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The Efficacy of Peroral Endoscopic Myotomy vs Pneumatic Dilation as Treatment for Patients With Achalasia Suffering From Persistent or Recurrent Symptoms After Laparoscopic Heller Myotomy: A Randomized Clinical Trial

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BACKGROUND & AIMS: For patients with achalasia experiencing persistent or recurrent symptoms after laparoscopic Heller myotomy (LHM), pneumatic dilation (PD) is the most frequently used treatment. Per-oral endoscopic myotomy (POEM) is increasingly being investigated as rescue therapy. This study aimed to determine the efficacy of POEM vs PD for patients with persistent or recurrent symptoms after LHM. **METHODS:** This randomized multicenter controlled trial included patients after LHM with an Eckardt score >3 and substantial stasis (≥2 cm) on timed barium esophagogram and randomized to POEM or PD. The primary outcome was treatment success, defined as an Eckardt score of ≤3 and without unscheduled re-treatment. Secondary outcomes included the presence of reflux esophagitis, high-resolution manometry, and timed barium esophagogram findings. Follow-up duration was 1 year after initial treatment. **RESULTS:** Ninety patients were included. POEM had a higher success rate (28 of 45 patients [62.2%]) than PD (12 of 45 patients [26.7%]; absolute difference, 35.6%; 95% CI, 16.4%–54.7%; $P = .001$; odds ratio, 0.22; 95% CI, 0.09–0.54; relative risk for success, 2.33; 95% CI, 1.37–3.99). Reflux esophagitis was not significantly different between POEM (12 of 35 [34.3%]) and PD (6 of 40 [15%]). Basal lower esophageal sphincter pressure and integrated relaxation pressure (IRP-4) were significantly lower in the POEM group ($P = .034$; $P = .002$). Barium column height after 2 and 5 minutes was significantly less in patients treated with POEM ($P = .005$; $P = .015$). **CONCLUSIONS:** Among patients with achalasia experiencing persistent or recurrent symptoms after LHM, POEM resulted in a significantly higher success rate than PD, with a numerically higher incidence of grade A–B reflux esophagitis. Netherlands Trial Registry: NL4361 (NTR4501), https://trialsearch.who.int/Trial2.aspx?TrialID = NTR4501.

Keywords: Per-Oral Endoscopic Myotomy; Pneumatic Dilation; Laparoscopic Heller Myotomy; Eckardt Score; High-Resolution Manometry.

Achalasia is a rare esophageal motility disorder characterized by dysfunctional or absent motility of the esophageal body and insufficient relaxation of the lower esophageal sphincter (LES). Treatment options for patients with achalasia include the traditional pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), and per-oral endoscopic myotomy (POEM). POEM and LHM provide longer-lasting symptomatic responses in treatment-naïve patients with achalasia than a single series of PDs.[1,2] Despite the high efficacy rates of POEM and LHM, persistent or recurrent symptoms occur in 10%–20% of patients treated with LHM.[3,4]

Until now, treatment of persistent or recurrent symptoms after LHM remained controversial. Rescue therapy includes PD, revisional LHM, POEM, and as a last resort, esophagectomy.[3,5–11] Studies investigating the efficacy of PD for recurrent or persistent symptoms after LHM show a variable success rate ranging from 57%–96%.[12–15] A retrospective study conducted in our center showed a long-term success rate of 57%. Revisional LHM has a reported efficacy of 71%–90%.[16–19] However, this procedure requires extensive expertise, as it is invasive and with more difficulties due to adhesions, fibrosis, and the loss of tissue planes in the area of the gastric esophageal junction caused by the original operation.[10,19] The latter may support a preference to initially treat persistent or recurrent symptoms with PD before moving on to a revisional LHM, although multiple PDs may be required.[10]

Over the past decade, POEM gained acceptance as an endoscopic alternative to LHM for the primary treatment of achalasia. Considering the technique and its high efficacy rates, POEM is increasingly being investigated as a rescue therapy for patients with persistent or recurrent symptoms after LHM. Case series suggest that POEM has an efficacy ranging from 81%–100% when applied as rescue therapy after LHM.[10,20] Unfortunately, these studies represent small

Abbreviations used in this paper: **ADSQoL, achalasia disease-specific quality of life questionnaire; AE, adverse event; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; PD, pneumatic dilation; POEM, per-oral endoscopic myotomy; PPI, proton pump inhibitor; SAE, serious adverse event; SF-36, 36-Item-Short Form Health Survey.**

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series with relatively short follow-up times and retrospectively collected data. More importantly, no studies have compared POEM with other performed rescue therapies, such as PD, the most widely used.

Therefore, this study aimed to determine and compare the efficacy of POEM vs PD for patients with persistent or recurrent symptoms after LHM.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Patients with achalasia experiencing persistent or recurrent symptoms after laparoscopic Heller myotomy are most frequently treated with pneumatic dilation. Per-oral endoscopic myotomy is being investigated increasingly as rescue therapy; this study aimed to determine the efficacy of per-oral endoscopic myotomy vs pneumatic dilation for patients with persistent or recurrent symptoms after laparoscopic Heller myotomy.

NEW FINDINGS

Per-oral endoscopic myotomy resulted in a significantly higher success rate than pneumatic dilation (62.2% and 26.7%, respectively) in patients with achalasia experiencing recurrent or persistent symptoms after laparoscopic Heller myotomy.

LIMITATIONS

Primary and secondary outcomes were assessed at 1-year follow-up, meaning no conclusions can be drawn for longer-term treatment success, which is important, given that achalasia is a lifelong chronic disease. Furthermore, like most endoscopic or surgical studies that evaluate new interventional techniques, patients and caregivers were not blinded to treatment allocation. Lastly, multiple pneumatic dilation sessions might form a potential bias in the comparison with 1 treatment intervention; however, this was done deliberately to optimally reflect routine clinical care in these patients.

CLINICAL RESEARCH RELEVANCE

Per-oral endoscopic myotomy can be considered as the initial treatment option for patients with achalasia experiencing persistent or recurrent symptoms after laparoscopic Heller myotomy.

BASIC RESEARCH RELEVANCE

This randomized controlled trial found that per-oral endoscopic myotomy results in significantly lower Eckardt scores than pneumatic dilation for patients with achalasia experiencing persistent or recurrent symptoms after laparoscopic Heller myotomy.

Methods

Study Design

This study was designed as a multicenter randomized controlled trial. Inclusion occurred in 3 achalasia expert centers in the Netherlands, Belgium, and Italy, from January 2014 to June 2020. The Institutional Medical Ethics Board approved the study protocol in each hospital.

Patients were enrolled in the study after obtaining written informed consent. The primary end point was measured at 1-year follow-up. Follow-up of patients took place at 3 months and 1 year after initial treatment.

