Per-oral endoscopic myotomy versus laparoscopic Heller's myotomy plus Dor fundoplication in patients with idiopathic achalasia: 5-year follow-up of a multicentre, randomised, open-label, non-inferiority trial

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Summary

Background In this trial, we previously showed per-oral endoscopic myotomy (POEM) to be non-inferior to laparoscopic Heller's myotomy (LHM) plus Dor fundoplication in managing symptoms in patients with idiopathic achalasia 2 years post-procedure. However, post-procedural gastro-oesophageal reflux was more common after POEM at 2 years. Here we report 5-year follow-up data.

Methods This study is a multicentre, randomised, open-label, non-inferiority trial performed at eight centres in six European countries (Germany, Italy, Czech Republic, Sweden, the Netherlands, and Belgium). Patients with symptomatic primary achalasia were eligible for inclusion if they were older than 18 years and had an Eckardt symptom score higher than 3. Patients were randomly assigned (1:1; randomly permuted blocks of sizes 4, 8, or 12) to undergo either POEM or LHM plus Dor fundoplication. The primary endpoint was clinical success, defined by an Eckardt symptom score of 3 or less without the use of additional treatments, at 2 years, and was reported previously. Prespecified secondary endpoints at 5 years were clinical success; Eckardt symptom score; Gastrointestinal Quality of Life Index score; lower oesophageal sphincter function by high-resolution manometry; and parameters of post-procedural reflux (reflux oesophagitis according to the Los Angeles classification; pH-metry, and DeMeester clinical score). We hypothesised that POEM would be non-inferior (with a non-inferiority margin of –12·5 percentage points) to LHM plus Dor fundoplication with regards to clinical success. All analyses were performed on a modified intention-to-treat (mITT) population, which included all patients who underwent the assigned procedure. This study is registered with ClinicalTrials.gov (NCT01601678) and is complete.

Findings Between Dec 7, 2012, and Oct 9, 2015, 241 patients were randomly assigned (120 to POEM and 121 to LHM) and 221 had the assigned treatment (112 POEM and 109 LHM; mITT). 5-year follow up data were available for 90 (80%) patients in the POEM group and 87 (80%) patients in the LHM group. Clinical success rate at 5 years was 75·0% (95% CI 66·2 to 82·1) after POEM and 70·8% (61·7 to 78·5) after LHM (difference 4·2 percentage points [95% CI –7·4 to 15·7]). The mean Eckardt symptom score decreased from baseline to 5 years in both groups and the overall difference in mean scores was –0·29 (95% CI –0·62 to 0·05). Change in Gastrointestinal Quality of Life Index scores, as well as in integrated relaxation pressure on manometry, from baseline to 5 years, did not differ significantly between the groups. At 5 years, 26 (41%) of 63 patients after POEM and 18 (31%) of 58 patients after LHM had reflux oesophagitis (difference 10·2 percentage points [95% CI –7·0 to 26·8]). Significant oesophagitis (Los Angeles classification grade B, C, or D) was observed in nine (14%) of 63 patients after POEM and in four (7%) of 58 patients after LHM. pH-metry was performed in 81 (37%) of 221 patients, with higher mean acid exposure time for POEM (10·2% [95% CI 7·6 to 14·2]) than for LHM (5·5% [3·1 to 11·8]). Significantly more patients in the POEM than in the LHM group had abnormal acid exposure time at 5 years (>4·5%; 28 [62%] of 45 *vs* 11 [31%] of 36; difference 31·7 percentage points [95% CI 9·8 to 50·5]). The presence of reflux symptoms at 5 years was similar in both groups, with a mean DeMeester clinical score of 1·3 (95% CI 1·0 to 1·6) after POEM and 1·1 (0·9 to 1·4) after LHM. The complications of peptic stricture, Barrett's oesophagus, and oesophageal adenocarcinoma were not reported.

Interpretation Our long-term results support the role of POEM as a less invasive myotomy approach that is non-inferior to LHM in controlling symptoms of achalasia. Gastro-oesophageal reflux was common in both groups, but with a tendency towards higher rates in the POEM group. Thus, patients should be provided with the advantages and disadvantages of each approach in decision making.

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Introduction

Achalasia is a chronic motility disorder of the oesophagus characterised by impaired relaxation of the lower oesophageal sphincter and absence of oesophageal peristalsis. Due to abnormal transit and stasis of food, this condition typically results in symptoms of dysphagia, regurgitation of undigested food, chest pain, and weight loss. Current treatment options are not curative, but rather intended to palliate symptoms by reducing lower oesophageal sphincter pressure and subsequently improving oesophageal outflow. This has successfully been achieved by either disrupting lower oesophageal sphincter muscle fibres with endoscopic pneumatic dilation or dividing them by surgical laparoscopic Heller's myotomy (LHM) and combining with partial fundoplication to prevent the development of gastro-oesophageal reflux.[1]

Per-oral endoscopic myotomy (POEM) represents another approach to oesophageal myotomy. It has been accepted worldwide as a standard treatment for achalasia as many retrospective, as well as a few prospective, studies have shown its safety and excellent short-term and mid-term clinical efficacy.[2–4] Due to the minimally invasive and scarless nature of this procedure, its low morbidity and virtually no mortality, and possible same-day or next-day discharge, POEM quickly became the preferred form of myotomy in many centres. However, higher rates of gastro-oesophageal reflux after POEM compared with pneumatic dilation or LHM can be considered a disadvantage of POEM. Defining post-POEM reflux has not been standardised from a clinical, as well as a scientific, point of view, and, thus, four partially independent parameters are commonly assessed: the rate of oesophagitis, consumption of

Research in context

Evidence before this study

Before trial continuation we searched PubMed for trials of achalasia treatment published from Jan 1, 2001, to Jan 1, 2020, using the terms "achalasia", "peroral endoscopic myotomy OR POEM", "Heller myotomy", and "endoscopic dilation"; with no language restriction. We restricted the search to reviews, clinical trials, large prospective and retrospective studies, and case series. Studies of greatest interest were randomised controlled trials (RCTs) and those most pertinent to our analyses were results from two large studies comparing endoscopic dilation to Heller's or endoscopic myotomy. Each of these three methods represent possible treatment options for patients with achalasia. This was validated by our 2-year results of this current trial comparing laparoscopic Heller's myotomy (LHM) plus Dor fundoplication versus per-oral endoscopic myotomy (POEM) published in 2019, as the study found non-inferior efficacy and similar safety of both treatments after 2 years. Nevertheless, little was known about the long-term effect of POEM and the clinical relevance of gastro-oesophageal reflux after the procedure. Reflux is considered a disadvantage of POEM compared with the other two methods. Existing literature has often reported higher short-term rates of post-procedural reflux in patients undergoing POEM compared with those receiving LHM. These results raised important questions about the long-term implications for patient management.

