ORIGINAL ARTICLE

Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy

An Moonen,[1] Vito Annese,[2] Ann Belmans,[3] Albert J Bredenoord,[4] Stanislas Bruley des Varannes,[5] Mario Costantini,[6] Bertrand Dousset,[7] J I Elizalde,[8] Uberto Fumagalli,[9] Marianne Gaudric,[10] Antonio Merla,[11] Andre J Smout,[4] Jan Tack,[1] Giovanni Zaninotto,[12] Olivier R Busch,[13] Guy E Boeckxstaens[1]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2015-310602)

For numbered affiliations see end of article.

Correspondence to
Professor G E Boeckxstaens, Department of Gastroenterology, Translational Research Center for Gastrointestinal Disorders (TARGID), University Hospital Leuven, Catholic University Leuven, O&N1, Herestraat 49, Box 701, Leuven 3000, Belgium; Guy.boeckxstaens@med.kuleuven.be

Received 21 August 2015
Revised 27 October 2015
Accepted 1 November 2015
Published Online First 27 November 2015

ABSTRACT

Objective Achalasia is a chronic motility disorder of the oesophagus for which laparoscopic Heller myotomy (LHM) and endoscopic pneumodilation (PD) are the most commonly used treatments. However, prospective data comparing their long-term efficacy is lacking.

Design 201 newly diagnosed patients with achalasia were randomly assigned to PD (n=96) or LHM (n=105). Before randomisation, symptoms were assessed using the Eckardt score, functional test were performed and quality of life was assessed. The primary outcome was therapeutic success (presence of Eckardt score ≤3) at the yearly follow-up assessment. The secondary outcomes included the need for re-treatment, lower oesophageal sphincter pressure, oesophageal emptying and the rate of complications.

Results In the full analysis set, there was no significant difference in success rate between the two treatments with 84% and 82% success after 5 years for LHM and PD, respectively (p=0.92, log-rank test). Similar results were obtained in the per-protocol analysis (5-year success rates: 82% for LHM vs 91% for PD, p=0.08, log-rank test). After 5 years, no differences in secondary outcome parameter were observed. Redilation was performed in 24 (25%) of PD patients. Five oesophageal perforations occurred during PD (5%) while 12 mucosal tears (11%) occurred during LHM.

Conclusions After at least 5 years of follow-up, PD and LHM have a comparable success rate with no differences in oesophageal function and emptying. However, 25% of PD patients require redilation during follow-up. Based on these data, we conclude that either treatment can be proposed as initial treatment for achalasia.

Trial registration numbers Netherlands trial register (NTR37) and Current Controlled Trials registry (ISRCTN56304564).

Significance of this study

What is already known on this subject?

- Achalasia is a rare oesophageal motility disorder and is classically treated by endoscopic pneumatic dilation (PD) or laparoscopic Heller's myotomy (LHM) combined with an antireflux procedure.
- After 2 years of follow–up, pneumodilation and laparoscopic Heller myotomy have comparable success rates.
- Success rates of both treatment modalities decline over time.

What are the new findings?

- Success rate of PD and LHM was not significantly different after a follow-up of at least 5 years.
- At 5-year follow-up, the success rates for LHM (84%) and PD (82%) are comparable.
- Redilation was performed in 25% of PD patients.
- No difference was observed in lower oesophageal sphincter pressure, oesophageal stasis and quality of life after 5 years of follow-up between the two treatments.

How might it impact on clinical practice in the foreseeable future?

- Our data indicate that either treatment can be proposed as initial treatment for achalasia, but patients have to be informed that PD requires re-treatment in 25% of cases.
- In view of the low incidence of achalasia, the risk for perforation during PD and the surgical expertise required for LHM, we suggest that the choice between LHM and PD should be based on the expertise available in the respective centre.

Linked

▶ http://dx.doi.org/10.1136/gutjnl-2015-311016

CrossMark

To cite: Moonen A, Annese V, Belmans A, *et al*. *Gut* 2016;**65**:732–739.

INTRODUCTION

Achalasia is a rare oesophageal motility disorder characterised by the absence of oesophageal peristalsis and a defective swallow-induced relaxation of the lower oesophageal sphincter (LOS).[1] Currently, treatment consists of disruption of the LOS, classically either by endoscopic pneumatic dilation or laparoscopic Heller's myotomy combined with an antireflux procedure. Since its

introduction, laparoscopic Heller myotomy (LHM) is increasingly advocated as the treatment of choice based on multiple studies reporting short-term success rates >90%.[2–5] Recent studies, however, reveal that similar to pneumodilation (PD), success rates of LHM decline in time with 5-year success rates dropping to 65–85%.[6–8] In line, a single-centre retrospective study indeed reported comparable long-term success rates for PD and LHM, questioning the superiority of LHM.[7] Especially as achalasia is a chronic disease, long-term rather than short-term data are of utmost importance to guide the clinician in choosing the most optimal treatment. However, no prospective randomised data from sufficiently powered studies are currently available to provide objective evidence to make this choice.

In 2003, the European Achalasia Trial, a large randomised prospective multicentre clinical trial, was designed to compare PD and LHM as treatment of patients with naive achalasia.[9] Our study revealed that after at least 2 years of follow-up both treatment modalities are equally effective with success rates of 86% (PD) and 90% (LHM).[9] In view of the importance of long-term follow-up data, we here report on the 5 years or more follow-up data of this trial.

METHODS

Patients and study design

From February 2003 through February 2008, patients with newly diagnosed achalasia were enrolled in 14 hospitals in five European countries. Inclusion and exclusion criteria are described in online supplementary table S1.

