for subsequent treatments.[18]

The optimal treatment after failed LHM has been studied before, particularly through retrospective analyses with relatively short follow-up periods. A multicenter retrospective study compared the outcomes of POEM in 90 patients after failed LHM with 90 treatment-naive patients with achalasia. No difference in technical success was observed. Patients with prior LHM had significantly lower treatment success compared with untreated patients with achalasia after a median follow-up of 9 months (81% vs 94%).[19] Tyberg et al reported a technical success rate of 100% and a treatment success rate of 94% 1 year after POEM in 51 patients after failed LHM.[20] Both studies found no major adverse events.[19,20] Additionally, PD after failed LHM demonstrated good short-term efficacy, but required repeated on-demand dilations to maintain long-term benefit. Reported clinical efficacy rates for repeated on-demand dilations after failed LHM are 78% to 95% after a median follow-up of 30 to 33 months. Notably, patients with prior LHM again showed lower treatment success rates compared with untreated patients with achalasia.[21–23] Several smaller studies examining redo LHM have reported symptom improvement, but to a lesser extent than in patients undergoing their first LHM.[24,25] These findings suggest that the benefits of repeat procedures may diminish over time and highlights the importance of considering individual patient history and prior treatments when determining the most appropriate treatment approach.

Our findings underscore the complexity of managing persistent or recurrent symptoms in treated patients with achalasia, as they tend to have lower treatment success rates compared with treatment-naive patients. Furthermore, in this study, retreatment after initial randomized treatment had limited success, particularly in the short term, as most treatment failures occurred after retreatment within 1 year after allocated treatment. Patients who had treatment failure at 3 months after PD and subsequently underwent POEM showed poor long-term outcomes, as only 8% achieved remission at 2-year follow-up and none at 5-year follow-up. In contrast, patients who underwent POEM 1 year after PD demonstrated a markedly higher effect, as one-third achieved treatment success at 5-year follow-up. Despite the relatively small number of patients who underwent retreatment, there is an observed trend that suggests this subgroup, characterized by recurrent or

persistent symptoms and requiring multiple treatments, have a higher risk of treatment failure. This could be due to procedural challenges of retreatment, such as fibrosis, or other factors underlying the persistent or recurrent symptoms. It is therefore important to exclude alternative causes, such as gastroesophageal reflux or blown-out myotomy that mimic achalasia symptom recurrence.[26–28] Furthermore, absent peristalsis or a distorted esophagus in achalasia could contribute to persistent symptoms. Therefore, a thorough workup to rule out these alternative causes is essential, as misdiagnosis could lead to inappropriate treatment and more treatment failure.

A known drawback of POEM is the development of reflux symptoms and reflux esophagitis after treatment.[6] In this study, approximately one-third of the patients had reflux esophagitis during upper gastrointestinal endoscopy at 5-year follow-up, with the majority of cases being graded as mild (grade A/B). Reflux esophagitis was more frequently observed after POEM compared with PD; however, this difference was not statistically significant, likely due to the small sample size, as well as the underestimation of the rate of reflux esophagitis after treatment due to concomitant PPI use. Reported long-term incidence of reflux esophagitis after POEM varies between 13% and 33%.[29] The observed incidence in our study lies at the higher end of this range, but it may still be underestimated. Approximately two-thirds of the patients were taking PPIs at the time of the 5-year follow-up and did not stop them prior to upper gastrointestinal endoscopy as opposed to recommendations by clinical guidelines, which advise stopping PPIs at least 4 weeks before upper gastrointestinal endoscopy.[30] This continued use of PPIs could have masked some mild cases of reflux esophagitis and potentially underestimated the severity in others, leading to an underreporting of the true incidence in this study.

This is the first multicenter randomized controlled trial comparing the effect of POEM and PD in patients with prior LHM, providing high level of evidence and enhancing the generalizability of our findings. Furthermore, the study maintained a relatively low percentage of lost to follow-up (5.6% lost to follow-up and 5.6% died of unrelated causes), ensuring that the long-term results at 5-year follow-up are accurate. The consistency in results between the intention-to-treat analyses and per-protocol analyses further supports the validity of our findings, suggesting that the small proportion of patients lost to follow-up likely did not cause significant bias into the overall findings. However, a potential limitation of this study is the lack of blinding, which was not feasible due to the nature of the treatment procedures and the variation in post-procedural care. However, we believe that the impact of this limitation is minimal, as objective follow-up diagnostics were routinely performed. Previously, it was suggested that the low efficacy rate of PD at 1-year follow-up may be related to the inflation pressure used in this study.[31] The inflation pressure of 8 PSI used in this study is lower than recommended by some other authors. However, the protocol applied was consistent with those used in other major achalasia randomized controlled trials.[9,11] Furthermore, a systematic review and meta-analysis demonstrated variations in inflation pressures among the included studies; however, higher inflation pressures were not associated with improved efficacy after 1 year.[7]

In this study, both POEM and PD resulted in a significant reduction in symptom scores and quality of life scores at the 5-year follow-up compared with baseline. However, these outcomes were analyzed exclusively in patients who did not undergo retreatment after their initial randomized treatment. This approach was taken to ensure that the results accurately reflect the outcomes of the randomized procedures, as including patients who underwent retreatment could confound the results. Patients who underwent retreatment were considered treatment failures and likely would have worse symptom scores and quality of life scores, because they opted for an additional treatment due to insufficient symptom control. By excluding these patients, we aimed to obtain a more reliable assessment of the different types of treatment, although it is important to note that the observed improvements may be overestimated, as they do not account for the impact of retreatment.

Conclusion

In conclusion, our study demonstrates that POEM is more effective than PD for patients with achalasia and persistent or recurrent symptoms after prior LHM. This subgroup represents a clinically complex patient population, in whom symptom control remains challenging. These results underscore the need for careful patient selection, a more tailored approach when considering retreatment, and the importance of clearly informing patients regarding expected treatment outcomes.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2026.03.024.

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Conflicts of interest
These authors disclose the following: Guido Costamagna served as consultant for Olympus. Pietro Familiari served as a proctor for Olympus. Paul Fockens received consultancy from Olympus. Raf Bisschops received research Funding from Medtronic, and received speaker and/or consultancy fees from Medtronic and Olympus. Albert J. Bredenoord received speaker and/or consulting fees from Laborie and Medtronic. The remaining authors disclose no conflicts.

Data Availability
Deidentified individual participant data is available on request.