A data and safety monitoring board consisting of a methodologist, surgeon, and gastroenterologist was installed to monitor the safety and efficacy of treatment groups. Moreover, the study underwent an extensive randomly assigned internal quality audit in May 2017. Study sites were monitored by a research nurse, in which the case report forms and source data were checked.

This study was not classified as single-blind; to minimize bias several interventions were implemented. First of all, questionnaires were filled in by patients without the presence of research personnel. Diagnostic measurements were evaluated by an observer unaware of the patients' treatment. The interpretation whether an unscheduled treatment was indicated was solely based on a previously set cutoff.

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

Patients and Inclusion and Exclusion Criteria

Adult patients aged 18–80 years were eligible for enrollment if they had persistent or recurrent symptoms after LHM, defined as having an Eckardt symptom score >3 in combination with significant stasis (≥ 2 cm) seen on timed barium esophagogram after 2 minutes.

Exclusion criteria included previous PDs after LHM, previous attempt at POEM, previous surgery to the stomach or esophagus (except for LHM), known coagulopathy, presence of liver cirrhosis and/or esophageal varices, eosinophilic esophagitis, stricture of the esophagus, (pre)malignant esophageal lesions, 1 or more esophageal diverticula, and pregnancy at time of treatment.

Randomization

Randomization was done using a web-based program (ALEA Clinical B.V.) that assigned patients to POEM or PD in a 1:1 ratio, stratified according to the research site. Local study staff enrolled the patients. The number of patients treated with POEM or PD was similar for each center.

Interventions

Pneumatic dilation. For PDs, a series of dilations with Rigiflex balloons (Boston Scientific) was performed. Under fluoroscopic guidance, the balloon was positioned at the gastric esophageal junction and dilated at a pressure of 5 psi for 1 minute, followed by 7 psi for 1 minute.[21] A graded distension protocol was implemented; initial PD was performed using a 30-mm balloon and 1–3 weeks later a subsequent 35-mm balloon dilation was performed. In case of symptom persistence or recurrence within 3 months, a PD with a 40-mm balloon was performed. Patients presenting with symptom recurrence between 3 and 12 months after inclusion were offered additional PD treatment with a 35- and 40-mm balloon. If the treating physician judged that repeating a 30-mm PD was required before performing the 35-mm PD, this was allowed. PD was considered a failure in case of symptom persistence or recurrence after this additional round of PDs. All further re-treatments with PD were considered unscheduled re-treatments. Patients undergoing unscheduled PD re-treatments were considered failures at 1-year follow-up regardless of their Eckardt score at 1-year follow-up. Thus, all patients randomized to the PD treatment arm received at least

2 dilations, with the last dilation at least 35 mm. PDs were performed by experienced endoscopists who completed more than 20 PDs independently.

Preprocedural instructions consisted of a liquid diet for 3 days before PD, which included a clear liquid diet 24 hours before PD and nil per mouth 8 hours before PD. Post PD, patients were prescribed a proton pump inhibitor (PPI) once per day for 2 weeks after each dilation.

Per-oral endoscopic myotomy. POEM was performed under general anesthesia, including endotracheal intubation, with the patient in a supine position. The POEM procedure was performed as described by Ponds et al[21]; however, the mucosal incision, tunnel, and myotomy were slightly more toward the posterior orientation of the esophagus to stay away from the original myotomy scar. Patients randomized to undergo POEM received the same preprocedural instructions as those who underwent PD. Admission took place on the same day as treatment or the day before, depending on the travel distance to the hospital; patients were discharged at least 1 day after POEM. Before treatment, patients were administered prophylactic antibiotics according to local hospital recommendations and a double-dose PPI intravenously. Post-discharge patients were advised to adhere to a liquid diet for 7 days, followed by a soft diet for 1 more week and were prescribed a single-dose PPI for 2 weeks.

Outcomes

The primary outcome was treatment success after 1-year follow-up, which was defined as an Eckardt score of $\geq$3 without any unscheduled re-treatment. For patients randomized to the PD treatment arm, this meant dilation with a 30-mm and 35-mm balloon and possibly PDs up to 40 mm; for patients randomized to the POEM arm, this meant undergoing POEM without any PDs or other unscheduled re-treatments.

Secondary outcomes were assessed at baseline and 3-month and 1-year follow-up. The quality of life and the achalasia-specific quality of life were measured using the 36-Item-Short Form Health Survey (SF-36) and the achalasia disease-specific quality of life questionnaire (ADSQoL). The SF-36 measured general quality of life by scoring mental and physical aspects, ranging from 0 to 100, with higher scores indicating a better quality of life.[22] The presence of reflux symptoms and reflux esophagitis was assessed using the Gastroesophageal Reflux Disease Questionnaire and upper endoscopy; use of acid suppressant drugs was also documented. Esophageal stasis, as seen on the timed barium esophagogram, was measured.

All adverse events (AEs) and serious adverse events (SAEs) were documented. Treatment complications were defined as any AEs that arose after the treatment or secondary to the treatment. AEs were classified as "severe" when they resulted in (prolonged) admission of more than 24 hours, medium or intensive care unit admission, additional endoscopic procedures, blood transfusion, or death. Other complications were classified as "mild."

Clinical Assessment and Follow-Up

The clinical assessment started at baseline and included a medical history, physical examination, and routine laboratory tests. Patients completed the Gastroesophageal Reflux Disease Questionnaire, SF-36, and ADSQoL questionnaires. High-resolution manometry was performed to confirm the reoccurrence of achalasia.[23] Upper endoscopy and timed barium esophagogram were performed to quantify esophageal stasis by measuring barium column height at 0, 1, 2, and 5 minutes on radiographic images after ingestion of 100–200 mL of low-density barium sulfate suspension during a time window of 30–60 seconds.[24]

Symptoms (Eckardt score) and questionnaires were assessed at 3-month and 1-year follow-up. High-resolution manometry and timed barium esophagogram were obtained after 3-month and 1-year follow-up, whereas upper endoscopy was only performed after 1-year follow-up. The severity of reflux esophagitis was scored according to the Los Angeles Classification.[25] PPI use was documented and was prescribed 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 randomized to the PD treatment arm were initially treated with a 30- and 35-mm balloon. A 3-week follow-up was set to assess symptom severity; in case of an Eckardt score $>$3, patients were treated with a 40-mm PD. If symptoms recurred within 1 year, patients were treated with additional PDs, up to a maximum diameter of 40 mm. Patients were offered POEM if symptoms persisted or recurred after 1 year or if they refused additional or unscheduled re-treatment with PDs within 1 year from initial PD treatment.

Patients who failed after POEM treatment were offered unscheduled re-treatment consisting of PDs, according to the graded distension protocol described above.

Follow-up after re-treatment was continued according to the initial treatment protocol.