Randomisation was performed using a computerised randomisation algorithm, and patients were stratified according to hospital and age (<40 or ≥40 years).

Interventions and follow-up

PD and LHM were performed as previously described.[9] Detailed information can be found in online supplementary text 1. In the PD group, a graded distension protocol with the allowance of redilation was used. In this protocol, patients were considered as failure if the Eckardt score remained >3 4 weeks after the initial series of dilation. If patients responded to PD, redilation was allowed twice (second and third series) but the third series of dilations was allowed only if symptoms recurred more than 2 years after the second series. If symptoms recurred within 2 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 haematological 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 online supplementary table S2).[10]

Outcomes

The primary outcome of the study was therapeutic success, 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 LOS, oesophageal stasis), quality of life and the rate of complications.

Statistical analysis

The full analysis set (FAS) includes all patients with achalasia who are randomised according to the amended protocol. Patients who are given the wrong treatment are analysed in the FAS according to their randomised treatment. Data of dropouts are included until the moment they leave the study. The per protocol set (PPS) includes all FAS patients who are treated strictly according to protocol, meaning that patients who are randomised to PD but are treated using LHM are included according to their actual treatment. Kaplan–Meier curves are constructed for time to treatment failure by randomized group and compared using a log-rank test. First, the analysis of primary interest was performed whereby refusals to redilate in the PD group are considered to be treatment failures and whereby perforations in the PD group are censored at the time of perforation. To test the robustness of our main analysis, a worst-case scenario was analysed whereby perforations and refusals are considered to be treatment failures. Also, a best-case scenario analysis was performed where refusals and perforations are considered to be competing risks. In this analysis, failure rates are estimated using cumulative incidence functions and comparisons between groups are made using Gray's test for a difference in the underlying subdistributions. Power calculation showed that with 80 patients in each group the study would have 90% power to detect a significant difference in the success rate between LHM and PD, assuming success rates of 90% and 70% with LHM and pneumatic dilation, respectively, with a two-sided α level of 0.05. To allow for dropouts, we aimed to enrol 200 patients.

For secondary outcome measures, the FAS data were used, and continuous variables are summarised by the number of available non-missing data, mean and SD. Comparisons between randomised groups were done using a Student's t test. In case serious deviations from a normal distribution were observed, data are summarised using their median and IQR (Q1, Q3). Comparisons between groups were made using Wilcoxon rank-sum test. Categorical data are summarised by their observed frequency and percentage per category. Comparisons between groups were made using a χ^2 test or a (two-tailed) Fisher's exact test if cell counts <5 were observed. All analyses have been performed using SAS software, V.9.3 of the SAS System for Windows. All reported p values were two-tailed, and p values of <0.05 were considered to indicate statistical significance.

RESULTS

Patients

A total of 218 patients were initially included in the study. In total, 17 patients were excluded; 4 patients due to pseudo-achalasia while the 13 first PD patients were treated with a different dilation protocol (first dilation with 35 mm balloon). As reported previously, this protocol was amended and abandoned due to an unacceptably high perforation risk.[9] Hence, 201 patients (n=105 (52%) LHM; n=96 (48%) PD) were included in the FAS. In the PD group, two patients were excluded because of protocol violation and seven patients refused further treatment. In addition, two patients randomised to PD but erroneously treated by LHM are analysed according to the actual treatment (LHM) (figure 1). Hence, a total of 192 patients were included in the PPS (n=107 (53%) LHM; n=85 (47%) PD). Baseline characteristics of the groups were well balanced (table 1). Maximum length of follow-up was 10 years. All patients were at least 5 years in follow-up yielding a median

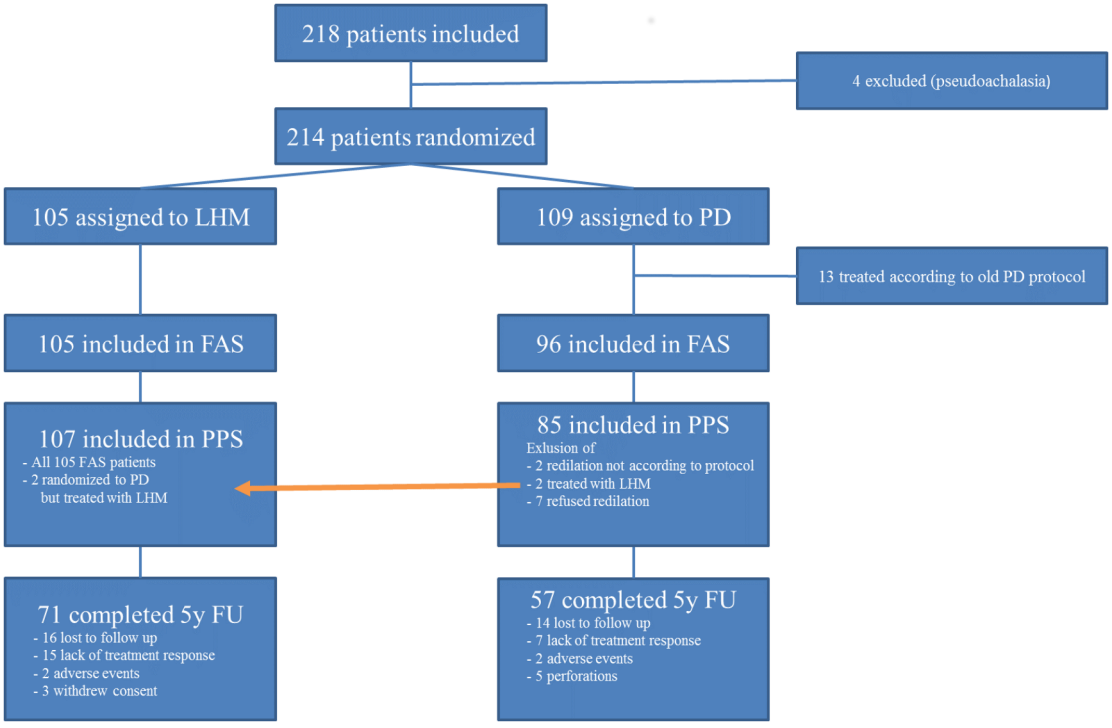

Figure 1 Patient disposition. The patients who were randomly assigned to the pneumodilation (PD) group, but erroneously treated with laparoscopic Heller myotomy (LHM) were included in the PD group in the full analysis set (FAS) and in the LHM group in the per protocol set (PPS). FU, follow-up.