Added value of this study

To our knowledge, our study was the first RCT comparing the efficacy of POEM with LHM plus Dor fundoplication in patients with achalasia. After 5 years of follow-up, our data show non-inferior efficacy in the management of symptoms between the two procedures. Moreover, our long-term analysis specifically focused on the issue of post-procedural reflux over time and therefore provides crucial data. The difference between the groups in rates of reflux oesophagitis appeared to decrease over time, being significantly higher in the POEM versus LHM group at 3 months (57% *vs* 20%) but not at 5 years (41% *vs* 31%). The presence of reflux symptoms at 5 years was also similar between groups. Although a higher proportion of patients after POEM than after LHM were on proton-pump inhibitors (53% *vs* 39%), this difference was not significant. However, significantly more patients in the POEM group than in the LHM group had abnormal acid exposure time at 5 years (62% *vs* 31%).

Implications of all the available evidence

Our study shows that POEM is an efficacious and less invasive option for myotomy that has supporting evidence of a long-lasting effect and so can be offered to patients with achalasia. It also shows that although LHM with partial fundoplication can provide temporary reflux protection, this effect might lessen over time. Our findings could help clinicians to navigate patients towards more informed decision making, addressing their concerns regarding long-term quality of life and the benefits and risks of both procedures.

proton-pump inhibitors, acid reflux on pH-metry, and reflux symptoms. In 2019, we published results of a randomised, multicentre, non-inferiority trial comparing POEM with LHM plus Dor fundoplication.[5] 2 years after the procedure, POEM was non-inferior to LHM plus Dor fundoplication in terms of efficacy (clinical success rate); however, POEM resulted in more cases of post-procedural gastro-oesophageal reflux in terms of the rate of reflux oesophagitis and the administration of proton-pump inhibitors. Yet, between-group differences in reflux oesophagitis decreased between 3 months of follow-up and 2 years. Moreover, oesophageal pH monitoring showed similar proportions of patients with abnormal acid reflux at 3 months and 2 years after both procedures.

In this report, we present long-term results of our randomised non-inferiority trial.[5] We aimed to evaluate the efficacy of POEM compared with LHM plus Dor fundoplication and the presence of gastro-oesophageal reflux 5 years after the procedures in patients with symptomatic achalasia.

Methods

Study design and participants

This multicentre, randomised, open-label, non-inferiority trial was performed at eight centres in six European countries (Germany, Italy, Czech Republic, Sweden, the Netherlands, and Belgium; appendix 1 p 27).[5] The trial was approved by the institutional review board at each participating centre. Detailed description of the study population has been previously reported.[5] In brief, patients with symptomatic primary achalasia confirmed by oesophageal manometry (and classified into subtypes I, II, and III) were eligible for inclusion if they were older than 18 years, had an Eckardt symptom score higher than 3, and a medical indication for surgical myotomy or pneumatic dilation. Patients who had undergone previous surgery of the stomach or oesophagus, including surgical therapy of achalasia, were excluded. Patients who had previously undergone endoscopic therapy were not excluded. Further details on the inclusion and exclusion criteria are provided in appendix 1 (p 18) and the protocol (appendix 2 p 48). All patients provided written informed consent. This study is registered with ClinicalTrials.gov, NCT01601678, and is complete.

Randomisation and masking

Patients at each centre were randomly assigned in a 1:1 ratio to undergo either POEM or LHM plus Dor fundoplication. A computer-generated randomisation list was created for each centre using randomly permuted blocks of varying sizes (4, 8, or 12). A trial nurse who was unaffiliated with the research group and otherwise not involved with the trial provided the randomisation result to the centres upon an email request. The study was open-label and the personnel, including the data analysts, were not masked.

Procedures

Procedures (POEM and LHM plus Dor fundoplication) were performed as previously described; for more details see appendix 2 (pp 8–10) and our previous publication.[5] In brief, POEM involved the creation of an oesophageal submucosal tunnel, which was extended 2–3 cm into the gastric cardia, and transection of the muscular fibres of the lower oesophageal sphincter was performed. LHM was performed surgically by dividing the muscle fibres of the lower oesophageal sphincter and extending the division to at least 6 cm into the oesophageal side and at least 2–3 cm into the gastric cardia. Dor anterior fundoplication was performed.

Patients completed Eckardt symptom questionnaires and had their proton-pump inhibitor intake and DeMeester clinical score assessed at baseline, 3 months, 6 months, 1 year, 2 years, 3 years, and 5 years. Patients completed the Gastrointestinal Quality of Life questionnaire (appendix 1 p 20) and had manometry scheduled at baseline, 3 months, 2 years, and 5 years. Objective evaluation by endoscopy was planned at baseline, day 2, 3 months, 2 years, and 5 years, and by pH-metry at 3 months, 2 years, and 5 years. Endoscopy and pH-metry were done at least 1 week after the discontinuation of proton-pump inhibitors. Proton-pump inhibitor prescriptions were by physician discretion and the exact indication for this treatment (reflux symptoms or other) was not documented. Patient-reported outcomes were assessed by means of telephone calls, mail, or follow-up appointments by dedicated trial personnel who were aware of the treatment group assignments (appendix 1 p 19). Unscheduled visits were possible in cases of symptom recurrence or other health-related problems. Additional unscheduled examinations (endoscopy, manometry, etc) could be performed at the discretion of the physician. Safety and adverse events were assessed ad hoc and were reported to the leading study centre (Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany) and from there to the safety monitoring board and the study steering committee. Systematic monitoring was performed during the initial 2-year study and maintained to a lesser degree by the central study nurse beyond 2 years. Data on the sex of patients were obtained from the respective centres' data management systems and were not re-examined for the purpose of the trial. Race and ethnicity data were not collected.

See Online for appendix 1

See Online for appendix 2

Outcomes

The primary outcome of the trial was clinical success, defined by an Eckardt score of 3 or less without the use of additional treatments, at 2 years, and was reported previously.[5] The original primary outcome of this study was lower oesophageal sphincter pressure on manometry 3 months post-procedure. Change of the primary outcome was approved by the Hamburg Ethics Committee on Jan 2, 2013 (before any study procedures

were performed), to align with other relevant achalasia treatment studies.[6,7] Clinical success was not centrally assessed. Each centre individually reported the Eckardt scores and decided on eventual re-treatments.

