10 years follow-up results of the European Achalasia Trial: a multicentre randomised controlled trial comparing pneumatic dilation with laparoscopic Heller myotomy

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Abstract (max 250 words)

Objective: As achalasia is a chronic disorder, long-term follow-up data comparing different treatments are essential to select optimal clinical management. Here, we report on the 10 years follow-up of the European Achalasia Trial comparing endoscopic pneumodilation (PD) with laparoscopic Heller myotomy (LHM).

Design: A total of 201 newly diagnosed achalasia patients were randomised to either a series of PDs (n=96) or LHM (n=105). Patients completed symptom (Eckardt score) and quality of life questionnaires, underwent functional tests and upper endoscopy. Primary outcome was therapeutic success defined as Eckardt score $\leq$ 3 at yearly follow-up. Secondary outcomes were the need for retreatment, lower oesophageal sphincter pressure, oesophageal emptying, gastro-oesophageal reflux and the rate of complications.

Results: After 10 years of follow-up, LHM (n=40) and PD (n=36) were equally effective in both the full analysis set (74% vs 74%, p=0.84) and the per protocol set (74 % vs 86 % respectively, p=0.07). Subgroup analysis revealed that PD was superior to LHM for type 2 achalasia (p=0.03) while there was a trend, albeit not significant (p=0.05), that LHM performed better for type 3 achalasia. Barium column height after 5 minutes at timed barium oesophagram was significantly higher for patients treated with PD compared to LHM, while other parameters, including gastro-oesophageal reflux, were not different.

Conclusions: PD and LHM are equally effective even after 10 years of follow-up with limited risk to develop gastro-oesophageal reflux. Based on these data we conclude that PD and LHM can both be proposed as initial treatment of achalasia.

Key Messages

- What is already known on this topic
  - Achalasia is a chronic motility disorder of the oesophagus of which symptoms can be effectively treated with endoscopic pneumodilation, peroral endoscopic myotomy or laparoscopic Heller myotomy combined with an anti-reflux procedure.
  - Success rates however decline over time, emphasizing the need for long-term follow-up data.
- What this study adds
  - After 10 years of follow-up, the treatment success of LHM and PD is comparable
  - Treatment success of PD is significantly better than LHM for patients with type 2 achalasia
  - Patients with type 3 achalasia respond better, albeit not statistically significant, to LHM than PD
  - The risk to develop gastroesophageal reflux is low and comparable for both treatments
- How this study might affect research, practice or policy
  - Our data indicate that both LHM and PD result in long-term clinical success in 74% of patients after 10 years with a minimal risk to develop gastroesophageal reflux.

- Hence, both treatments can be proposed as initial treatment of achalasia, taking into account the available expertise and the patients preference.
- These data are of outmost importance to update current treatment guidelines and should ultimately lead to an evidence-based and individualized treatment proposal.

Introduction

Achalasia is a chronic motility disorder of the oesophagus characterised by absence of peristalsis and impaired relaxation of the lower oesophageal sphincter (LOS), resulting in abnormal transit and stasis of food in the oesophagus(1). As a result, patients mainly report dysphagia, regurgitation, retrosternal pain and weight loss. Although the underlying pathophysiology remains still unknown, loss of enteric neurons in the LOS and oesophageal body is generally accepted to be responsible for the absence of food transport from the oesophagus to stomach(2).

To date, treatment is confined only symptomatic by destruction of the LOS via an endoscopic or surgical procedures, in particular pneumatic dilation (PD), peroral endoscopic myotomy (POEM) or laparoscopic Heller myotomy (LHM)(3). Especially on the short-term, these treatments effectively restore oesophageal transit and reduce symptoms with success rates above 90% after 1 year(4-6). In an attempt to identify the most effective treatment, several meta-analyses have compared the different treatment options(7-9). However, the use of different treatment outcome parameters, study protocols and duration of follow-up compromise the quality and reliability of their outcome(10). Additionally, as achalasia is a chronic disorder with declining success rates at longer follow-up(11, 12), especially data on long-term outcome, preferentially of prospective and randomized trials are the only reliable source of information to guide the decision which treatment option should be proposed to patients.