follow-up period of 6.6 (range 0–10.1) and 6.0 (range 0–10.1) years for the LHM and PD groups, respectively. After 5 years, 71 patients in the LHM group and 57 patients in the PD group were still in active follow-up.

Clinical outcome and secondary outcome parameters

Time to treatment failure is presented as Kaplan–Meier plots for the FAS and the PPS in figure 2. The FAS yielded a success rate of 94% for LHM and 90% for PD after 1 year, 89% (LHM) and 86% (PD) after 2 years and 84% (LHM) and 82% (PD) after 5 years of follow-up. No statistically significant difference was observed between the two therapies in the FAS (log-rank test, p=0.92) (table 2 and figure 2A). In the PPS analysis, similar results were seen (table 2 and figure 2B) (log-rank test, p=0.07).

In the above-mentioned analyses, seven PD patients refusing further dilation were considered as treatment failure, while five PD patients who had a perforation were censored. A more stringent method of analysis is to consider perforations as failures. Still, no difference in 5-year success rate was detected (table 2).

Table 1 Baseline characteristics of the patients

		Randomised treatment		
Patient characteristic	**Statistic**	**LHM**	**PD**	**Total**
Gender				
Male	n/N (%)	56/105 (53%)	61/96 (64%)	117/201 (58%)
Female	n/N (%)	49/105 (47%)	35/96 (36%)	84/201 (41%)
Age (years)	N	105	96	201
	Mean	45.7	46.4	46.0
	SD	14.29	15.57	14.88
Age (years)				
≤40	n/N (%)	42/105 (40%)	38/96 (40%)	80/201 (40%)
>40	n/N (%)	63/105 (60%)	58/96 (60%)	121/201 (60%)
Weight (kg)	N	105	95	200
	Mean	72.4	71.4	71.9
	SD	14.69	14.06	14.37
BMI (kg/m^2)	N	105	94	199
	Mean	24.6	23.9	24.3
	SD	4.91	3.61	4.35

BMI, body mass index; LHM, laparoscopic Heller myotomy; PD, pneumodilation.