Herein, we report the prespecified secondary endpoints of clinical success at 3 months and 5 years; assessment of achalasia-related symptoms (Eckardt score) and reflux-related symptoms (DeMeester clinical score, ranging from 0 [no symptoms] to 6 [severe symptoms])[8] at baseline, 3 months, 6 months, 1 year, 2 years, 3 years, and 5 years; Gastrointestinal Quality of Life Index score (range 0–144, with higher scores indicating better quality) at baseline, 3 months, 2 years, and 5 years; assessment of lower oesophageal sphincter function by high-resolution manometry (integrated relaxation pressure) at baseline, 3 months, 2 years, and 5 years; grading of reflux oesophagitis on endoscopy according to the Los Angeles classification and 24-h pH monitoring at 3 months, 2 years, and 5 years; number of therapy failures; and number and kind of retreatments. Acid exposure time (total percentage of time with pH <4) on pH-metry was considered abnormal when more than 4·5%. The pH-metry composite DeMeester score was calculated as well.[9] Further details on some of these clinical measures are provided in appendix 1 (pp 20–21).

Prespecified secondary endpoints not reported herein are adverse events and procedure data (laboratory values, days of hospitalisation, myotomy length, and duration of procedure) as these were both reported in the previous publication and did not change or evolve over time.[5]

Post-hoc secondary endpoints reported herein are clinical success at 6 months, 1 year, and 3 years; proton-pump inhibitor use at baseline, 3 months, 2 years, 3 years, and 5 years; reflux oesophagitis rate at baseline; reflux oesophagitis rate according to proton-pump inhibitor status at baseline, 3 months, 2 years, and 5 years; and the use of proton-pump inhibitors in patients with available pH-metry at baseline, 3 months, 2 years, and 5 years.

Statistical analysis

Details concerning the sample size calculation have been previously reported.[5] The primary hypothesis was that POEM would be non-inferior (with a non-inferiority margin of –12·5 percentage points) to LHM plus Dor fundoplication with regard to the primary endpoint at 2 years. Herein we evaluate non-inferiority for the post-hoc and prespecified secondary outcomes of clinical success at 3 years and 5 years. If a patient did not reach an Eckardt score of 3 or less within 3 months after the procedure, it was considered a treatment failure. Increase of the score to more than 3 after initial clinical success was considered a clinical recurrence (in cases where the symptoms were not caused by other conditions such as mycotic oesophagitis). If there was a subsequent decrease of the score to 3 or less without retreatment, the patient was considered as still having a treatment success. The time period for the definition of clinical recurrence was from 6 months to the time of assessment (3 years, 5 years, etc). All analyses were performed on a modified intention-to-treat (mITT) population, which included all patients who underwent the assigned procedure. For analyses regarding the Eckardt scores (including the analyses of clinical success), missing values were imputed by multiple imputation with chained equation using 100 imputations and with available Eckardt scores (including baseline), type of achalasia, previous treatment for achalasia (yes or no), BMI, age, and sex. We estimated Wilson CIs for proportions and Miettinen–Nurminen CIs for differences in proportions on the multiply imputed data according to Lott and Reiter[10] and Lu and Guo.[11] Only available Eckardt score values before a potential retreatment were used and clinical failure was assumed after retreatment.

Following prespecified subgroup analysis at 2 years,[5] we report post-hoc subgroup analyses for clinical success at 5 years. Exploratory subgroups were defined according to age (<40 years or ≥40 years), sex (male or female), achalasia subtype (I, II, or III), and previous treatment of achalasia (yes or no). Post-hoc, we also analysed patients with pH-metry at 2 years and 5 years and those with pH-metry only at one of the given timepoints.

As a post-hoc sensitivity analysis, clinical success at 3 years and 5 years and the evolution of the Eckardt score over baseline, 3 months, 6 months, 1 year, 2 years, 3 years, and 5 years were evaluated in an available data analysis. A tipping point analysis was performed indicating the influence of treatment success or failure in the patients with missing data on the conclusion of the between-group comparison. Generalised estimating equations models with robust SEs were used to evaluate data across visits—binomial with logit link to compare clinical success rates between treatment groups and Gaussian to study the between-group difference of the Eckardt score. Predictors of clinical success were searched for among age (<40 years *vs* ≥40 years), sex, achalasia subtype, and previous treatment group (yes *vs* no) by separate logistic regression models for the 5-year timepoint. In these regression models, Rubin's rules were used to incorporate the additional imputation variability into the SEs.

For the analyses of variables other than the Eckardt score, only available data were used. Fisher's exact test was used for comparing groups for categorical variables and the Wilcoxon rank sum test for continuous variables. CIs for means and medians of continuous variables were constructed by the percentile bootstrap method.

Because no test families for α error control were predefined for the analysis, p values and CIs are presented without multiple testing corrections, and therefore the α error rate is controlled for each result individually and not across the whole report. The standard α level of 5% was used as the threshold for significance and all CIs have 95% expected coverage.

The analyses were performed in R (version 4.3.2). On-site data monitoring was provided by Clinical Trial Center North at the University Hospital Hamburg-Eppendorf, Hamburg, Germany, and the European Clinical Research Infrastructure Network for the initial analysis.

Role of the funding source

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

Results

Between Dec 7, 2012, and Oct 9, 2015, 241 patients were enrolled and randomly assigned (120 to POEM and 121 to LHM). 20 patients were excluded and 221 underwent the assigned treatment (mITT population; 112 patients received POEM and 109 received LHM; for the trial profile see appendix 1 p 3 and previous publication).[5] Overall, 91 (81%) of 112 patients in the POEM group and 90 (83%) of 109 patients in the LHM group had completed 3-year follow-up. Respective numbers for the 5-year follow-up were 90 (80%) of 112 patients in the POEM group and 87 (80%) of 109 patients in the LHM group. No differences between groups were seen in terms of age, sex, type of achalasia, and baseline integrated relaxation pressure of the lower oesophageal sphincter. Details on patients' baseline characteristics are shown in table 1.