To date, a limited number of sufficiently powered, prospective and randomized trials have been conducted, i.e. the European Achalasia Trial comparing graded PD and LHM(4), the POEMA trial, comparing PD with POEM(5), and the LHM vs POEM trial by Werner et al.(6). After 2 years of follow-up, only POEM was found to be superior to a single series of PD, while no differences in clinical success were reported between PD versus LHM or POEM versus LHM. Longer follow-up data are currently only available for the POEMA(13) and European Achalasia Trial(14). The 5 year follow-up data of the POEMA trial showed superior results for POEM with success rates of 81% for POEM compared to 40% for a single series of PD. We have reported on the 5 year follow-up of the European Achalasia Trial and showed that both treatments were equally effective with clinical success rates of 84% for LHM and 82% for graded PD. As achalasia is a chronic disorder with declining success rates at longer follow-up, data collection was extended up to 10 years. Here, we report on the 10 year follow-up after randomisation to either graded PD or LHM in the European Achalasia trial.

Methods

Patients and study design

Detailed description of the study population, study design and outcomes have been previously reported(4, 14) and can be found in Supplementary Material. Newly diagnosed achalasia patients were enrolled in 14 hospitals in 5 European countries between February 2003 and February 2008. The institutional review board at each hospital approved the study protocol and written informed consent was obtained from all patients. The study was prospectively registered in the 'Nederlands trial register' (NTR37) and in the Current Controlled Trials registry (ISRCTN56304564).

Patient and public involvement statement:
Patients were not involved in the development of the research questions or the design, conduct and recruitment of the study.

Interventions and follow-up
PD and LHM were performed as previously described (see Supplementary Material)(4, 14). Patients randomized to PD were treated with a graded distension protocol with the allowance of redilation on strict indication. In this protocol, patients were considered a failure if the Eckardt score remained >3 at four weeks after the initial series of dilation. If symptoms recurred, redilation was allowed twice (second and third series) but the third series of dilations was allowed only if symptoms recurred more than two years after the second series. If symptoms recurred within two years after the second series of dilations, the patient was considered a treatment failure. Patients who underwent LHM and had an Eckardt score >3 were considered as failure.
At baseline, medical history, physical examination and routine hematologic and blood chemical laboratory tests were recorded. In addition, patients were asked to complete a quality-of-life questionnaire (SF-36). Oesophageal manometry and upper endoscopy were performed, and a timed barium oesophagogram was obtained to quantify oesophageal stasis at predefined points in time (see Supplementary Table 2).

Outcomes
The primary outcome of the study was therapeutic success at two years of follow up, defined by an Eckardt score ≤3, at the yearly follow-up assessment. The time until treatment failure was calculated from the date of surgery or first dilation until the final or last follow up visit. The secondary outcomes included functional parameters (pressure at the lower oesophageal sphincter, oesophageal stasis), quality of life, and the rate of complications.

Statistical analysis
The Full Analysis Set (FAS) includes all achalasia patients who are randomized according to the amended protocol and will be analysed according to randomised treatment. In the PD group, 3 patients who had redilations not according to protocol and 10 patients who refused further required redilations were excluded from the Per Protocol Set (PPS). Two patients who were randomized to PD but treated with LHM are included in the LHM group for analyses on the PPS. Kaplan-Meier curves are constructed for time to treatment failure by randomized group and compared using a log-rank test. For the analysis of primary interest, refusals to redilate in the PD group were considered as failures and perforations in this group are censored at the time of perforation. To test the robustness of our main analysis a 'worst case' scenario was analysed whereby both perforations and refusals are considered to be treatment failures. Also, a 'best case' scenario analysis was performed were refusals and perforations are considered to be competing risks. In this analysis, cumulative failure rates are estimated using cumulative incidence functions (CIF) and comparisons between groups are made using Gray's test for a difference in the underlying subdistributions.
Subgroup analyses on the time to failure were performed (refusals as failure, perforation as censored) using Cox regressions that included factors for treatment, the subgroup and their interaction. Hazard ratios between treatment groups are presented with their 95% confidence intervals. In addition, the interaction between subgroup and treatment was assessed using a

chi-squared test. The following subgroups were assessed: age, sex at birth, basal LES pressure (<=20 mmHg vs >20 mmHg) and chest pain (None/occasional vs daily/several times a day).
For secondary outcome measures, the Full Analysis Set was used; continuous variables were summarized by the number of available non-missing data, mean and standard deviation. Comparisons between randomized groups were done using a Student's t-test. In case serious deviations from a normal distribution were observed, data were summarized using their median and interquartile range (Q1, Q3). Comparisons between groups were made using Wilcoxon rank-sum test. Categorical data are summarized by their observed frequency and percentage per category. Comparisons between groups were made using a chi-square test or a (two-tailed) Fisher's exact test if cell counts<5 were observed.
All analyses have been performed using SAS software, version 9·4 of the SAS System for Windows. All reported P values were two-tailed, and P values of less than 0·05 were considered to indicate statistical significance.