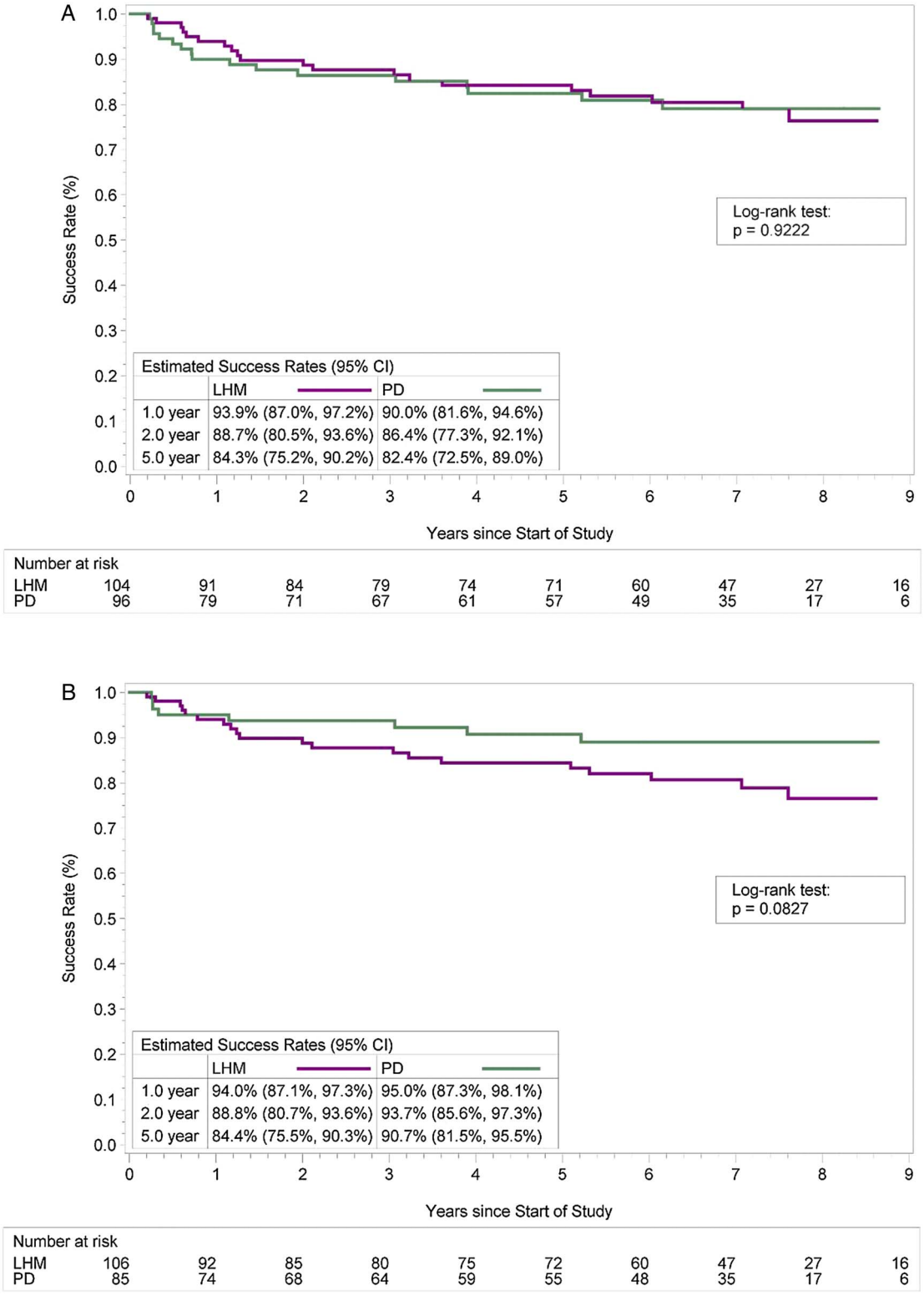

Figure 2 Kaplan–Meier curves for the rate of treatment success. Kaplan–Meier survival curves showing the rate of treatment success with pneumodilation (PD) compared with laparoscopic Heller myotomy (LHM) in the full analysis set (A) and per protocol set (B) for the primary analysis. In this analysis, patients who refused redilation were considered as failures while patients with a perforation after PD were censored.

If perforation and refusals are considered as competing risks (best-case scenario), superior success rates for PD were obtained after 5 years of follow-up in the FAS (Gray's test, p=0.03), but not in the PPS (Gray's test, p=0.06) (table 2).

In the LHM group (FAS), a total of 22 out of 105 patients had a treatment failure; eight patients within the first year, four between the first and the second year and six after more than 5 years. In the PD group, a total of eight patients had treatment failure; four failed to respond to the initial PD and had an immediate treatment failure. Twenty-four patients had a second series of dilation for symptom recurrence of these. Three patients evolved to treatment failure. Five patients had a final

Table 2 Primary outcome for the different analyses at 1, 2 and 5 years of follow-up, according to treatment

	Number		1 year		2 years		5 years		
Outcome	LHM	PD	LHM	PD	LHM	PD	LHM	PD	p Value
Treatment success—mean % (95% CI)									
Main analysis									
Full analysis set	105	96	94 (87 to 97)	90 (82 to 95)	89 (81 to 94)	86 (77 to 92)	84 (84 to 90)	82 (73 to 89)	0.92
<40	42	38	95 (80 to 99)	83 (66 to 92)	89 (73 to 96)	77 (59 to 88)	80 (63 to 90)	66 (46 to 80)	0.3
≥40	63	58	93 (83 to 97)	94 (84 to 98)	88 (77 to 94)	92 (81 to 97)	87 (75 to 93)	92 (81 to 97)	0.2
Per protocol set	107	85	94 (87 to 97)	95 (87 to 98)	89 (81 to 94)	94 (86 to 97)	84 (75 to 90)	91 (82 to 86)	0.08
<40	42	31	95 (81 to 99)	90 (72 to 97)	89 (74 to 96)	86 (67 to 95)	81 (64 to 90)	77 (55 to 89)	0.89
≥40	65	54	93 (83 to 97)	98 (87 to 100)	88 (77 to 94)	98 (87 to 100)	87 (75 to 93)	98 (87 to 100)	0.01
Best-case scenario analysis									
Full analysis set	105	96	94 (88 to 97)	96 (90 to 99)	89 (81 to 94)	95 (89 to 98)	84 (76 to 91)	92 (85 to 96)	0.02
Per protocol set	107	85	94 (88 to 98)	95 (89 to 98)	89 (82 to 94)	94 (87 to 98)	84 (76 to 91)	91 (83 to 96)	0.06
Worst-case scenario analysis									
Full analysis set	105	96	94 (87 to 97)	86 (77 to 98)	89 (81 to 94)	83 (73 to 89)	84 (75 to 90)	78 (68 to 85)	0.47
Per protocol set	107	85	94 (97 to 97)	91 (82 to 95)	89 (81 to 94)	89 (80 to 94)	84 (76 to 90)	85 (75 to 91)	0.52

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 failures.
LHM, laparoscopic Heller myotomy; PD, pneumodilation.

third series of dilations of which one patient did not respond (figure 3). In total, 24 of the 96 (25%) patients of the PD group required redilation. In addition, seven patients refused further redilation, five patients experienced an oesophageal perforation and two patients were excluded because of protocol violation.

After a follow-up of 5 years, symptoms were reduced to a similar extent compared with baseline values in both groups. As shown in table 3, basal LOS pressure (7±6 vs 11±9 mm Hg, p=0.2, Wilcoxon rank-sum test) and oesophageal emptying (0.5 (0.0–3.2) vs 1.6 (0.0–5.0), p=0.7, Wilcoxon rank-sum test) were not significantly different between LHM and PD, respectively. No correlation was found between Eckardt score and oesophageal emptying (Pearson correlation 0.04, see online supplementary figure S1).

Both groups had comparable quality of life as measured by the SF-36 questionnaire (physical component: 55 (52–58) vs 53 (46–56), p=0.07; mental component 55 (48–58) vs 56 (49–59), p=0.7, Wilcoxon rank-sum test).