	POEM (n=112)	LHM (n=109)
Age, years	48·6 (14·9)	48·6 (14·6)
Sex*		
Male	68 (61%)	60 (55%)
Female	44 (39%)	49 (45%)
BMI, kg/m²	24·8 (4·6)	24·5 (4·5)
Oesophageal function according to IRP, mm Hg	26·8 (11·4)	26·0 (10·9)
Achalasia subtype		
I	15 (13%)	21 (19%)
II	85 (76%)	78 (72%)
III	12 (11%)	9 (8%)
Unclassified	0	1 (1%)
Previous therapy		
None	73 (65%)	69 (63%)
Endoscopic pneumatic dilation	27 (24%)	31 (28%)
Endoscopic botulinum toxin injection	7 (6%)	8 (7%)
Endoscopic pneumatic dilation and botulinum toxin injection	5 (4%)	1 (1%)
Eckardt symptom score	6·8 (2·0)	6·7 (2·0)
Gastrointestinal Quality of Life Index score	89·2 (23·1)	90·4 (18·1)
Clinical DeMeester score	1·4 (1·7)	1·7 (1·7)
pH-metry composite DeMeester score	24·9 (26·4)	24·3 (39·3)
Proton-pump inhibitor use		
Daily	17 (15%)	25 (23%)
Occasional (any use other than daily)	11 (10%)	8 (7%)
None	84 (75%)	76 (70%)

Data are mean (SD) or n (%). Percentages might not total 100 because of rounding. IRP=integrated relaxation pressure. LHM=laparoscopic Heller's myotomy plus Dor fundoplication. POEM=per-oral endoscopic myotomy. *Data on the sex of patients were obtained from the respective centres' data management systems and were not re-examined for the purpose of the trial. Race and ethnicity data were not collected.

Table 1: **Demographic and clinical characteristics of patients at baseline**

In the mITT population, clinical success at 5 years was 75·0% (95% CI 66·2 to 82·1) after POEM and 70·8% (61·7 to 78·5) after LHM (figure 1). The estimated between-group difference was 4·2 percentage points (95% CI –7·4 to 15·7), in favour of POEM. Missing data on clinical success at 5 years were imputed (through imputation of missing Eckardt scores) for 22 patients in each group. At 3 years (post-hoc), clinical success was 79·5% (95% CI 71·1 to 85·9) of patients after POEM and 76·7% (68·0 to 83·7) of patients after LHM (between-group difference 2·8 percentage points [95% CI –8·1 to 13·6]). Missing data were imputed for 21 patients in the POEM group and for 19 patients in the LHM group at 3 years. Both analyses at 5 years and 3 years satisfied the non-inferiority of POEM at the –12·5 percentage point margin, which was used for the original analysis at 2 years. Data in all 100 realisations of our imputation model were in favour of non-inferiority both at 3 years and 5 years (data not shown). Rates of clinical success over time using only available data are shown in appendix 1 (p 4) and did not differ considerably from the imputed version. When using only available data, between-group differences were 4·7 percentage points (95% CI –7·9 to 17·2) at 3 years and 5·6 percentage points (–8·0 to 19·0) at 5 years. A tipping point analysis is available in appendix 1 (pp 5–6). In an analysis of clinical success across timepoints, which was performed using a generalised estimating equations logistic regression model (mITT population, imputed), the odds ratio (OR) of the overall clinical success across visits after POEM versus after LHM was 1·29 (95% CI 0·78 to 2·15).

In post-hoc subgroup analyses of 5-year clinical success, POEM tended to be more successful in patients with achalasia subtypes II and III and LHM tended to be more successful in achalasia subtype I, but differences were not significant (figure 2). Furthermore, there was a trend for a better effect of POEM in treatment-naive patients (figure 2). When testing for predictors of 5-year clinical success with logistic regression models, we did not find an effect for treatment group, age, achalasia subtype, or previous treatment, but found male sex to be associated with higher success rates (OR 2·00 [95% CI 1·06–3·76]; appendix 1 p 22).

In both groups, the mean Eckardt symptom score decreased from baseline and slightly increased during follow-up (POEM *vs* LHM: 6·8 [95% CI 6·4 to 7·1] *vs* 6·7 [6·3 to 7·1] at baseline, 1·9 [1·6 to 2·2] *vs* 2·2 [1·7 to 2·4] at 3 years, and 2·1 [1·8 to 2·5] *vs* 2·4 [2·0 to 2·8] at

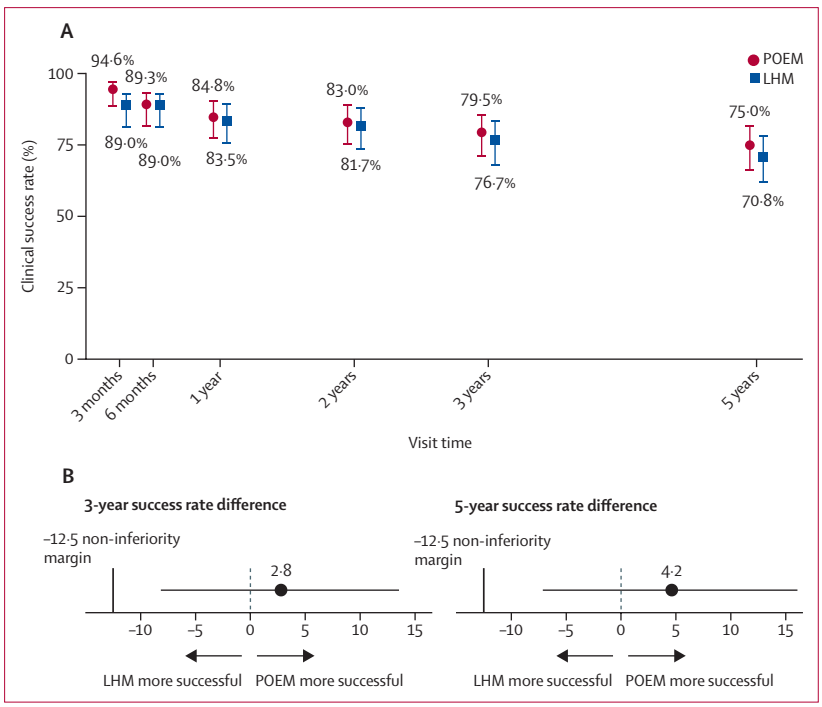

Figure 1: **Rates of clinical success over time and between-group differences**
(A) Estimated proportion of patients with clinical success in each treatment group (modified intention-to-treat population, missing data multiply imputed); circles (POEM) and squares (LHM) represent point estimates of clinical success rates at given times with the error bars indicating 95% CIs. Results until 2 years have already been reported.[5] (B) Estimated differences in clinical success rates between the POEM and LHM groups with 95% CIs at 3 years and 5 years post-procedure. At both timepoints, non-inferiority with a non-inferiority margin of 12·5% is reported. For more details see appendix 1 (p 28). LHM=laparoscopic Heller's myotomy plus Dor fundoplication. POEM=per-oral endoscopic myotomy.