Statistical Methods

Sample size calculation was based on the reported long-term success rates of PD after Heller myotomy (50%–67%) and the reported short-term success rates of POEM after Heller myotomy (91%–100%).[1,26,27] One study in previously non-surgically treated patients reported a success rate of 82% after 12-month follow-up.[28] Therefore, we assumed long-term success rates of 58% for PD and 85% for POEM after Heller myotomy. With these success rates, we estimated that with 43 patients in each group, the study would have 80% power to detect a significant difference in success rate between PD and POEM, with a 2-sided α level of .05. To cope with an estimated 5% loss to follow-up, we aimed to enroll 90 patients.

Primary Analysis

An intention-to-treat analysis was performed containing all patients as randomized to their treatment group. According to distribution, continuous data are presented as mean (SD) or median (interquartile range). Categorical data are presented as percentages.

The primary outcome included treatment effectivity based on Eckardt score at 1-year follow-up without re-treatment. Fisher exact test was used to calculate the odds ratio and relative risk for treatment outcome and treatment-related SAEs.

The secondary outcomes were analyzed using Mann-Whitney U test for continuous data or Fisher exact test for categorical data.

Absolute differences of comparative results were calculated by subtracting percentages, means, or medians of the groups and calculating the 95% CIs of the difference.

Post-Hoc Sensitivity Analysis

A sensitivity analysis was performed to increase the credibility of the results.[29] For the primary outcome, a per-protocol analysis was used. For the secondary outcomes, the post-hoc analysis included the use of linear mixed models and generalized linear models to account for missing values and to adjust for repeated effects or possible confounders. Specifically, linear mixed models were used to analyze the effect of treatment type on continuous secondary outcome parameters with fixed effects for time and treatment. An unstructured covariance structure was used when running the linear mixed models. The generalized linear models were used to analyze the association between treatment on binary outcome parameters, such as the presence of reflux esophagitis or PPI use. The generalized linear models used a binomial distribution and logit link function.

Results

Enrollment and Patient Characteristics

Between January 2014 and June 2020, ninety patients with achalasia and experiencing persistent or recurrent symptoms after LHM were randomized; 45 were randomly assigned to receive POEM and 45 were assigned to receive PD (Figure 1). All patients were treated with LHM and a Dor fundoplication. One patient randomized to POEM never received treatment. In 2 patients, the myotomy as part of POEM was not possible because the submucosal tunnel could not be created due to submucosal fibrosis (Figure 1). A protocol deviation occurred related to the PD treatment, as 1 patient received a single 30-mm PD and refused further treatment because of a significant reduction of symptoms. The final date of the 1-year follow-up period of the last patient was June 2021. Baseline characteristics were similar between groups (Table 1).

Primary Outcome

Analysis of the primary outcome showed higher treatment success at 1-year follow-up in the patients treated with POEM (28 of 45 patients [62.2%]) compared with the patients treated with PD (12 of 45 patients [26.7%]; absolute difference, 35.6%; 95% CI, 16.4%–54.7%; $P = .001$; odds ratio, 0.22; 95% CI, 0.09–0.54; relative risk for success, 2.33; 95% CI, 1.37–3.99) (Figure 2 and Table 2). A total of 5 missing values were observed, which were assumed failures according to the intention-to-treat principle (Figure 2 and Supplementary Figure 1). Single imputations were used for 3 missing values by logically inferencing; 2 patients were considered successful at 1 year, as they were successfully treated at 3-month and 2-year follow-up (without any retreatments), and 1 patient was deemed a failure, as this patient was a failure at 3-month follow-up.

In the patients randomized to receive POEM, 3 patients did not undergo a complete POEM; 2 patients did not receive POEM because fibrotic submucosa prohibited the creation of a submucosal tunnel and performance of the endoscopic myotomy, and 1 patient was lost to follow-up after randomization (Figure 1).

In the patients randomized to PD, 1 patient underwent only a single 30-mm PD with a good response and refused further dilation with a 35-mm balloon. The other patients received dilations with 30- and 35-mm balloons (n = 19) or up to 40-mm balloon (n = 25). Waist obliteration was obtained in all PDs.

Secondary Outcomes

Reflux esophagitis, proton pump inhibitor use, and reflux symptoms (Gastroesophageal Reflux Disease Questionnaire). At 1-year follow-up, a numerically higher incidence of reflux esophagitis was observed in patients treated with POEM (12 of 35 [34.3%]) than PD (6 of 40 [15%]), but this was not statistically significant. Further specified, for the patients randomized to POEM, 11 of 12 (91.7%) were assigned grade A–B and 1 (8.3%) grade C, and for patients randomized to PD, 5 of 6 (83.3%) were assigned grade A–B and 1 (16.7%) grade C. Reflux symptoms and daily use of PPI did not differ between treatment groups (Table 3 and Figure 3 and Supplementary Table 1).

Eckardt score, high-resolution manometry, timed barium esophagogram, and quality of life (achalasia disease-specific quality of life questionnaire and Medical Outcomes Study 36-Item-Short Form Health Survey). This study found a significantly lower Eckardt score was measured in the patients treated with POEM vs those treated with PD ($P = .016$) (Figure 4 and Supplementary Table 1). Basal LES pressure and integrated relaxation pressure (IRP-4) were significantly lower at 1-year follow-up for patients treated with POEM vs patients treated with PD ($P = .034$; $P = .002$). A significant difference was found between POEM and PD for barium column height after 2 and 5 minutes, with less stasis observed in the POEM group ($P = .005$; $P = .015$). There was no significant difference between POEM and PD when evaluating the maximum esophageal width measured during timed barium esophagogram ($P = .121$) (Figure 3 and Supplementary Table 1).

With regard to the baseline measurements, this study found no significant differences in median Eckardt score ($P = .920$), basal LES pressure ($P = .109$), IRP-4 ($P = .631$), achalasia subtype ($P = .927$), and barium column height after 2 minutes ($P = .282$) and 5 minutes ($P = .830$) between unsuccessfully and successfully treated patients. The same applied when performing subgroup analysis within the treatment groups; for patients treated with POEM and PD, there were no significant differences in median Eckardt score ($P = .910$; $P = .699$), basal LES pressure ($P = 1.0$; $P = .501$), IRP-4 ($P = .756$; $P = .926$), achalasia subtype ($P = .765$; $P = .843$), and barium column height after 2 minutes ($P = .597$; $P = .669$) and 5 minutes ($P = .597$; $P = .830$) between unsuccessfully and successfully treated patients.