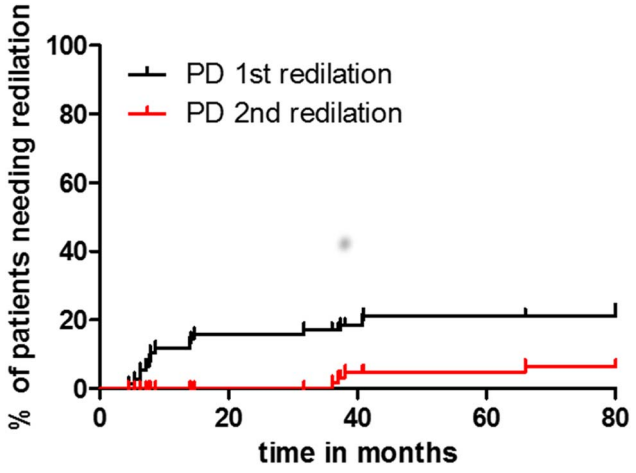

Figure 3 Percentage of pneumodilation (PD) patients requiring redilation after the initial PD series for recurrent. Symptoms. Percentage of PD patients that underwent one additional series of redilation (black line) and those that underwent a second and final series (red line) of redilation for recurrent symptoms.

Subgroup and risk factor analysis

As previous studies report age-dependent differences in outcome, stratification according to age (<40 vs ≥40) was performed.[6 11] No statistical difference in success rate was shown in the FAS between the two age categories. However, in the PPS, PD showed significantly better results than LHM in the group >40 years of age (86% LHM vs 98% PD, log-rank test, p=0.01).

In a post hoc analysis, success rates were compared between the three manometric subtypes of achalasia (type I: n=44 (25%), type II: n=114 (65%), type III: n=18 (10%)).[12] After a follow-up period of 5 years, PD had a significantly higher success rate in type II (LHM: 88% vs PD: 96%; p=0.03) than LHM, while type III tended to respond better to LHM (LHM: 86% vs PD: 48%; p=0.09). For type I achalasia, LHM and PD had similar rates of success (75% vs 69%; p=0.7) in the FAS. Similar results were seen in the PPS: 75% (LHM) vs 82% (PD, p=0.6) for type I; 88% (LHM) vs 100% (PD, p=0.003) for type II; 86% (LHM) vs 57% (PD, p=0.2) for type III achalasia (see online supplementary table S3).

In a Cox regression analysis, the following factors were identified as predictors of treatment failure irrespective of the treatment group: younger age (HR 1.03, 95% CI 1.01 to 1.06, p=0.007), pre-existing daily chest pain (HR 1.9, 95% CI 1.1 to 3.7, p=0.05) and a width of the oesophagus <4 cm before treatment (HR 2.1, 95% CI 1.05 to 4.3, p=0.04). No risk factors were predictive of treatment failure for LHM. For PD, age <40 (HR 1.2, 95% CI 1.3 to 9.2, p=0.02), pre-existing daily chest pain (HR 1.1, 95% CI 0.9 to 6.5, p=0.07) and a width of the oesophagus of <4 cm before treatment (HR 1.03, 95% CI 0.9 to 8.6, p=0.07) were identified as risk factors for failure. Younger age (<40), a width <4 cm of the oesophagus and a type III achalasia were identified as independent risk factor for redilation (see online supplementary table S4). The remaining stasis after therapy was not identified as a risk factor for treatment failure. In line with these data, no correlation was

Table 3 Secondary outcomes at 1, 2 and 5 years of follow-up, according to treatment

Outcome	Baseline					1 year					2 years					5 years				
	LHM		PD			LHM		PD			LHM		PD			LHM		PD		
	n		n		p Value	n		n		p Value	n		n		p Value	n		n		p Value
Eckardt score																				
Mean (SD)	105	8.4 (2.11)	96	7.0 (1.75)	0.23	91	1.2 (1.1)	79	1.4 (1.3)	0.68	84	1.2 (1.0)	71	1.4 (1.2)	0.29	71	1.1 (1.0)	57	1.4 (1.0)	0.09
LOS pressure																				
Mean (SD)	100	30.5 (13.0)	94	33.4 (16.6)	0.39	87	10.2 (7.0)	71	14.1 (9.1)	0.009	74	10.0 (7.2)	63	11.7 (7.9)	0.28	34	7.4 (5.5)	28	10.8 (8.7)	0.19
Height of barium-contrast column after 5 min																				
Median (IQ range)	93	11.6 (8.1–17.5)	87	12.0 (8.0–17.5)	0.80	76	0.0 (0.0–5.9)	70	0.4 (0.0–6.1)	0.82	73	2.0 (0.0–7.2)	64	4.5 (0.0–8.0)	0.19	35	0.5 (0.0–3.2)	26	1.6 (0.0–5.0)	0.70
SF-36																				
Physical component—median (IQR)	102	50 (42–55)	92	51 (43–55)	0.80	87	57 (53–59)	76	55 (50–59)	0.14	79	55 (53–59)	66	54 (50–59)	0.94	41	55 (52–58)	35	53 (46–56)	0.07
Mental component—median (IQ range)	102	44 (32–54)	92	44 (33–54)	0.49	87	54 (46–58)	76	54 (45–58)	0.92	79	55 (50–58)	66	54 (45–58)	0.10	41	55 (48–58)	35	56 (49–59)	0.67

Data for the two treatment groups were compared at the different time points with the use of Wilcoxon rank-sum test.
No significant differences were observed between the two treatment groups except for pressure at the LOS after 1 year, which was higher in the PD group than in LHM group (p=0.008, Wilcoxon rank-sum test).
LHM, laparoscopic Heller myotomy; LOS, lower oesophageal sphincter; PD, pneumodilation.

found between stasis after therapy and failure rates (see online supplementary table S5).