Results

Patients

As previously reported(4, 14), 218 patients were initially included in this study of which 17 were excluded: 4 patients were diagnosed with pseudo-achalasia and the first 13 patients were treated with a different dilation protocol (starting with 35 mm Rigiflex balloon). As the initial PD protocol resulted in an unacceptable high risk of oesophageal perforation, the protocol was amended and patients were treated with a 30 mm instead of a 35 mm balloon in the first dilation session. As a result, 201 patients were randomised to either LHM (n=105) or PD (n=96) and included in the FAS. As 2 patients randomised to PD were erroneously treated with LHM, 107 were included in the PPS of LHM. Of the 96 FAS patients in the PD group, 81 were included in the PPS; 2 patients were treated with LHM, 10 refused redilation and 3 patients were not treated according to the protocol (Figure 1). Baseline characteristics were well balanced and are shown in Table 1. The median length of follow-up was 7.3 (range 0.0-15.4) and 7.3 years (range 0.0 – 16.4) for the LHM and PD group respectively. After 10 years, 40 patients of the LHM group and 36 of the PD group were still in follow-up. The reasons for exclusion from the study are listed in Figure 1.

Clinical outcome and secondary outcome parameters

In Figure 2, the cumulative success rates are presented for both FAS (Figure 2A) and PPS (Figure 2B). When in the PD group refusals to be redilated were considered as failures and perforations were censored at the time of perforation, the success rates in the FAS were 88% (79-93) for LHM and 83% (74-90) for PD at 2 years, 83% (74-89) for LHM and 79% (69-86) for PD at 5 years, and 74% (62-82) for LHM and 74% (62-83) for PD at 10 years of follow-up. The success rates were not significantly different between LHM and PD using a log-rank test (p=0.84). In the PPS, there was a tendency that PD yielded better results although no statistical significance was reached (log-rank test, p=0.07): success rates were 88% (80-93) for LHM and 93% (85-97) for PD at 2 years, 83% (74-90) for LHM and 90% (81-95) for PD at 5 years, and 74% (63-83) for LHM and 86% (74-93) for PD at 10 years (Figure 2B).
When PD patients with a perforation were also considered as failures, representing a more stringent method of analysis (worst-case scenario), again, success rates in both the FAS and PPS did not differ between LHM and PD (Table 2). Notably, in the best-case scenario (perforations and refusals are considered as competing risks), the success rates for PD were

significantly better than for LHM in both the FAS (Gray's test, p=0.01) and PPS (Gray's test, p=0.049) (Table 2).

During the entire period of follow-up, 25 of the 105 patients treated with LHM had a treatment failure. After more than 5 years of follow-up, 7 patients had recurrent symptoms with an Eckardt score >3, of which 3 after more than 10 years. In the PD group, a total of 9 patients had a treatment failure. Compared to the previous analysis (5 years follow-up), 2 additional patients were considered as a treatment failure. One patient had already received 2 series of PD and had recurrent symptoms in year 7. He received a third and final series of PD but failed to respond. The other patient had received a final series of PD in year 8 but developed recurrent symptoms after 2 years. Of the 96 patients in the PD group, 11 patients were initially treated with a 40 mm balloon. 19 required a second series of PD, of which one patient required a 40 mm balloon dilatation, because of recurrent symptoms. 4 of these patients failed to respond and thus were considered as treatment failure. In addition, 9 patients had a final third series of PD of which 1 failed to respond. The estimated redilation rates are shown in Figure 3.