Importantly, our study found a significantly lower mean ADSQoL score in the POEM group. The overall quality of life

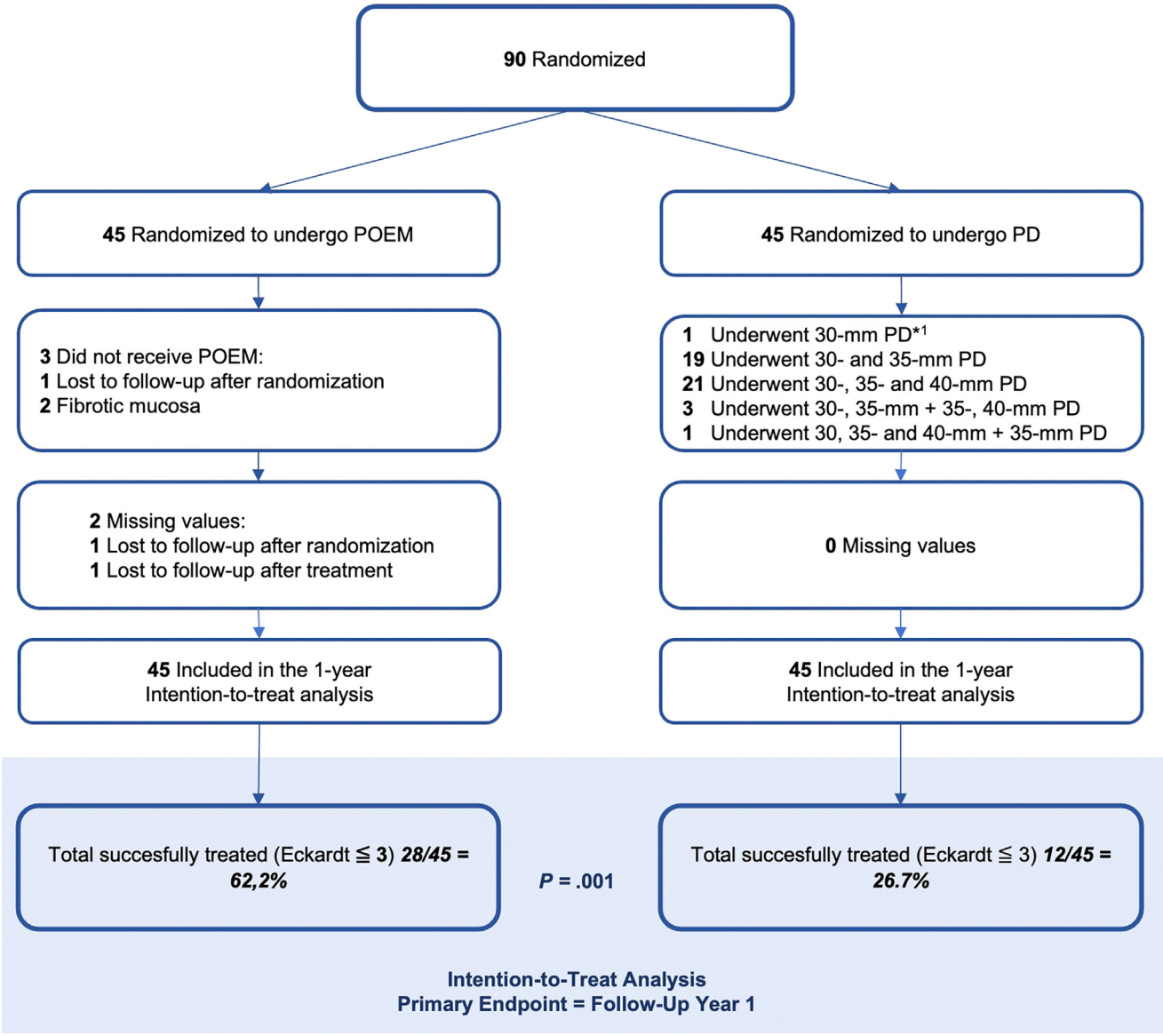

Figure 1. Flowchart, randomization, and follow-up according to intention-to-treat analysis. *1This patient underwent a PD with a 30-mm balloon only because adequate symptom control (Eckardt score <3) was achieved after a single PD, the patient refused PD with a 35-mm balloon.

was measured using the SF-36 score, which is composed of 8 sections. There was a significant difference between POEM and PD, favoring POEM for Physical Functioning, Emotional Well-Being, and Social Functioning. For the components General Health, Limitations Due to Physical Health, Limitations Due to Emotional Problems, Energy/Fatigue, and Pain, we found no difference (Table 3).

Serious Adverse Events and Adverse Events

Eight SAEs occurred during the study, 2 were related to treatment and 6 occurred independently of the study intervention. One microperforation occurred after a POEM, which required admission and treatment with antibiotics for 2 days with subsequent discharge; this patient was initially randomized and treated with PD and failed. Another SAE consisted of chronic severe reflux symptoms after PD and was treated with a Toupet fundoplication. Both patients continued in the study. Detailed information on SAEs independent of the study interventions is provided in the Supplementary Material.

AEs were more common after POEM (14 of 45 patients [31.1%]) vs after PD (9 of 45 [20%]). AEs in the POEM group were related to candida esophagitis (n = 1), *Helicobacter pylori* infection (n = 3), periprocedural mucosal bleeding (n = 2), gastric perforations (1 caused by the spray catheter that was managed conservatively and 1 that was treated by placement of 3 clips) (n = 2), food impaction (n = 1), and several not-upper-gastrointestinal–related AEs (n = 5).

In the PD group, reported AEs were retrosternal pain after PD (n = 2), pneumoperitoneum and subcutaneous

Table 1. Baseline Characteristics of Included Patients Presented per Treatment Group (n = 90)

Characteristic	POEM (n = 45)	PD (n = 45)
Sex, female, n (% male)	27 (40)	29 (35.6)
Age, *y*, median (IQR)	53 (29–77)	52 (25–79)
Eckardt score,[a] median (IQR)	6 (4–8)	6(4–6)
Achalasia subtypes, n (%)		
I (n = 19)	9 (47)	10 (53)
II (n = 30)	15 (50)	15 (50)
III (n = 7)	4 (57)	3 (43)
Basal LES pressure, *mmHg*, mean (95% CI)	22.7 (17.9–27.5)	25.4 (19.3–31.5)
Basal IRP-4, *mmHg*, mean (95% CI)	17.2 (13.6–20.8)	21.3 (16.1–26.6)
Barium esophagogram, median (IQR)		
Column height T = 2 min, *cm*	4.7 (1.9–7.5)	4.3 (1–7.6)
Column height T = 5 min, *cm*	3.4 (0.3–6.5)	4.0 (1.2–6.8)
Maximum diameter, *cm*	3.5 (2.6–4.4)	3.3 (2.1–4.7)
ADSQoL score,[b] median (IQR)	25 (25–27)	26 (23–28)
SF-36 score,[c] median (IQR)		
General Health	50 (35–70)	45 (35–60)
Physical Functioning	80 (65–93.8)	82.5 (57.5–95)
Limitations Due to Physical Health	25 (0–100)	50 (0–100)
Limitations Due to Emotional Problems	100 (41.7–100)	66.7 (0–100)
Energy/Fatigue	50 (35–65)	42.5 (30–60)
Emotional Well-Being	72 (53–88)	70 (37–84)
Social Functioning	75 (50–87.5)	56.3 (28.2–75)
Pain	57.5 (45–80)	45 (32.5–67.5)

IQR, interquartile range.
[a]Eckardt score ranges from 0 to 12, with a higher score indicating more severe symptoms.
[b]ADSQoL score ranges from 10 to 33, with a lower score indicating a better quality of life.
[c]SF-36 score consisted of a Physical Component Summary score and Mental Component Summary score, each ranging from 0 to 100, with higher scores indicating better quality of life.

emphysema after PD (n = 1), mild bleeding during PD managed conservatively (n = 1), an allergic reaction after endoscopy (n = 1), and not-upper-gastrointestinal–related AEs (n = 4).