Complication and adverse events

Oesophageal perforation occurred in 5 of the 96 patients (5%). Considering the number of dilatations, this corresponds to a perforation rate of 2.1% per procedure. As reported before, four patients had a perforation during the initial series of dilation.[9] One additional perforation occurred during re-treatment for recurrent symptoms using a 35 mm balloon. Perforations were managed conservatively (ie, restriction of oral food and antibiotic therapy) in three patients, and surgically in two patients. All patients recovered without complications.

As previously reported, a mucosal tear occurred in 13 of the 105 LHM patients (12%). In all patients, this tear was corrected during the procedure, except in one patient who required conversion to an open procedure. The outcome was not influenced by this complication.[9]

Four years after treatment, an upper endoscopy was performed in 76 of the 201 patients (38%, 39 LHM, 37 PD). In the LHM group, 18% had oesophagitis (3 grade A and 4 grade B) compared with 14% in the PD group (four grade A and one grade C) (p=0.76, Fisher's exact test). A 24 h pH measurement was performed 4 years after treatment in 66 patients (33%, 33 LHM vs 33 PD). Oesophageal acid exposure was not significantly different between the two treatment groups (5.6±10.1% for laparoscopic Heller myotomy vs 2.3±3.9% for PD, p=0.7, Fisher's exact test). In the LHM group, 34% of patients had an abnormal exposure of gastric acid compared with 12% in the PD group (p=0.14, Fisher's exact test).

DISCUSSION

In this large European multicentre randomised trial comparing LHM (with Dor's fundoplication) with pneumatic dilation as treatment for achalasia, we show that the long-term treatment success rate is similar. Using a reduction in Eckardt symptom score to ≤3 as criterion for treatment success, the 5-year success rate is 84% in the LHM group compared with 82% in the pneumatic dilation. Moreover, no differences in oesophageal function or emptying, oesophagitis, 24 h acid exposure or quality of life could be demonstrated. Based on these data, we conclude that both PD and LHM are equally efficient as treatment for achalasia, although 25% of the PD patients will need redilation during follow-up. These long-term data are crucial in deciding on the initial treatment choice for achalasia.

Achalasia is classically treated by either PD or LHM. Based on the excellent short-term success rates of LHM, this minimal invasive procedure has been proposed as the preferred initial therapy for achalasia.[13 14] However, as achalasia is a chronic disorder, the choice of treatment should be based on long-term rather than short-term results. This is especially of great clinical relevance as therapeutic success gradually decreases in time for both treatments and thus may lead to significant differences in outcome with longer follow-up. To date, only a few cross-sectional retrospective studies report on the long-term follow-up of achalasia patients, in most cases presenting data on the success rates of either PD or laparoscopic Heller myotomy from a single centre.[7 15] Moreover, different criteria of therapeutic success are used among different centres, making an evidence-based choice between these two therapeutic options based on the available long-term follow-up data inappropriate. To date, only one randomised trial with long-term follow-up has been published, showing higher success rates for laparoscopic myotomy compared with PD.[16] However, this concerns a small

trial that was ended prematurely for practical reasons and difficulty in recruiting patients, with only 17 PD and 21 LHM patients in follow-up after 5 years. Although LHM was reported to be superior to PD, it has to be emphasised that the definition of failures was rather unusual. Moreover, patients who underwent surgery with incomplete symptom control or symptom relapse were allowed to undergo two additional treatments other than those given initially. Moreover, no difference in symptom score was found between the two groups at 5 years. Other long-term data, and probably the best available so far, involve a cross-sectional study of a large cohort of achalasia patients treated at the Cleveland Clinic Foundation (the USA).[7] This study clearly demonstrates a steady decrease in clinical efficacy for both graded PD and LHM to similar therapeutic success rates of 44% and 57% (not significant) at 6 years. In the present study, we report on the long-term follow-up of the European Achalasia Trial, a unique large multicentre randomised study comparing PD and LHM. The main strengths of our study are that data are collected prospectively from a large number of patients from 14 different centres and that identical objective measures were used for the assessment of clinical success and functional improvement for both treatments. Similar to Vela and colleagues, a steady decrease in success rate was observed from 94% and 90% after 1 year to 84% and 82% after 5 years of follow-up for LHM and PD, respectively.[7] Although no data on the possible underlying mechanism are available, disease progression with additional loss of neurons seems the most logical explanation. Our main finding, however, is that similar to our previous report, treatment success, defined as a reduction in Eckardt symptom score to ≤3, was similar for PD and LHM in both the FAS and PPS analysis.[9] Treatment success was only defined by the Eckardt score and not on functional data on oesophageal stasis.[17] In contrast to previous reports, no good correlation could be found between symptoms and stasis. This implies that some patients were redilated or had a treatment failures based on the Eckardt score, although no stasis was noted on the timed barium oesophagogram.

As recurrence of symptoms led to a different approach in the PD versus the LHM group, the evaluator was unblinded with respect to the initial treatment. This potential shortcoming is, however, unlikely to have affected the outcome of the study as all questionnaires, including the Eckardt questionnaire, were completed by the patients themselves.

In line with the primary outcome, no significant difference in quality of life, and functional parameters as basal LOS pressure and oesophageal emptying was observed between the two treatment groups. To further evaluate the robustness of our analysis, we next performed a best-case and worst-case scenario analysis. Even in the worst-case scenario, in which all PD refusals were considered as failures, no difference in success rate was observed. Of note, the 'best-case scenario' analysis, in which patients who experienced an oesophageal perforation or refused further PD are considered as competing risks, showed even significantly higher success rates for PD compared with LHM, that is, 92% vs 84% (Gray's test, p=0.03) at 5 years follow-up, respectively. Nevertheless, based on the more conservative and worst-case analyses, we conclude that LHM does not result in therapeutic success rates that are superior to those of pneumatic dilation for the primary treatment for achalasia after a follow-up period of at least 5 years.