With respect to the secondary outcome parameters, no differences in Eckardt score were observed at the 10 year follow-up visit between the two treatment arms (mean $\pm$ SD: LHM n=29: 1.7 $\pm$ 1.4 versus PD n=29: 1.8 + 1.1, p=0.6, Wilcoxon rank-sum test). At 10 years follow-up, 22 patients in the LHM group and 22 in the PD group underwent high resolution manometry showing no differences in basal LOSp (mean $\pm$ SD: LHM n=22: 7.4 $\pm$ 4.0 mmHg versus PD n=22: 15.8 + 13.9, p=0.1, Wilcoxon rank-sum test). In addition, 23 patients in the LHM and 22 in the PD group underwent a timed barium oesophagram to determine oesophageal emptying. Of interest, the barium contrast column after 5 minutes at 10 years follow up was significantly higher in the PD group compared to the LHM group (mean $\pm$ SD: LHM n=23: 1.0 $\pm$ 1.5 cm versus PD n=22: 2.8 $\pm$ 3.0 mm, p=0.03, Wilcoxon rank-sum test). Finally, we assessed quality of life using the SF-36 questionnaire, which did not reveal significant differences between patients treated with LHM (n=26) or PD (n=28) (data not shown).

Subgroup and risk factor analysis

In post-hoc univariate Cox regression analyses on the FAS of time to failure, including refusals as failures and perforations as censored, only the width of the barium column at 5 min prior to treatment was found to be associated with treatment failure (HR=0.66 (0.49-0.88), p=0.005). No significant associations with failure time could be found for age, sex at birth, basal LOS pressure, daily chest pain or height of barium contrast.

In subgroup analyses, no significant interactions between subgroup and treatment were observed. In the PD group, patients younger than 40 years had a significantly higher hazard ratio for treatment failure compared to older patients (2.6 (1.1-6.3), p=0.03). Also the presence of daily chest pain prior to PD treatment was associated with treatment failure in the PD group. In contrast, gender, or basal LOS pressure prior to treatment were not identified as risk factor for treatment failure for patients randomised to PD (Table 3). None of the above factors was associated with treatment failure in the LHM group.

In another post-hoc analysis (FAS), treatment success was compared between the different subtypes of achalasia. As shown in Figure 4, LHM and PD were equally effective in type 1,

while success rates were significantly better for PD in type 2 (log-rank test, p=0.03). Although not statistically significant (log-rank test, p=0.05) due to the low number of patients (PD: n=10, LHM: n=7), LHM performs better than PD in type 3 achalasia. Similar results were obtained in the PPS.
Next, we compared the need for redilation between the three manometric subtypes (Figure 3B). In the FAS, the need for redilation was significantly associated with the manometric subtype (log-rank test, p=0.001). The majority of redilations occurred in the first 2 years. At 2 years, only 10% (4-23) of type 2 patients compared to 43% (25-66) of type 1 and 66% (37-92) of type 3 patients needed redilation. In the following years, mainly patients with type 2 required redilation resulting in estimated redilation rates at 10 years of 32% (20-50) compared to 48% (29-71) for type 1 and 78% (48-97) for type 3. Only 9 patients required a third PD session. These data confirm that PD is less efficient as treatment for type 3 achalasia compared to type 1 and 2.

Complications and adverse events
No additional perforations in the PD group occurred compared to the previous analysis at 5 years follow-up. In total, 5 perforations were recorded which equals 3 % of the total number of pneumodilations that were performed. As reported previously(4), perforations were managed conservatively or with surgery and patients recovered without problems. In the LHM group, a mucosal tear occurred in 13 of the 105 patients (12%) and were corrected during the laparoscopy in all but 1 patient who required conversion to an open procedure.
At the 10 year visit, 24 of the 40 patients of the LHM group and 22 of the 36 patients in the PD group underwent upper endoscopy. In the LHM group, 4 (17%) patients were diagnosed with reflux oesophagitis (LA grade A: n=2, LA grade B: n=1, LA grade D: n= 1) compared to 2 (9%) (LA grade A: n=1; LA grade C: n=1) in the PD group. In addition, 16 patients in the LHM and PD group underwent 24hr pH recording. Oesophageal acid exposure was comparable between the two treatment groups (LHM: 3.5% (0.0-21.5) vs PD: 3.0% (0.5.8.0), Wilcoxon rank-sum test, p=0.76).

Discussion
Given that achalasia is a chronic disorder(1), long-term outcome data of the currently available treatments for symptom relieve are of key importance to guide clinical decision making. Here, we report on the 10 year follow-up success rates of the European Achalasia Trial, a multicentre randomized clinical trial comparing LHM and graded PD(4). This analysis reports on the longest follow up of a randomized clinical trial in the field of achalasia. In the FAS and PPS, both treatment options were equally effective when refusals to be redilated in the PD group were considered as failures and perforations were censored at the time of perforation. Although oesophageal emptying was slightly reduced in patients treated with PD, no significant differences in basal LOS pressure, Eckardt score, reflux oesophagitis, oesophageal acid exposure or quality of life was demonstrated between the two treatment groups. Based on these data, we conclude that PD and LHM can both be proposed as initial treatment of achalasia.