Post-Hoc Sensitivity Analysis

Primary outcome. Post-hoc sensitivity analysis of the primary outcome was performed by looking at the data with the "per-protocol" principle. Within the POEM group, 2 patients received PD as the primary treatment after randomization to POEM because of fibrotic mucosa, which prohibited the performance of POEM. Furthermore, 1 patient was lost to follow-up after treatment with POEM, and 1 was lost to follow-up after randomization. Within the POEM group, 27 of 41 patients (65.8%) vs 12 of 47 (25.5%] in the PD group were successfully treated at 1-year follow-up (absolute difference, 40.3%; 95% CI, 21.2%–59.5%; relative risk, 2.6; 95% CI, 1.51–4.41).

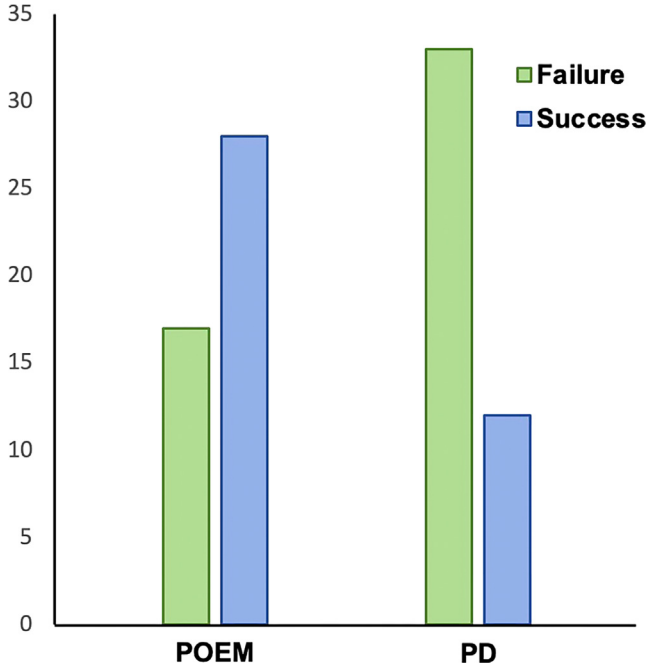

Figure 2. Primary outcome for POEM and PD (absolute numbers).

In the PD group, 14 patients received re-treatment with POEM; 6 of 14 (42.9%) were successfully treated at 1-year follow-up. Within the POEM group, 2 patients received re-treatment with PD and both failed.

Secondary outcomes. Linear mixed models were used to determine the difference in treatment effect on secondary outcomes. The differences are represented as parameter estimates (Supplementary Table 1 and Table 3). Linear mixed models adjusted for time showed a significant difference in Eckardt score, basal LES pressure, IRP-4, and barium contrast height at T = 2 minutes and 5 minutes, at 1-year follow-up in favor of POEM. This study did not find significant differences in the maximum esophageal width measured during timed barium esophagogram between POEM and PD using linear mixed models. With regard to the ADSQoL and SF-36 scores, linear mixed models showed similar results as the classical statistical analysis (Table 3).

By using generalized linear models, the association between treatment and binary outcomes, such as the occurrence of reflux esophagitis and reflux symptoms, could be determined. The strength of this association is represented as a β-coefficient. With the generalized linear model, it was also possible to adjust for certain confounding factors, such as PPI use within the first year of follow-up. Both with and without adjustment, there was no significant association between treatment and occurrence of reflux esophagitis and reflux symptoms (Supplementary Table 1). The same

Table 2. Primary Outcome of Patients With Achalasia at 1-Year Follow-Up After POEM or PD as Intention-to-Treat Analysis

1-y follow-up primary end point	POEM, n (%) (n = 45)	PD, n (%) (n = 45)	*P* Value	Odds ratio (95% CI)	Relative risk (95% CI)	Unadjusted absolute difference, % (95% CI)
Overall treatment success	28 (62.2)	12 (26.7)	.001	0.22 (0.09–0.54)[a]	2.33 (1.37–3.99)[b]	35.6 (16.4–54.7)

[a]POEM is less likely to result in failure than PD.
[b]Relative risk for success, success was 2.33 times more likely in patients randomized to receive POEM.

applies to the use of a PPI within the first year of follow-up (Supplementary Table 1). These results fall in line with the classical statistical analysis presented above and thereby showed consistent results.

Discussion

This randomized controlled clinical study demonstrated that POEM is more efficacious than PD as rescue therapy for patients with achalasia who experience persistent or recurrent symptoms after LHM.

Regarding the secondary outcomes parameters, this study found significant differences in LES pressure, IRP-4, and barium height at T = 2 minutes and 5 minutes, in favor of POEM at 1-year follow-up. Importantly, no statistically significant differences between groups were measured for occurrence of reflux esophagitis, PPI use, and reflux symptoms. When looking at treatment effect on the quality of life, a significant difference in ADSQOL score was found, again favoring POEM. However, for quality of life measured by the SF-36, significant differences were observed for only 3 of 8 components, that is, Physical Functioning, Emotional Well-Being, and Social Functioning.