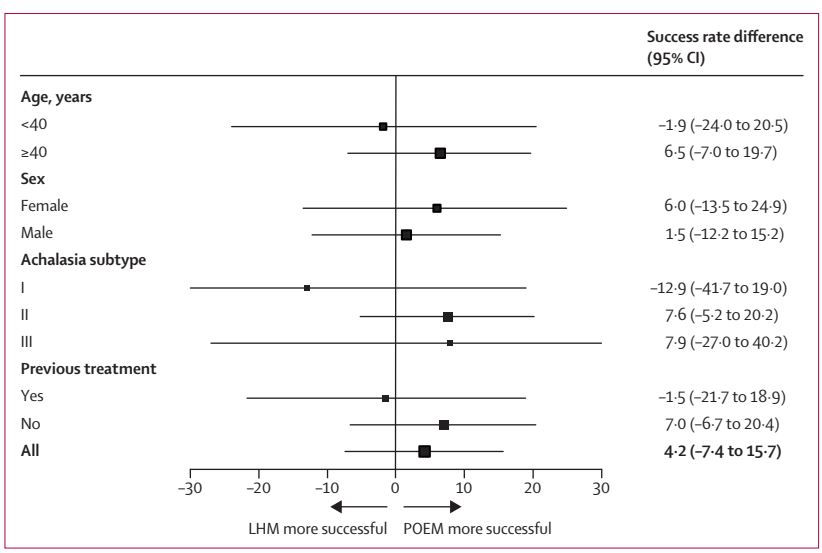

Figure 2: **Post-hoc subgroup analysis of absolute 5-year clinical success differences**
Absolute differences and 95% CIs with respect to clinical success at 5 years for subgroups by age, sex, achalasia subtype, and previous treatment in the modified intention-to-treat population (missing data imputed). The size of the squares represents the sample size in the respective subgroups. CIs have not been adjusted for multiplicity and cannot be used to draw inferences about effects. LHM=laparoscopic Heller's myotomy plus Dor fundoplication. POEM=per-oral endoscopic myotomy.

5 years; appendix 1 p 7). The overall difference in mean scores (POEM minus LHM) across visits (except baseline) in a linear generalised estimating equations model was –0·29 (95% CI –0·62 to 0·05). For the available data analysis of the Eckardt symptom score see appendix 1 (p 8).

As previously reported, a total of 11 patients had treatment failure (persistent symptoms after having undergone the assigned intervention; three patients after POEM and eight after LHM) and reintervention was performed in ten of them.[5] Recurrence of symptoms occurred in 34 patients after POEM and in 31 patients after LHM at the 5-year follow-up. Of those with a recurrence after POEM, 12 (35%) underwent retreatment (four with pneumatic dilation, three with POEM again, and five with LHM). Eight (26%) patients after recurrence after LHM underwent retreatment (six with pneumatic dilation and two with POEM; appendix 1 p 23).

Among the 164 patients who had data at both baseline and 5 years (87 in the POEM group and 77 in the LHM group), change in Gastrointestinal Quality of Life Index scores between baseline and 5 years did not differ significantly between the groups (mean change from baseline to 5 years 23·6 [95% CI 17·4 to 29·4] for POEM *vs* 23·9 [19·3 to 28·4] for LHM; difference in mean change from baseline –0·3 [95% CI –8·1 to 6·9]; appendix 1 p 9).

Change in integrated relaxation pressure from baseline was analysed in 48 patients after POEM and in 39 patients after LHM at 5 years (patients with both baseline and 5-year data available). Change from baseline in integrated relaxation pressure did not differ significantly between the groups (mean change from baseline to 5 years 15·1 mm Hg [95% CI 12·0 to 19·0] for POEM *vs* 14·2 mm Hg [10·4 to 18·3] for LHM; difference in mean change from baseline 0·9 mm Hg [95% CI –4·3 to 6·3]; appendix 1 p 10).

The presence of reflux symptoms 5 years after the procedure was similar in both groups, with a mean DeMeester clinical score of 1·3 (95% CI 1·0–1·6) after POEM and 1·1 (0·9–1·4) after LHM (appendix 1 p 11). Patients with daily reflux symptoms were infrequent in both groups (15 [17%] of 89 patients after POEM and eight [10%] of 83 patients after LHM; table 2.

A post-hoc analysis of administration of proton-pump inhibitors showed that a higher proportion of patients after POEM than after LHM were given these drugs across timepoints after baseline (POEM *vs* LHM: 28 [25%] of 112 *vs* 33 [30%] of 109 at baseline, p=0·45; 33 [31%] of 108 *vs* 29 [28%] of 105 at 3 months, p=0·65; 56 [53%] of 106 *vs* 28 [27%] of 103 at 2 years, p<0·0002; 52 [58%] of 90 *vs* 30 [35%] of 86 at 3 years, p=0·0026; 47 [53%] of 88 *vs* 33 [39%] of 85 at 5 years, p=0·067; appendix 1 p 12). Difference in proton-pump inhibitor use at 5 years was 14·6 percentage points (95% CI –0·3 to 28·8). Oesophagitis was more frequent in patients not receiving proton-pump inhibitors (appendix 1 p 13).

	Baseline		3 months		2 years		5 years	
	POEM	LHM	POEM	LHM	POEM	LHM	POEM	LHM
DeMeester clinical score	1·4 (1·1–1·8)	1·7 (1·4–2·0)	0·9 (0·7–1·1)	0·5 (0·4–0·7)	1·2 (0·9–1·5)	1·0 (0·6–1·0)	1·3 (1·0–1·6)	1·1 (0·9–1·4)
Daily reflux symptoms (DeMeester clinical score ≥3)	29/112 (26%)	34/109 (31%)	5/108 (45%)	2/105 (2%)	7/107 (7%)	2/103 (2%)	15/89 (17%)	8/83 (10%)
Occasional reflux symptoms (DeMeester clinical score 1–2)	34/112 (30%)	33/109 (30%)	42/108 (39%)	29/105 (28%)	49/107 (46%)	45/103 (44%)	41/89 (46%)	41/83 (49%)
Daily PPI use	17/112 (15%)	25/109 (23%)	25/108 (23%)	16/105 (15%)	41/106 (39%)	20/103 (19%)	36/88 (41%)	22/85 (26%)
Occasional PPI use (any use other than daily)	11/112 (10%)	8/109 (7%)	8/108 (7%)	13/105 (12%)	15/106 (14%)	8/103 (8%)	11/88 (13%)	11/85 (13%)
Los Angeles classification grade of reflux esophagitis*								
Overall, grades A to D	3/110 (3%)	5/104 (5%)	57/100 (57%)	19/96 (20%)	38/87 (44%)	23/78 (29%)	26/63 (41%)	18/58 (31%)
Grade A	3/110 (3%)	4/104 (4%)	32/100 (32%)	13/96 (14%)	18/87 (21%)	13/78 (17%)	17/63 (27%)	14/58 (24%)
Grade B	0/110	1/104 (1%)	19/100 (19%)	3/96 (3%)	16/87 (18%)	5/78 (6%)	6/63 (10%)	2/58 (3%)
Grade C	0/110	0/104	5/100 (5%)	2/96 (2%)	4/87 (5%)	2/78 (3%)	3/63 (5%)	0/58
Grade D	0/110	0/104	1/100 (1%)	1/96 (1%)	0/87	3/78 (4%)	0/63	2/58 (3%)
Oesophageal acid exposure†								
Acid exposure time	NA	NA	7·1% (5·4–8·9)	6·7% (4·1–9·3)	5·7% (2·8–8·5)	5·4% (2·2–8·5)	10·2% (7·6–14·2)	5·5% (3·1–11·8)
Acid exposure time >4·5%	NA	NA	41/93 (44%)	27/82 (33%)	21/70 (30%)	17/56 (30%)	28/45 (62%)	11/36 (31%)
Acid exposure time >6%	NA	NA	38/93 (41%)	24/82 (29%)	19/70 (27%)	14/56 (25%)	23/45 (51%)	8/36 (22%)
DeMeester pH-metry score	NA	NA	24·9 (19·9–30·8)	24·3 (17·2–34·7)	16·8 (12·8–21·9)	17·5 (10·9–39·6)	36·6 (27·0–52·1)	18·0 (11·1–30·4)