Despite the above-mentioned strengths of our study, the PD protocol used has been criticised and forwarded as potential bias explaining the lack of superiority of LHM.[9 18] Re-treatment of patients with recurrent symptoms was indeed only allowed in the PD and not in the LHM group. This decision has been based on the fact that repeated dilation is internationally accepted and most importantly widely reflects daily clinical practice.[6–8 19] Moreover, it should be emphasised that the number of pneumatic dilations was limited to a maximum of three series of dilations, while the third and final series was allowed only if it occurred more than 2 years after the second series of dilations. Although one might argue that this protocol could favour PD especially with regard to short-term results, the long-term data presented in the current study argue against this reasoning.[18] The 5-year success rate of PD indeed remained comparable and was even significantly higher than that of LHM in the 'best-case' scenario analysis. It should be emphasised though that after a median follow-up of >6 years 25% of patients treated with PD required re-treatment, a figure comparable to previous studies.[8] Of these patients, only five were treated with a third and final dilation, indicating that patients responding to PD can be efficiently managed with repeated PD. These findings are in line with those of Zerbib and colleagues, reporting a success rate of 96% for repeated PD in patients responding to the initial PD.[8] Similarly, Per Protocol analysis in our study yielded even significantly higher 5-year success rate for PD (98%) than LHM (86%) in patients >40 years of age. Notably, these high success rates are only achieved if redilation is allowed, in our study in 25% of patients. In practice, patients thus will have to be informed about the fact that 25% will have to be re-treated, which should be taken into account when deciding on the initial treatment choice for achalasia.

Even though our study shows that both treatments have comparable success rates, it remains of utmost importance to determine risk factors for failure and to identify subgroups of patients that may preferentially respond to either LHM or PD. Similar to our 2-year follow-up data, pre-existing daily chest pain and a width of the oesophagus of <4 cm were identified as predictors of treatment failure.[9] These data confirm that chest pain, mostly reported by patients with type III achalasia, remains a difficult symptom to treat and significantly contributes to treatment failure.[12 20] The finding that a slim oesophagus before treatment is a risk factor remains hard to explain. Although speculative, one potential explanation could be that a small width of the oesophagus may be related to type III achalasia, known to be less responsive to treatment.[12 21] Indeed, our data confirm that type III achalasia is an important predictor of treatment failure, at least for PD, implying that type III achalasia may preferentially be treated by LHM. Age was an important risk factor for treatment failure, however, as there is no difference in success rate between PD and LHM in the younger age group. Our long-term follow-up results thus would argue against current guidelines, suggesting that younger patients should preferentially be treated with LHM.[1 22]

One of the major drawbacks of PD is undoubtedly the risk for oesophageal perforation. In the present study, 5 of the 96 (5%) patients treated with PD suffered from a perforation. Considering that 236 dilations were performed in the entire PD group, the perforation risks equals 2% per procedure. These numbers are in line with those reported previously, ranging between 0.5% and 5%.[23 24] As reported recently, also in our study, perforation resulted in prolonged hospitalisation, but no long-term complications were registered and all patients left the hospital in excellent conditions.[25] Nevertheless, it remains a significant complication implying that the procedure should be performed with care and by experienced endoscopists. In the LHM group, a mucosal tear during surgery occurred in 11% of patients, a rate that is similar to that is previously reported.[24]

The clinical outcome was not affected by this complication. Also here, the experience of the surgeon performing the procedure is of great importance, implying that the choice of treatment should undoubtedly take the available expertise and experience available into account. Finally, both 24 h pH-metry and upper endoscopy performed 4 years after treatment showed that the most frequent complication of both treatments was gastro-oesophageal reflux. These results should be interpreted with care, however, as only a low number of patients were willing to undergo endoscopic evaluation and 24 h pH-metry. We cannot exclude though that patients who encountered symptoms of reflux were more willing to undergo examinations inducing a bias. However, this bias would apply to both arms of the study and thus it is rather unlikely that it would influence outcome. Nevertheless, as increased acid exposure is a risk factor for the development of Barrett's oesophagus, physicians should be aware of this potential long-term complication.

In conclusion, our study showed that after 5 years of follow-up no difference in the success rate of LHM and PD could be detected, at least if limited redilation is allowed in the PD group. Our data indicate that either treatment can be proposed as initial treatment for achalasia, but patients have to be informed that PD requires re-treatment in 25% of cases. Finally, based on the above, we suggest that the choice between LHM and PD should be based on the expertise available in the respective centre.

Author affiliations
[1]Department of Gastroenterology, Catholic University of Leuven, Leuven, Belgium
[2]Head of Gastroenterology, Department of Emergency, AOU Careggi, Florence, Italy
[3]Interuniversity Centre for Biostatistics and Statistical Bioinformatics, KU, Leuven, Belgium
[4]Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands
[5]Institut des Maladies de l'Appareil Digestif, University Hospital of Nantes, Nantes, France
[6]Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Padua, Italy
[7]Department of GI and Endocrine Surgery, Hôpital Cochin, Paris, France
[8]Department of Gastroenterology, Hospital Clínic, CIBERehd, IDIBAPS, University of Barcelona, Barcelona, Spain
[9]Upper GI Surgery, Humanitas Clinical and Research Hospital, Rozzano, Italy
[10]Department of Gastroenterology, Hopital Cochin, Paris, France
[11]Division of Gastroenterology, IRCCS, "Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy
[12]Department of Academic Surgery, St Mary's Hospital, Imperial College, London, UK
[13]Gastrointestinal Surgery, Academic Medical Center, Amsterdam, The Netherlands