With respect to safety, there were 2 treatment-related SAEs, including a microperforation caused by POEM, which was treated with antibiotics and 2 days of admission,

Table 3. Secondary Objective Outcomes After 1-Year Follow-Up After POEM or PD

				POEM vs PD			
Variable	POEM, mean (SD)	PD, mean (SD)	*P* Value[a]	Parameter estimate[b]	SE	*P* Value[c]	95% CI
Eckardt score	2.95 (1.44)	3.77 (1.78)	.016	–0.788	0.361	.031	–1.505 to –0.071
LES pressure, mmHg	14.81 (7.37)	19.97 (9.99)	.034	–4.95	2.41	.043	–9.73 to –0.160
IRP-4, seconds	9.64 (4.96)	15.62 (9.08)	.002	–5.998	1.727	.001	–9.425 to –2.571
Barium height T = 2 min	2.97 (1.74)	4.64 (2.90)	.005	–1.658	0.592	.006	–2.833 to –0.483
Barium height T = 5 min	2.47 (1.77)	4.02 (2.89)	.015	–1.558	0.592	.01	–2.732 to –0.384
Maximum width, cm	3.23 (1.25)	3.65 (1.36)	.121	–0.363	0.283	.203	–0.925 to 0.199
Variable	POEM, n (%)	PD, n (%)	*P* Value[a]	β-coefficient[d]	SE	*P* Value[e]	95% CI
Reflux esophagitis (n = 75)	12/35 (34.3)	6/40 (15)	.062	–0.770 (1.022[f])	0.658 (1.398[f])	.242 (.465[f])	–2.06 to 0.530 (–3.762 to 1.718 [e])
Grade A	7/35 (20)	4/40 (10)	NA	NA	NA	NA	NA
Grade B	4/35 (11.4)	1/40 (2.5)	NA	NA	NA	NA	NA
Grade C	1/35 (2.9)	1/40 (2.5)	NA	NA	NA	NA	NA
Grade D	0 (0)	0 (0)	NA	NA	NA	NA	NA
PPI use (n = 87)	29 (69)	26 (57.8)	0.374	–0.489	0.45	0.277	–1.37 to 0.393

[a]*P* value for the difference in outcome of continuous data analyzed using Mann-Whitney U test and categorical data using $\mathscr{X}2$ test between treatment groups at 1-year follow-up.
[b]Parameter estimates represent the difference in outcome of continuous data between treatment groups at 1-year follow-up, adjusted for repeated measurements over 1 year time; measured by linear mixed models with PD as the reference treatment.
[c]*P* value for parameter estimates as measured by linear mixed models with PD as the reference treatment.
[d]β-coefficients represent the association between categorical data at 1-year follow-up and the treatment groups; measured by generalized linear models using PD as the reference treatment.
[e]*P* value for β-coefficients as measured by generalized linear models with PD as the reference treatment.
[f]Results of generalized linear models adjusted for PPI use during 1-year follow-up.

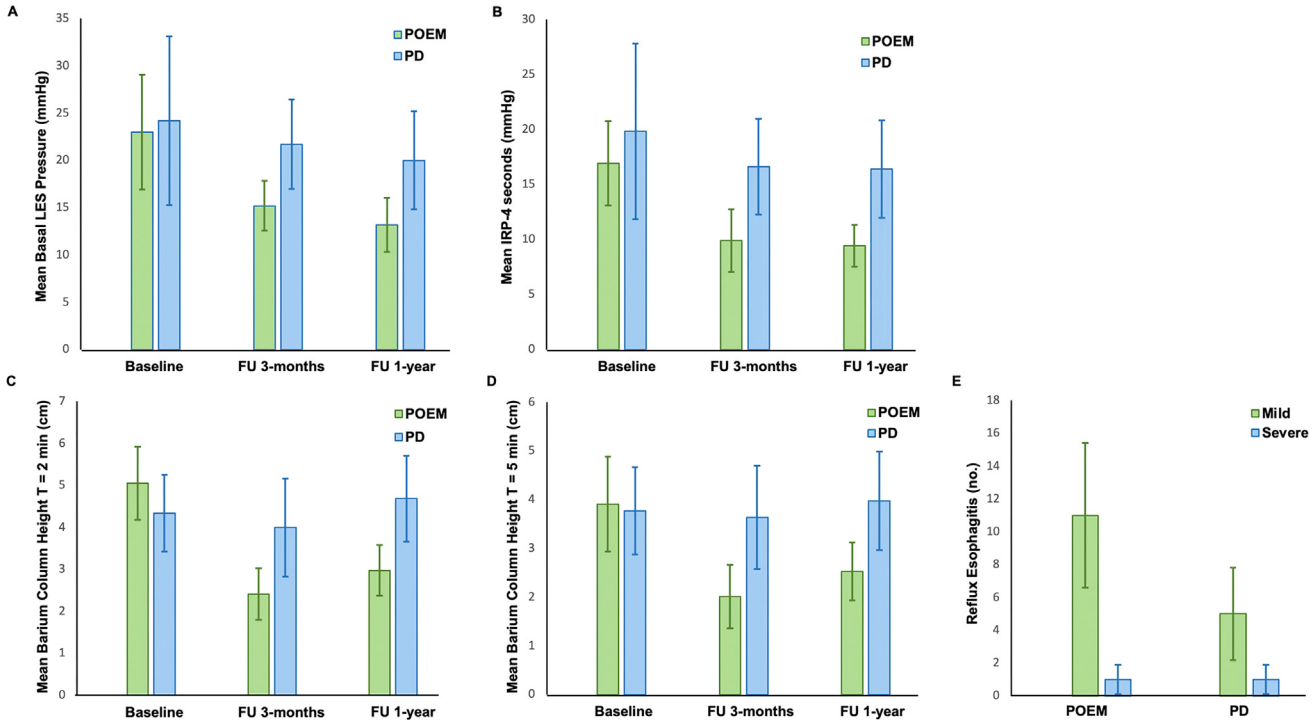

Figure 3. Mean basal LES pressure, IRP-4, barium column height at 2 and 5 minutes over 1 year, and presence of reflux esophagitis at 1-year follow-up for POEM and PD.

and extreme reflux symptoms as a result of PD, which were treated with a Toupet fundoplication. In contrast to studies comparing POEM and PD for treatment-naïve patients with achalasia, this study did not find a statistically significant difference in development of reflux esophagitis, experience of reflux symptoms, and use of PPI between patients treated with POEM and patients treated with PD.[21]

To our knowledge, this is the first randomized controlled trial that compared POEM with PD as treatment in patients with achalasia experiencing persistent or recurrent symptoms after LHM. The efficacy rate of POEM observed in our study (62.2%) was lower compared with uncontrolled prospective and retrospective studies, where clinical success rates ranged between 81% and 96%.[9,20,26,29–33] This discrepancy cannot be attributed to a difference in the definition of success, as these studies also defined clinical success as an Eckardt score $\leq$3. However, most of these studies included small samples, had a retrospective design in which inclusion in the cohort was determined afterward, and presented shorter follow-up times, which could explain higher success rates.[8,9,20] This study's observed success rate of 62.2% at 1 year should be considered a medium-term outcome. Longer follow-up data will help provide information about the duration of the treatment effect. Moreover, our data confirmed the low-risk nature of POEM.