Data are mean (95% CI) or n/N (%). LHM=laparoscopic Heller's myotomy plus Dor's fundoplication. NA=not available. POEM=per-oral endoscopic myotomy. PPI=proton-pump inhibitor.*Los Angeles classification grade was assessed on endoscopy performed in 196 patients at 3 months, 165 patients at 2 years, and 121 patients at 5 years. Grade A indicates one or more mucosal breaks of 5 mm in length or less; grade B, one or more mucosal breaks of longer than 5 mm; grade C, mucosal breaks that extend between two or more mucosal folds (but involve <75% of the circumference of the oesophagus); and grade D, mucosal breaks that involve at least 75% of the oesophageal circumference. †Oesophageal acid exposure was assessed in 175 patients at 3 months, 126 patients at 2 years, and 81 patients at 5 years, with the use of 24-h pH monitoring; acid exposure time is the total percentage of time with a pH lower than 4.

Table 2: **Clinical and objective evaluation of gastro-oesophageal reflux disease over time**

Among 121 patients in the mITT population who underwent endoscopy at 5 years, there were numerically higher rates of reflux oesophagitis after POEM (26 [41%] of 63) than after LHM (18 [31%] of 58; figure 3). The between-group difference was not significant (10·2 percentage points [95% CI –7·0 to 26·8], p=0·26) and had decreased over time (37·2 percentage points [95% CI 24·0 to 49·1], p<0·0001, at 3 months and 14·2 percentage points [95% CI –0·6 to 28·3], p=0·076, at 2 years). Significant oesophagitis (Los Angeles classification grade B, C, or D according to the Lyon Consensus 2·0[12]) was observed in nine (14%) of 63 patients after POEM and in four (7%) of 58 patients after LHM at 5 years. Combining results of reflux symptoms, proton-pump inhibitor use, and endoscopic oesophagitis of any grade, the proportion of patients without reflux symptoms, off proton-pump inhibitors, and without oesophagitis was 15% (nine of 61) after POEM and 15% (eight of 55) after LHM at 5 years.

At 2 years, similar proportions of participants had abnormal acid exposure time (>4·5%; 21 [30%] of 70 after POEM and 17 [30%] of 56 after LHM; difference –0·4 percentage points [95% CI –16·7 to 15·5], p=1·0). However, there was a significant difference between these groups at 5 years (28 [62%] of 45 after POEM and 11 [31%] of 36 after LHM; difference 31·7 percentage points [95% CI 9·8 to 50·5], p=0·0070), although pH-metry data were available in only 81 (37%) of 221 patients initially included. At 3 months, the rates were 44% (41 of 93) after POEM and 33% (27 of 82) after LHM (difference 11·2 percentage points [95% CI –3·4 to 25·1], p=0·16; table 2; appendix 1 pp 14–15). To further characterise patients with pathological reflux in this study, those with pH-metry at 2 years and 5 years and

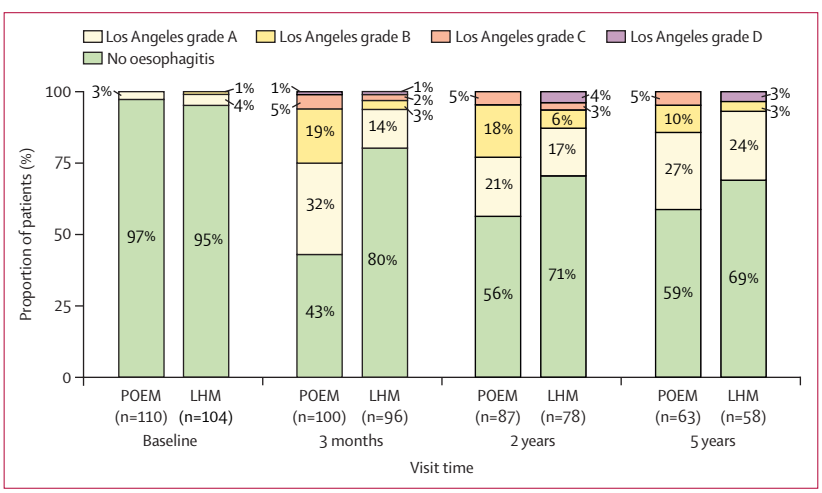

Figure 3: **Development of reflux oesophagitis over time**

Rates of reflux oesophagitis for both treatment groups in the modified intention-to-treat population at baseline, 3 months, 2 years, and 5 years. The total numbers of patients with available data in each group at each timepoint are shown at the bottom of the plot. Percentages might not add to 100 due to rounding. LHM=laparoscopic Heller's myotomy plus Dor fundoplication. POEM=per-oral endoscopic myotomy.

those with pH-metry only at one of these given timepoints were analysed. Results show that the proportions of patients with abnormal acid exposure time were rising over time (appendix 1 p 24) and that more patients with abnormal acid exposure time were taking proton-pump inhibitors, even if subgroup numbers were small (appendix 1 pp 16–17). Data about endoscopy, manometry, and pH-metry were mostly (with four exceptions for manometry and two exceptions for pH-metry) obtained from patients without retreatment in both groups.