For both treatments with LHM and graded PD, clinical effectiveness gradually drops over time, most likely as the disease progresses, emphasizing the need for long-term follow-up data. A recent meta-analysis reported a pooled rate of clinical success for POEM of 84% in 6 mainly observational studies with a follow-up of > 60 months(15). Costantini et al.(16) analysed 1001

LHM procedures performed in Italy showing a probability of being symptom-free above 80% after 20 years. Similarly, Krishnamoham et al. reported good dysphagia control in 86% of cases treated with LHM at a median follow-up of 77 months(17). Vela et al. reported long-term clinical success rates of graded PD in the USA of 44% at 6 years follow-up(12), somewhat in line with the 60% success rate of patients treated between 5 and 9 years reported by West et al. in the Netherlands(11) and the 72% success rate at 70 months reported from Belgium(18). Comparison between the above-mentioned success rates of the different treatment options is however inaccurate given that different patient selection criteria, outcome measures and definitions of clinical success have been used(10). Instead, it is more appropriate to compare the long-term clinical effectiveness of different treatments in a multicentre randomized prospective setting, using validated outcomes and standardized study protocols.

In the present study, we analysed the 10 years follow-up data of the European Achalasia Trial(4). Our study shows that both LHM and graded PD are equally effective with initial success rates above 90% at one year follow-up, slowly declining to a success rate of 74% at 10 years for both LHM and graded PD in the FAS. In this analysis, refusals to be redilated in the PD group were considered as failures and perforations were censored at the time of perforation. However, if PD patients with a perforation or refusal to be redilated are considered as competing risk, PD is significantly more effective than LHM with a success rate at 10 years of 89% for PD vs 74 % for LHM. The long-term effectiveness of graded PD in our study strongly contrasts with the 5 year success rate of only 40% in the POEMA study(13). In the latter study, patients requiring redilation were considered as failures while in our study, patients randomized to PD with recurrent symptoms were allowed to receive additional pneumodilations. This was limited to two additional series of redilation, with at least 2 years between the second and last series of PD. Notably, 42% required a second and only 10 % a third series of pneumodilations, with mainly patients with type 3 achalasia at risk to require redilation. Although our PD protocol has been criticized for being too aggressive(19), graded pneumodilation with occasional redilation is generally applied in clinical practice(11, 18) and advocated in recent achalasia guidelines(3, 20, 21). Taken together, we conclude that graded PD is equally effective as LHM in the treatment of achalasia patients as a group.

In line with the primary outcome parameter, no differences in Eckardt score, LOS pressure or quality of life were observed between the two treatment groups. Only the height of the barium column at 5 min of the timed barium oesophagram was significantly higher in the PD group compared to LHM. However, as the median height in the PD group at 10 years was only 1.6 (0.0-5.0) cm and we previously showed a barium column <5cm is a good predictor of sustained clinical success(22), it is rather unlikely that success rates will significantly drop in the near future. With respect to the other secondary outcome measures, it should be emphasized that only data collected from subjects with an Eckardt score below 3 and still in follow-up were included in the analysis, most likely explaining the lack of differences between PD and LHM.

Especially with the introduction of POEM, the risk of developing gastroesophageal reflux has gained a lot of attention(23). We managed to perform upper endoscopy in 61 % of patients still in follow-up at the 10 years visit. Notably, reflux oesophagitis was detected in 17% of patients in the LHM group compared to 9% in the PD group, with only 1 patient showing LA grade D in the LHM and 1 patient with LA grade C oesophagitis in the PD group. Also no significant difference in acid exposure on 24hr pHmetry was observed between the two

treatment groups. These data contrast with the higher rates of reflux oesophagitis reported for POEM. In the POEMA study for example, reflux oesophagitis was detected at the 5 years follow-up in 33% of patients treated with POEM compared to 13% of patients treated with PD(13). Similarly, in the randomized trial of Werner et al.(6), 44% of patients treated with POEM had reflux oesophagitis compared to 29% of patients treated with LHM after 2 years of follow up. Our data thus confirm that the risk to develop reflux oesophagitis following LHM or PD is limited and much lower than for POEM. With respect to other complications, no additional perforations were noted during pneumodilations performed for recurrent symptoms since the previous 5 year follow-up, further reducing the risk to 3% of the dilations. Obviously, patients should be informed about this potential risk when the different treatment options are proposed. It should be emphasized though that the outcome is good if a perforation is immediately recognized. If a patient reports intense or prolonged chest or abdominal pain after the dilation procedure or if fever develops during hospitalisation, a water-soluble contrast oesophagogram should be urgently performed, preferentially within 2 hours. If a perforation is diagnosed, patients can be successfully treated with conservative treatment (nothing by mouth and intravenous broad-spectrum antibiotics and intravenous acid-suppressive drugs) or with placement of a stent(24).