Contributors ORB and GEB shared senior authorship. This investigator-initiated trial was conceived by the last author (GB). All the authors had substantial roles in the design of the study, the interpretation of the data and the writing of the manuscript. The data were analysed by one of the authors (AM) with the assistance of another author (AB), who is a statistician. The first author and the last author wrote the first and final versions of the manuscript and, in consultation with the other authors, made the decision to submit the manuscript for publication. No commercial entity had any role in the study. All the authors vouch for the completeness and accuracy of the data.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The institutional review board at each hospital approved the study protocol.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. *Lancet* 2014;383:83–93.
2 Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. *Arch Surg* 2003;138:490–5.
3 Perrone JM, Frisella MM, Desai KM, *et al*. Results of laparoscopic Heller-Toupet operation for achalasia. *Surg Endosc* 2004;18:1565–71.
4 Rossetti G, Brusciano L, Amato G, *et al*. A total fundoplication is not an obstacle to esophageal emptying after Heller Myotomy for Achalasia: results of a long-term follow up. *Ann Surg* 2005;241:614–21.
5 Schuchert MJ, Luketich JD, Landreneau RJ, *et al*. Minimally-invasive esophagomyotomy in 200 consecutive patients: factors influencing postoperative outcomes. *Ann Thorac Surg* 2008;85:1729–34.
6 Hulselmans M, Vanuytsel T, Degreef T, *et al*. Long-term outcome of pneumatic dilation in the treatment of achalasia. *Clin Gastroenterol Hepatol* 2010;8:30–5.
7 Vela MF, Richter JE, Khandwala F, *et al*. The long-term efficacy of pneumatic dilatation and Heller myotomy for the treatment of achalasia. *Clin Gastroenterol Hepatol* 2006;4:580–7.
8 Zerbib F, Thétiot V, Richy F, *et al*. Repeated pneumatic dilations as long-term maintenance therapy for esophageal achalasia. *Am J Gastroenterol* 2006;101:692–7.
9 Boeckxstaens GE, Annese V, des Varannes SB, *et al*. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011;364:1807–16.
10 de Oliveira JM, Birgisson S, Doinoff C, *et al*. Timed barium swallow: a simple technique for evaluating esophageal emptying in patients with achalasia. *AJR Am J Roentgenol* 1997;169:473–9.
11 Torquati A, Richards WO, Holzman MD, *et al*. Laparoscopic myotomy for achalasia: predictors of successful outcome after 200 cases. *Ann Surg* 2006;243:587–91.
12 Rohof WO, Salvador R, Annese V, *et al*. Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology* 2013;144:718–25.
13 Schoenberg MB, Marx S, Kersten JF, *et al*. Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Ann Surg* 2013;258:943–52.
14 Yaghoobi M, Mayrand S, Martel M, *et al*. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: a meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2013;78:468–75.
15 Costantini M, Zaninotto G, Guirroli E, *et al*. The laparoscopic Heller-Dor operation remains an effective treatment for esophageal achalasia at a minimum 6-year follow-up. *Surg Endosc* 2005;19:345–51.
16 Persson J, Johnsson E, Kostic S, *et al*. Treatment of achalasia with laparoscopic myotomy or pneumatic dilatation: long-term results of a prospective, randomized study. *World J Surg* 2015;39:713–20.
17 Rohof WO, Lei A, Boeckxstaens GE. Esophageal stasis on a timed barium esophagogram predicts recurrent symptoms in patients with long-standing achalasia. *Am J Gastroenterol* 2013;108:49–55.
18 Patti MG, Pellegrini CA. Esophageal achalasia 2011: pneumatic dilatation or laparoscopic myotomy? *J Gastrointest Surg* 2012;16:870–3.
19 West RL, Hirsch DP, Bartelsman JF, *et al*. Long term results of pneumatic dilation in achalasia followed for more than 5 years. *Am J Gastroenterol* 2002;97:1346–51.
20 Eckardt VF, Stauf B, Bernhard G. Chest pain in achalasia: patient characteristics and clinical course. *Gastroenterology* 1999;116:1300–4.
21 Pandolfino JE, Kwiatek MA, Nealis T, *et al*. Achalasia: a new clinically relevant classification by high-resolution manometry. *Gastroenterology* 2008;135:1526–33.
22 Richter JE, Boeckxstaens GE. Management of achalasia: surgery or pneumatic dilation. *Gut* 2011;60:869–76.
23 Lynch KL, Pandolfino JE, Howden CW, *et al*. Major complications of pneumatic dilation and Heller myotomy for achalasia: single-center experience and systematic review of the literature. *Am J Gastroenterol* 2012;107:1817–25.
24 Campos GM, Vittinghoff E, Rabl C, *et al*. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. *Ann Surg* 2009;249:45–57.
25 Vanuytsel T, Lerut T, Coosemans W, *et al*. Conservative management of esophageal perforations during pneumatic dilation for idiopathic esophageal achalasia. *Clin Gastroenterol Hepatol* 2012;10:142–9.

Long-term results of the European achalasia trial: a multicentre randomised controlled trial comparing pneumatic dilation versus laparoscopic Heller myotomy

An Moonen, Vito Annese, Ann Belmans, Albert J Bredenoord, Stanislas Bruley des Varannes, Mario Costantini, Bertrand Dousset, J I Elizalde, Uberto Fumagalli, Marianne Gaudric, Antonio Merla, Andre J Smout, Jan Tack, Giovanni Zaninotto, Olivier R Busch and Guy E Boeckxstaens

Gut 2016 65: 732-739 originally published online November 27, 2015
doi: 10.1136/gutjnl-2015-310602