The complications of peptic stricture, Barrett's oesophagus, and oesophageal adenocarcinoma were not reported over the 5-year follow-up.

Discussion

In the 5-year analysis of our randomised trial comparing two methods of myotomy for achalasia, endoscopic (POEM) versus surgical (LHM plus Dor fundoplication), two major outcomes were analysed: clinical success and the occurrence of post-procedural gastro-oesophageal reflux. Clinical success was non-inferior between the two groups over an extended follow-up period. Results with regards to reflux showed that mild reflux was common in both groups; however, POEM was associated with higher rates of oesophagitis, abnormal acid exposure time, and consumption of proton-pump inhibitors. Of note, no cases of serious reflux complication were observed over the 5-year follow-up. The role of the third major treatment option, pneumatic dilation, was not the topic of the present study, but was covered by another randomised trial, now also updated with 5-year results.[13]

Our study shows that both POEM and LHM are equally efficacious in improving symptoms 5 years after the procedure. There were, nevertheless, tendencies for differences in efficacy with regards to the subtype of achalasia. POEM achieved clinical success in 75·0% of patients and LHM achieved clinical success in 70·8% of patients. These numbers also indicate that about a quarter or even a third of patients will experience treatment failure or recurrence within 5 years. Comparing our results to the randomised trial by Kuipers and colleagues assessing the clinical efficacy of POEM versus pneumatic dilation, the 5-year rate of clinical success after POEM was similar.[13] Slightly higher percentages of success of POEM over time reported by Kuipers and colleagues might be attributed to enrolment of treatment-naive patients only, whereas more than 30% of patients we enrolled had had previous treatment. Not surprisingly, the efficacy of achalasia treatment decreased over time. In the European achalasia trial comparing clinical success 5 years and 10 years after LHM and pneumatic dilation, LHM efficacy at 5 years of 84% further decreased to 74% at 10 years.[6,7,14] Thus, our 5-year data cannot be considered as definitive as further decreases in the proportions of patients with long-term clinical success could be expected.

Long-term data on POEM efficacy are rare in the literature. Onimaru and Inoue, who introduced the technique into clinical practice, published long-term results on 15 of 36 patients with achalasia treated with POEM between 2008 and 2010, with good clinical success (14 [93%] of 15), but a 27% rate of secondary balloon dilation.[15] In a single-centre, retrospective analysis of 610 patients with achalasia receiving POEM over a 10-year period, Kaplan–Meier analysis suggested a 91% success rate at 7 years, but long-term follow-up data after 6 years and 7 years were available in only a limited number of patients (81 and 37, respectively) and there seemed to be no patients with 10-year follow-up.[16] Meta-analyses of retrospective case series with long-term follow-up mostly cover periods up to 5 years or less and claim clinical success rates of 82–87%.[17,18]

Long-term studies on LHM are available, but limited in number and many of them were published years ago, mostly without using the Eckardt score as a measure of clinical success, which is now universally accepted. A recent study involving 136 patients with achalasia receiving LHM with angle-of-His accentuation described treatment success in 94%, with a median follow-up of 65·5 months.[19] However, fewer than half of the patients had follow-up beyond 5 years.[19] In other mostly retrospective studies of patients with achalasia, in some of which there is no information about additional treatment, LHM as a sole therapy lost efficacy in 20–30% of patients over time.[20–23] The best evidence in terms of the long-term effect of LHM is provided by the aforementioned European achalasia trial, in which treatment success 5 years and 10 years after LHM was 84% and 74%, respectively.[7,14]

One major issue about POEM from the beginning has been post-procedural gastro-oesophageal reflux.[24] If clinically significant and more prominent with POEM than with LHM, it could hamper enthusiasm for POEM as a standard therapy for achalasia. Notably, POEM, in contrast to LHM, is not accompanied by an anti-reflux procedure. Methodologically, we recorded reflux symptoms, consumption of proton-pump inhibitors, endoscopic oesophagitis, and pH-metry in our study, as in other studies. These parameters do not seem to correlate well in individual patients and each has advantages and disadvantages (overlap between reflux and achalasia-related symptoms, inaccurate pH-metry measurement in case of stagnation of content in the oesophagus, not all proton-pump inhibitors are given due to reflux, etc). Thus, the true gold standard to define reflux according to clinical relevance is not known. Differentiation between true reflux and stasis of oesophageal content is only possible by manual analysis of pH-metry recordings, which was not done in our study. We acknowledge this limitation.

In general, and probably most importantly, with regards to final outcomes, rates of adenocarcinoma (as a possible consequence of prolonged reflux) do not appear

to be higher in patients after LHM as compared with balloon dilation,[25] although reflux rates have been shown to be significantly higher after myotomy than after dilation, both in two randomised trials[6,7,13,14] and in other reviews summarising various case series.[26]

With regards to initial reflux rates, short-term results of LHM versus POEM showed more reflux by clinical, endoscopic, and pH-metry parameters in the POEM group, assuming reflux rates of around 10% for LHM.[27] However, in the available randomised trials comparing dilation with POEM or LHM (appendix 1 p 25), results at 2 years and 5 years for oesophagitis and pathological pH-metry rates were higher for LHM than previously reported, namely between 20% and 30%.[5–7,13,14] Reflux has also been shown to increase over time in a few long-term assessments of surgical myotomy (45–65% of patients took antacid medications after LHM).[28–30] With regards to even longer observation times, a 17-year follow-up study of patients with achalasia undergoing LHM showed severe reflux with 24 h pH monitoring in 15 (17%) of 89 patients.[22] Another previous study showed that 37 (61%) of 62 patients with achalasia had reflux symptoms and 45 (72·5%) took antacid medications a mean of 17·5 years (SD 7·2) after Heller's myotomy.[31]

Also, a recent meta-analysis suggested decreasing differences over time in reflux between LHM and POEM.[32] Furthermore, Doubova and colleagues[33] showed that reflux rates started to increase 3–5 years after LHM, with an 88% rate of anti-reflux medication at the 7-year to 10-year follow-up. Conversely, the European achalasia trial reported decreasing rates of oesophagitis after LHM over time (21%, 18%, and 17% at years 1, 5, and 10, respectively).[6,7,14] Thus, this issue is not finally solved and it can only be speculated whether the anti-reflux protection provided by partial fundoplication wanes over time.