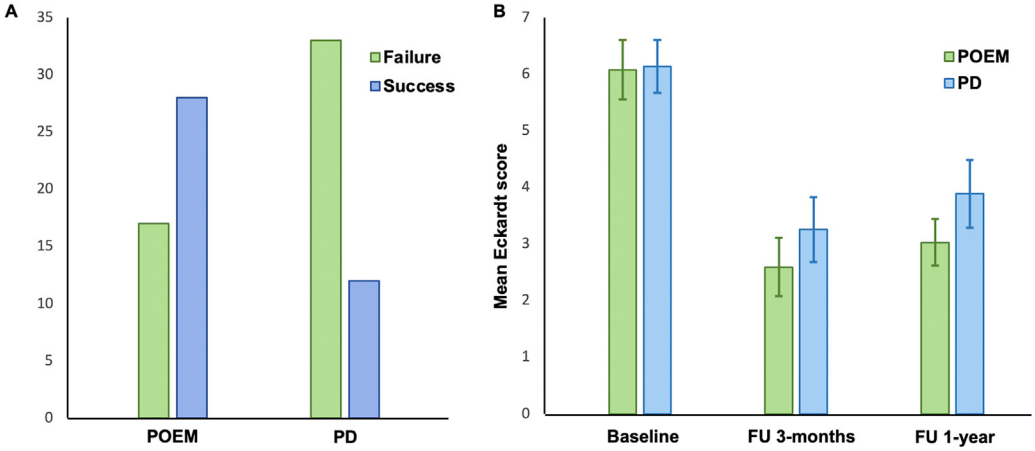

Figure 4. Mean Eckardt score over 1 year for POEM and PD.

As for PD, this study observed an efficacy rate of 26.7%, which is also lower than the efficacy reported by published case series, where efficacy ranged from 57% to 96%.[9,12,15,17,34] One reason for this discrepancy could be the heterogeneity of PD protocols used and the retrospective nature of most published reports. In this study, patients were initially treated with 30-mm and 35-mm PD (except for 1 patient), and in case of persistent symptoms after 3 weeks, an additional 40-mm PD was performed. If symptoms recurred within 1 year, patients were treated with another round of PDs. Repeat series of PD is an accepted clinical strategy and reflects daily practice. Still, patients may experience another series of PDs as failed treatment. Indeed, in this study, a few patients randomized to the PD arm refused additional rounds of PD when they experienced persistent or recurrent symptoms after their first round of PD. These patients were considered failures, and some received POEM in consultation with their physician; 14 patients were re-treated with POEM after failed PDs within their first-year of follow-up. Furthermore, in this study, pressurization of balloons started at 5 psi for 1 minute, followed by 7 psi for another minute. Although this might differ from other protocols, it is important to realize waist obliteration was obtained in all PDs, most of these already occurring with 5 psi. Therefore, it was considered unlikely that the difference in pressurizations used played a role in the high degree of PD failure.

Although POEM is more invasive and requires more technical endoscopic skills, the risk of severe complications was not higher than was seen with PD. Data from this study suggest that in previously treated patients with achalasia, POEM did lead to more grade A–B reflux esophagitis, although this was not statistically significant. This was most likely the result of the small number of events in this subgroup analysis. However, POEM did not conduce more reflux symptoms or PPI use than PD. Interestingly, it was after a series of PD that 1 patient experienced severe reflux symptoms and required a Toupet fundoplication.

Taking into account the efficacy rate, occurrence of complications, and presence of reflux esophagitis and reflux symptoms within the clinical context, it seems reasonable to offer POEM as the primary treatment option for patients with achalasia experiencing persistent or recurrent symptoms after LHM.

Strengths and Limitations

The strengths of this randomized controlled trial are the substantial number of patients included, particularly given the rare nature of this disorder, and the stratification of the randomization by center. In addition, this study used objective measures at baseline to determine the nature of the persistent or recurrent symptoms and the eligibility for the trial. The objective measures were also used to analyze treatment effect and esophageal function. Concerning the statistical methods: primary data analysis was performed according to the intention-to-treat principle. Nonetheless, to increase the credibility and strength of the forthcoming conclusions, a sensitivity analysis was implemented.[29]

There were also limitations identified. Firstly, primary and secondary outcomes were assessed at 1-year follow-up. Consequently, no conclusions can be drawn for longer-term treatment success, which is important, given that achalasia is a lifelong chronic disease. Secondly, like most endoscopic or surgical studies that evaluate new interventional techniques, patients and caregivers were not blinded for treatment allocation. Although a blinded study would have been very challenging—requiring general anesthesia and admission for the PD group and undergoing several sham PDs in the POEM group—bias was minimized to the greatest extent possible by blinding observers of diagnostic measurements to the patients' treatment; questionnaires were filled in by patients without the presence of research personnel; and indication for an unscheduled treatment was based solely on the previously set cutoff, that is, Eckardt score >3. Lastly, multiple PD sessions might form a potential bias in the comparison with 1 treatment intervention; however, as stated before, this was done deliberately to optimally reflect routine clinical care in these patients.

In conclusion, among patients with achalasia experiencing persistent or recurrent symptoms after LHM, treatment with POEM resulted in a significantly higher success rate compared with PD, with a numerically (not statistically significant) higher incidence of grade A–B reflux esophagitis. These findings support the consideration of POEM as the initial treatment option for patients with achalasia experiencing persistent or recurrent symptoms after LHM.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.02.048.

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Conflicts of interest

These authors disclose the following: Albert J. Bredenoord received research funding from Nutricia, Norgine, DrFalkPharma, Gossamer, Thelial, SST, and Bayer, and received speaker and/or consulting fees from Laborie, Arena, EsoCap, Medtronic, Dr. Falk Pharma, Calypso Biotech, Alimentiv, Sanofi/Regeneron, Reckett, and AstraZeneca. Pietro Familiari consults for Olympus and Cook Medical. The remaining authors disclose no conflicts.