In order to identify factors contributing to treatment success and to identify subgroups of patients preferentially responding to LHM or PD, we performed a post-hoc Cox regression. A slim oesophagus prior to treatment was identified as risk factor for treatment failure for both treatments. Although speculative, this might be explained by the potential link of a slim oesophagus and type 3 achalasia, known to represent an important predictor of treatment failure(25). Similar to our previous 2 and 5 years follow-up data(4, 14), age younger than 40 years and pre-existing chest pain were identified as risk factors for PD treatment failure, but not for LHM, suggesting that younger patients may be preferentially treated with LHM. With respect to the manometric subtype, well accepted as a major determinant of clinical success, we show that graded PD is superior to LHM in type 2, graded PD and LHM are equally effective in type 1, while better long-term results were observed for LHM in type 3 achalasia, albeit not statistically significant given the low number of patients in this subgroup. The latter is in line with the finding that chest pain is a predictor of treatment failure for patients treated with PD. These data would suggest that on the long-term, graded PD may be the preferred choice for patients with type 2 achalasia but should not be advocated for patients with type 3, in line with a recent consensus statement(3). Hence, endoscopists should continue to be trained to master the technique of PD as it is cheap fast, inexpensive and easy to learn, relatively safe and effective, and thus still remains an excellent option to treat patients with achalasia. Overall, our long-term follow-up data clearly demonstrate that both graded PD and LHM are effective treatment options with a limited risk to develop gastroesophageal reflux disease.

The strength of our study is the duration of the prospective follow-up of a large cohort of patients suffering from a chronic rare disease. We managed to collect extensive functional data, including oesophageal manometry, pHmetry, timed barium oesophagram and endoscopy in the majority of patients that were still in follow-up. A weakness is however that a significant proportion of patients were lost to follow-up, most likely due to the duration of the study and the fact that patients were not willing to travel long distances to complete a study visit. Nevertheless, 10 years follow-up data were collected from 75 achalasia patients,

providing invaluable information with respect to long-term management of this chronic disorder.

Taken together, although the ultimate choice between PD, LHM and POEM for a given patient will depend on the long-term results of the other prospective trials comparing PD and LHM with POEM, the expertise of the treating physician and finally the preference of the patient, our study indicates that PD and LHM should be considered as relatively safe and equally effective treatment options providing long-term symptom control in the majority of patients with achalasia.

Acknowledgements
The authors would like to thank drs. Stanislas Bruley des Varannes (France), Bertrand Dousset (France) and Ignasi Elizalde (Spain) for their contribution to the European Achalasia Trial.

Competing Interest Statement
GEB is Associate Editor of this journal.

Author Contributorship Statement
This investigator initiated trial was conceived by GEB. GEB, ORB, MC, AS, JT and GZ have participated in the initial design of the study during investigator meetings. GEB, VA, AJB, ORB, MC, UF, AS, JT, TV, GZ and RS included and/or treated patients for the clinical trial. The data were analysed by SE and GEB with the assistance of AB, who is a statistician. GEB wrote the first and final versions of the manuscript and, in consultation with the other authors (SE, AB, VA, AJB, ORB, MC, UF, AS, JT, TV, GZ, RS), made the decision to submit the manuscript for publication. No commercial entity had any role in the study. All the authors (GEB, SE, AB, VA, AJB, ORB, MC, UF, AS, JT, TV, GZ, RS) vouch for the completeness and accuracy of the data. GEB is responsible for the overall content as guarantor.

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Figures

Figure 1. Patient flow chart

Figure 2.

Kaplan–Meier survival curves showing the rate of treatment success with PD as compared with LHM in the FAS (Panel A) and PPS (Panel B) for the primary analysis. In this analysis patients who refused redilation were considered as failures while patients with a perforation after PD were censored.