For POEM, long-term results in the literature with regards to reflux mostly suffer from small case numbers in the subgroups with follow-up beyond 5 years (appendix 1 p 26). Depending on the method of assessment, long-term reflux rates are generally between 20% and 40% (appendix 1 p 26). Of note, almost none of these POEM patient series performed pH-metry. In general, in our trial, as well as in other studies, there were no, or almost no, serious reflux-related complications in either group, reflux after POEM was mild, and reflux symptoms were managed sufficiently with proton-pump inhibitors in most patients. However, there have been rare case reports of the occurrence of serious post-POEM reflux consequences, such as Barrett's oesophagus or oesophageal adenocarcinoma.[4,16,17,34] Therefore, there is a clear need for further detailed research in patients treated by POEM versus LHM with 10 years of follow-up or more, especially with regards to reflux and possible sequelae. To what extent these considerations should influence treatment choice in children was not topic of the present study but should also be studied further.

Even though serious reflux-related events seem very rare, all patients after POEM (and after LHM as well) should enter endoscopic surveillance as recommended by current guidelines.[35] The aim of surveillance is an early detection of reflux-related complications to allow endoscopic treatment (or adjustment of anti-reflux treatment in case of oesophagitis, which is often asymptomatic) as well as early detection of squamous cell carcinoma, which is about 5–10 times more frequent than adenocarcinoma.[25,36]

Thus, acid reflux appears to be more common after POEM than after LHM, at least in the initial years. Our results are also in line with a meta-analysis of 74 studies, in which initial reflux was more frequent after POEM than after LHM in terms of symptoms, oesophagitis rates (OR 9·3 in favour of LHM), and abnormal acid exposure time (OR 4·3 in favour of LHM).[27] From a clinical perspective, patients with achalasia should be offered all treatments available after full explanation of the advantages and disadvantages of each procedure. Advantages of POEM are its minimally invasive nature and excellent safety profile. In addition, for spastic disorders including achalasia type III, POEM can be considered the procedure of first choice as the length of myotomy can be extended into the middle and upper oesophagus depending on manometry findings. Disadvantages of POEM are reflux and need for long-term administration of proton-pump inhibitors in more than half of patients; thus, informed consent should include the choice between the two forms of myotomy in the framework of shared decision making with patients.

Our trial has several limitations. Most of our patients had type II achalasia, which is the most common type in Europe; therefore, results might not accurately reflect the situation in other areas. In the beginning of our trial, surgeons were more experienced in performing LHM than the endoscopists in performing POEM, which could have affected the results in favour of LHM. Patients and trial personnel were aware of the treatment group assignments because blinding was not possible. This was a potential source of bias given that the primary endpoint was based on patients' reports of symptoms. Objective assessment by manometry corroborated the primary finding; however, fewer than half of POEM patients and around a third of LHM patients underwent assessment at 5 years. This rate, however, was similar with that reported in the European achalasia trial, in which 31% and 33% of patients had manometry and pH-metry data, respectively, at 5 years.[7] In the trial comparing pneumatic dilation with POEM in patients with achalasia, Kuipers and colleagues reported manometry data in 56% of included patients and no pH-metry data at 5 years.[13] Moreover, in our study, approximately 20% of patients dropped out before 5 years, also similar to rates in the two other randomised trials.[7,13] We did not analyse individual components of the

Eckardt score to look for a symptom predominantly responsible for a recurrence. Also, patients were not followed up systematically after retreatment, meaning there are sparse objective data for these patients. Finally, reflux oesophagitis was assessed after a short withdrawal period of proton-pump inhibitors, which might also have influenced our results.

To summarise, both POEM and LHM plus Dor fundoplication can be offered to patients with achalasia. With regards to post-procedural reflux, it can be concluded that gastro-oesophageal reflux is common after both POEM and LHM, with a tendency toward higher rates after POEM. Patients with achalasia should choose their treatment after being provided with a full explanation of the advantages and disadvantages of the respective approaches. Our study contributes to the growing body of evidence that both myotomy methods provide similar long-term efficacy. Our long-term results support the role of POEM as a less invasive approach that is non-inferior to LHM in controlling symptoms of achalasia but that might be associated with more reflux.

Contributors

ThR designed the study and is the study's guarantor. HM, UFR, TH, ThR, JMart, JI, OM, PF, C-TG, BH, YBW, BHAvR, AE, GB, MS, TaR, SD, RB, DvR, AJB, RR, and AR acquired and analysed the data. KH, JMart, JMare, ThR drafted the manuscript. KH, JMart, JMare, and ThR accessed, assessed, and verified the data. JMare did the statistical analysis. All authors critically revised the manuscript for important intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DvR reports grants or contracts and personal fees from Boston Scientific; grants and personal fees from Pendopharm; and grants from Vantage, ERBE, and Pentax, outside the submitted work. RB reports grants or contracts, consulting fees, and payments or honoraria from Pentax; consulting fees and payments or honoraria from Fujifilm and Medtronic; consulting fees from Olympus; and leadership or fiduciary role in the European Society of Gastrointestinal Endoscopy. AJB reports grants or contracts from BMS, Sanofi/Regeneron, SST, Laborie, and Dr Falk Pharma; consulting fees from AlfaSigma, Uniquity, Laborie, Medtronic, BMS, Dr Falk Pharma, Calypso Biotech, Eupraxia, Aqilion, Alimentiv, Sanofi/Regeneron, Uniquity, Reckitt, and AstraZeneca; payment or honoraria from Laborie, Dr Falk Pharma, Aqilion, Sanofi/Regeneron, and AstraZeneca; and participation on a data safety monitoring or advisory board in AlfaSigma, Uniquity, BMS, Calypso Biotech, Eupraxia, Aqilion, Sanofi/Regeneron, Reckitt, and AstraZeneca. PF reports consulting fees from Olympus and Cook Endoscopy. AR reports consulting fees from ODIN Medical, Norgine, Boston Scientific, and Fujifilm; and payment or honoraria from Fujifilm and ERBE. ThR reports grants or contracts from Olympus, Fujifilm, ERBE, Microtech, and Norgine; consulting fees from Olympus; and since the initial planning of the work, research grants from Olympus and Grewe Foundation. MS reports grants or contracts from ZonMw Citrien Fund, the European Crohn's and Colitis Foundation, SyncVR, HealthyMind VR systems, MLDS foundation, and Horizon Europe; consulting fees from Angiodynamics and VRelax; support for attending meetings or travel from Angiodynamics and HLTH; and leadership or fiduciary role in ZonMw and Meander MC. All other authors declared no competing interests.

Data sharing

The complete patient data set with identifiers will be made available with publication. Pseudonymised data (centre and patient number, age, and sex) are kept in the Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Hamburg, Germany, reachable via ThR (t.roesch@uke.de). Individual patient data (de-identified) are kept at the participating centres. The informed consent form in German and English will be available upon request at the main study centre in Hamburg, Germany, and in other languages in participating centres.

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