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Data Availability

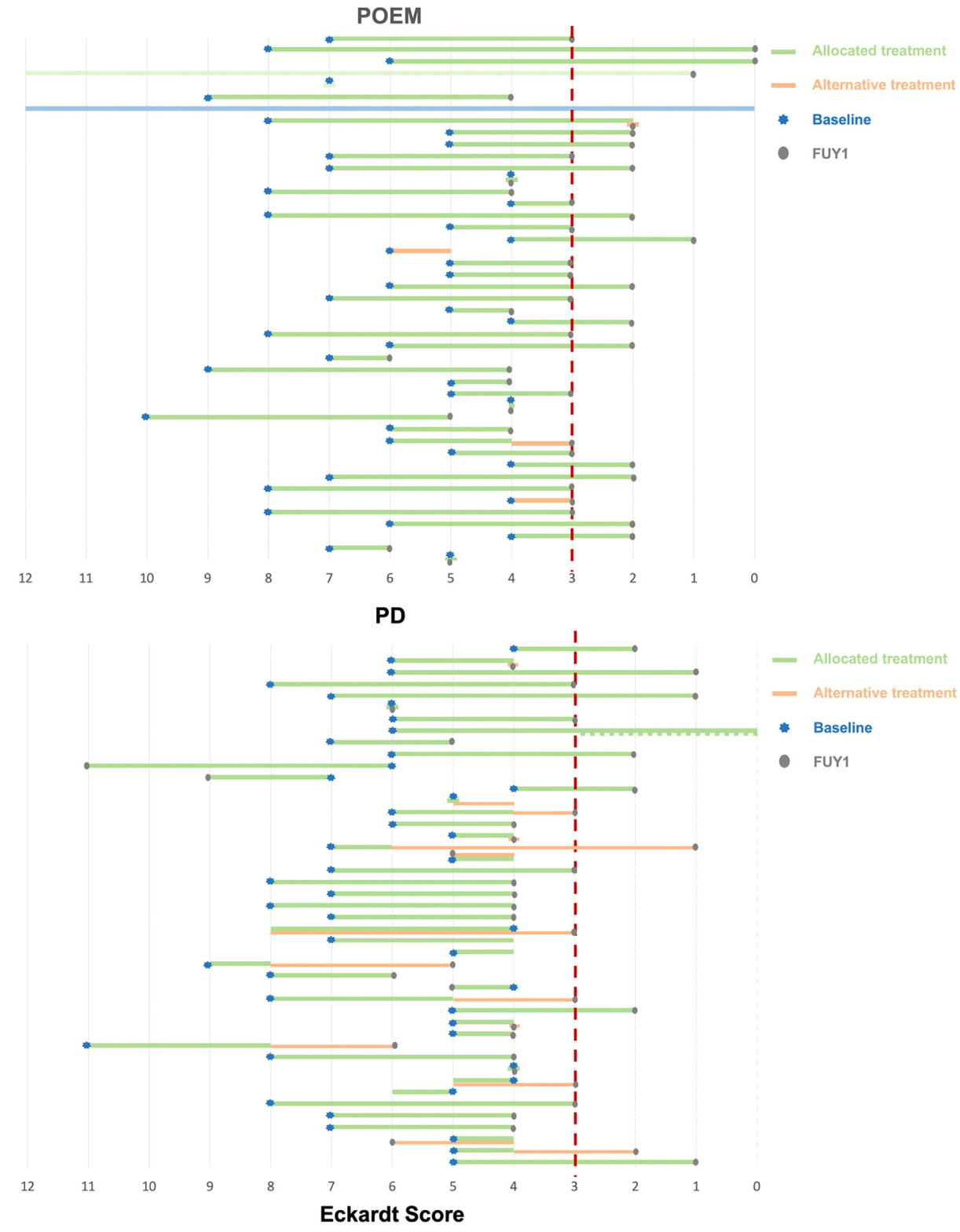
Data, analytic methods, and study materials are available to other researchers upon request. The study protocol is included as Supplementary Material available with the online version of this article.

Supplementary Material

Serious Adverse Events Independent of Study Intervention

Within the group of patients treated with POEM, there were 3 SAEs not related to the intervention. One patient was hospitalized because of worsened dysphagia symptoms, which required placement of a feeding tube; symptoms resolved spontaneously and the feeding tube could be removed swiftly. In another patient, an atrium septum defect type II (birth defect) was discovered during the trial, which was treated operatively. Lastly, 1 patient died due to liver cirrhosis and ischemic cardiomyopathy, which was identified shortly after receiving POEM; this is the only SAE not related to a treatment that resulted in early discontinuation of the study.

For the group of patients treated with PD, there were 2 SAEs not related to treatment. One patient was diagnosed with a viral pericarditis, for which they were admitted and treated with nonsteroidal anti-inflammatory drugs. The second patient was diagnosed with a, probably viral, pneumonia; because this SAE occurred shortly after PD, it was doubtful whether it was or was not related to the intervention. The patient required admission and was treated with antibiotics and antivirals.



Supplementary Figure 1. Eckardt score range from baseline to follow-up year 1 for POEM and PD.

Supplementary Table 1. Secondary Subjective Outcomes After 1-Year Follow-Up After POEM or PD

				POEM vs PD			
Variable	POEM, median (IQR)	PD, median (IQR)	*P* value[a]	Parameter estimate[b]	SE	*P* value[c]	95% CI
ADSQoL score	18 (15–21.25)	21 (16.5–24)	.023	–2.535	1.046	.017	–4.164 to –0.455
SF-36							
General Health	65 (36.25–80)	52.5 (45–75)	.636	3.258	4.902	.508	–6.504 to 13.021
Physical Functioning	95 (81.25–100)	80 (55 – 95)	.002	10.945	5.320	.043	0.359 to 21.531
Limitations Due to Physical Health	100 (0–100)	50 (0–100)	.217	12.493	8.964	.167	–5.333 to 30.319
Limitations Due to Emotional Problems	100 (33.3–100)	100 (0–100)	.110	12.838	8.703	.144	–4.465 to 30.141
Energy/Fatigue	62.5 (45–82.5)	55 (42.5–72.5)	.334	5.597	4.938	.260	–4.216 to 15.409
Emotional Well-Being	84 (76–92)	76 (48–84)	.007	12.458	4.294	.005	–3.926 to 20.991
Social Functioning	87.5 (75–100)	75 (56.25–87.5)	.005	16.186	5.729	.006	4.803 to 27.569
Pain	77.5 (60–90)	67.5 (45–90)	.096	9.459	5.263	.076	–1.001 to 19.918
GERDQ	7 (6–9.75)	8 (7–10)	.395	–0.500	0.587	.396	–1.665 to 0.644

Variable	POEM, n (%)	PD, n (%)	*P* value	β-coefficient[d]	SE	*P* value[e]	95% CI
GERDQ $\geq$8(n = 79)	18/40 (45)	22/39 (56.4)	.371	–0.458 (–0.649 [f])	0.453 (1.012 [f])	.312 (.521[f])	–1.347 to 0.430 (–2.633 to 1.334[f])

GERDQ, Gastroesophageal Reflux Disease Questionnaire; IQR, interquartile range.
[a]*P* value for the difference in outcome of continuous data analyzed using Mann-Whitney U test and categorical data using $\mathscr{X}2$ test between treatment groups at 1-year follow-up.
[b]Parameter estimates represent the difference in outcome of continuous data between treatment groups at 1-year follow-up, adjusted for repeated measurements over 1 year; measured by linear mixed models with PD as the reference treatment.
[c]*P* value for parameter estimates as measured by linear mixed models with PD as the reference treatment.
[d]β-coefficients represent the association between categorical data at 1-year follow-up and the treatment groups; measured by generalized linear models using PD as the reference treatment.
[e]*P* value for β-coefficients as measured by generalized linear models with PD as the reference treatment.
[f]Results of generalized linear model adjusted for PPI use during 1-year follow-up.