Figure 3.
Kaplan-Meier curves showing the freedom from redilation according to the manometric subtype of achalasia in the FAS for patients treated with PD. Subjects without redilation were censored at the time of the last known follow-up.

Figure 4.
Kaplan-Meier survival curves showing the rate of treatment success of PD vs LHM according to the manometric subtype (panel A: type 1, panel B: type 2, panel C: type 3) for the FAS. Patients who refused redilation were considered as failures while patients with a perforation after PD were censored.

Tables

Table 1. Baseline characteristics

		Randomised Treatment			
Patient Characteristic	**Statistic**	**LHM**	**PD**	**Total**	**P-value**
Gender					
Male	n/N (%)	56/105 (53.33%)	61/96 (63.54%)	117/201 (58.21%)	0.143
Female	n/N (%)	49/105 (46.67%)	35/96 (36.46%)	84/201 (41.79%)	
Age [y]	N	105	96	201	0.737
	Mean	45.7	46.4	46.0	
	Median	45.0	48.5	46.0	
	Std	14.29	15.57	14.88	
	(Q1, Q3)	(35.0; 56.0)	(33.5; 59.5)	(34.0; 57.0)	
Age					
<= 40 y	n/N (%)	38/105 (36.19%)	37/96 (38.54%)	75/201 (37.31%)	0.731
> 40 y	n/N (%)	67/105 (63.81%)	59/96 (61.46%)	126/201 (62.69%)	
Weight [kg]	N	105	95	200	0.621
	Mean	72.4	71.4	71.9	
	Median	72.0	70.0	70.2	
	Std	14.69	14.06	14.37	
	(Q1, Q3)	(61.0; 82.6)	(61.8; 79.0)	(61.0; 81.1)	

Table 2. Primary outcome for the different analyses at 2, 5 and 10 years of follow-up, according to treatment

Outcome	number		2 year		5 year		10 year		
	LHM	PD	LHM	PD	LHM	PD	LHM	PD	p value
treatment success - mean % (95%CI)									
Main analysis									
Full analysis Set	105	96	88 (79-93)	83 (74-90)	83 (74-89)	79 (69-86)	74 (62-82)	74 (62-83)	0·84
Per protocol Set	107	81	88 (80-93)	93 (85-97)	83 (74-90)	90 (81-95)	74 (63-83)	86 (74-93)	0·07
Best case scenario analysis									
Full analysis Set	105	96	88 (80-93)	95 (89-98)	83 (75-90)	92 (85-97)	74 (64-83)	89 (80-95)	0·01
Per protocol Set	107	81	88 (80-93)	94 (87-98)	83 (75-90)	91 (83-96)	74 (74-84)	87 (77-94)	0·049
Worst case scenario analysis									
Full analysis Set	105	96	88 (79-93)	80 (70-87)	83 (74-90)	75 (64-82)	74 (63-82)	70 (58-79)	0·34
Per protocol Set	107	81	88 (80-93)	89 (80-94)	83 (74-90)	85 (74-91)	74 (63-83)	80 (69-88)	0·46

Best case scenario analysis: in the PD group perforations and refusals were considered as competing risks
Worst case scenario analysis: in the PD group perforations and refusals were considered as failure

Table 3. Risk factors for treatment failure.

Variable		Comparison	Hazard Ratio Estimate	95% Confidence Interval	P-value	P(overall)
Age [y]	Interaction					0.0918
	HRs for LHM	< 40 y vs >= 40 y	0.927	(0.393; 2.186)	0.8621	
	HRs for PD	< 40 y vs >= 40 y	2.646	(1.112; 6.298)	0.0279	
Gender	Interaction					0.9474
	HRs for LHM	Male vs Female	0.965	(0.426; 2.188)	0.9321	
	HRs for PD	Male vs Female	1.005	(0.416; 2.427)	0.9913	
Basal LOS Pressure	Interaction					0.6410
	HRs for LHM	<= 20 mmHg vs > 20 mmHg	1.093	(0.423; 2.824)	0.8538	
	HRs for PD	<= 20 mmHg vs > 20 mmHg	0.787	(0.287; 2.155)	0.6414	
Chest Pain	Interaction					0.2825
	HRs for LHM	None/Occasional vs Daily/Several Times a Day	0.682	(0.295; 1.576)	0.3703	
	HRs for PD	None/Occasional vs Daily/Several Times a Day	0.352	(0.148; 0.837)	0.0181	