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A Thousand and One Laparoscopic Heller Myotomies for Esophageal Achalasia: a 25-Year Experience at a Single Tertiary Center

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Abstract

Background The aim of this study was to assess the long-term outcome of laparoscopic Heller-Dor (LHD) myotomy to treat achalasia at a single high-volume institution in the past 25 years.

Methods Patients undergoing LHD from 1992 to 2017 were prospectively registered in a dedicated database. Those who had already undergone surgical or endoscopic myotomy were ruled out. Symptoms were collected and scored using a detailed questionnaire; barium swallow, endoscopy, and manometry were performed before and after surgery; and 24-h pH monitoring was done 6 months after LHD.

Results One thousand one patients underwent LHD (M:F = 536:465), performed by six staff surgeons. The surgical procedure was completed laparoscopically in all but 8 patients (0.8%). At a median of follow-up of 62 months, the outcome was positive in 896 patients (89.5%), and the probability of being cured from symptoms at 20 years exceeded 80%. Among the patients who had previously received other treatments, there were 25/182 failures (13.7%), while the failures in the primary treatment group were 80/819 (9.8%) ($p = 0.19$). All 105 patients whose LHD failed subsequently underwent endoscopic pneumatic dilations with an overall success rate of 98.4%. At univariate analysis, the manometric pattern ($p < 0.001$), the presence of a sigmoid megaesophagus ($p = 0.03$), and chest pain ($p < 0.001$) were the factors that predicted a poor outcome. At multivariate analysis, all three factors were independently associated with a poor outcome. Post-operative 24-h pH monitoring was abnormal in 55/615 patients (9.1%).

Conclusions LHD can durably relieve achalasia symptoms in more than 80% of patients. The pre-operative manometric pattern, the presence of a sigmoid esophagus, and chest pain represent the strongest predictors of outcome.

Keywords Achalasia · Laparoscopic surgery · Laparoscopic Heller myotomy · Long-term results

Introduction

Achalasia is a relatively rare esophageal motility disorder characterized by impaired lower esophageal sphincter (LES) relaxations and the absence of esophageal peristalsis.[1] Although the pathogenesis of achalasia is still unknown (so no definitive therapy is available), an effective and durable palliation of the related dysphagia symptoms can be achieved in most patients by disrupting the LES muscle fibers with forceful endoscopic pneumatic dilations (PD) or by dividing them by means of a surgical myotomy.[2] There has been lively debate regarding the most effective treatment for long-term symptom relief. The relative rarity of achalasia means that most patients will be treated according to local preferences and expertise. The first-line treatment has traditionally been pneumatic dilation, reserving surgery for patients requiring repeated dilations or when this treatment fails.

Laparoscopic Heller myotomy (LHM) for achalasia was first described by Shimi et al. in 1991.[3] Following the experience with the open approach,[4] our group was the first to propose LHM with the addition of a partial anterior fundoplication, the so-called laparoscopic Heller-Dor (LHD)

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operation.[5] Since these early 1990s, LHM seems to have completely changed the achalasia treatment algorithm and, with its more limited surgical morbidity, it has rapidly become the procedure of choice for most gastroenterologists and surgeons treating primary achalasia.[6–8]

A new endoscopic procedure, the so-called per-oral endoscopic myotomy (POEM), was recently introduced[9] and is being used more and more. It achieves good short- to mid-term results and may be a candidate for replacing LHM (and PD too) as the first-line therapy for achalasia.[10]

The aim of the present study was to assess the long-term outcome of laparoscopic Heller myotomy and Dor fundoplication (LHD) for the treatment of esophageal achalasia at a single high-volume institution during the past 25 years. The focus was on morbidity, symptom control, functional results, and any factors predictive of success. The results of this study may serve as a benchmark against which any new procedure should be compared.

Materials and Methods

All consecutive patients with a definitive diagnosis of achalasia who underwent LHD performed by six staff surgeons from 1992 to October 2017 entered the study. Patients who had already undergone surgery or POEM for esophageal achalasia were ruled out. Patients' data, surgical details, and postoperative follow-up were prospectively recorded in a dedicated database. During the study period, our institution participated in two multicenter randomized trials (on laparoscopic Heller myotomy vs. botulinum toxin injection,[11] and on laparoscopic Heller myotomy vs. PD)[12]; the surgical patients involved in those trials are also included in the present study.

Pre-operative Assessment

The disease was diagnosed on the basis of well-established radiological, endoscopic, and manometric criteria.[1,13,14] Patients' clinical and demographic data were collected prospectively by means of a questionnaire, and symptoms were assessed using a detailed score as follows: dysphagia and food regurgitation were calculated by combining the severity of each symptom (0 = none, 2 = mild, 4 = moderate, 6 = severe) with its frequency (0 = never, 1 = occasionally, 2 = once a month, 3 = every week, 4 = twice a week, 5 = daily), while chest pain was assessed separately.[15]

The maximum esophageal diameter was measured at the barium-air interface in the standard anteroposterior image obtained during a barium swallow. Patients were classified according to their maximum esophageal diameter and the shape of the esophagogastric passage as follows: grade I, 4 cm or less; grade II, 4 to 6 cm; grade III, 6 cm or more; grade IV 6 cm or more, and/or a sigmoid-shaped esophagus.[16] Endoscopy was always performed to rule out malignant disease.

Conventional and High-Resolution Esophageal Manometry

Esophageal manometry was performed using the conventional (CM) or high-resolution method (HRM). A low-compliance pneumohydraulic perfusion system (Menfis, Bologna, Italy) was used for CM. HRM was performed using a catheter 4.2 mm in diameter with 36 solid-state circumferential sensors spaced at 1-cm intervals and spanning the whole esophagus (Medtronic, Minneapolis, MN, USA). The protocol included ten swallows of 5 ml of saline solution with a standardized electrolyte concentration to ensure proper catheter function, separated by intervals of at least 20 s. The manometric data were analyzed using ManoViewTM software (Medtronic). The protocols for the two techniques have been described elsewhere.[17,18] The manometric patterns identified on CM were originally classified as proposed by our group in a previous study: pattern I achalasia when 8/10 swallows elicited contractions with an amplitude < 30 mmHg; pattern II when two or more contractions had an amplitude > 30 mmHg; and pattern III when at least two spastic waves were detected (lasting > 6.0 s with an amplitude > 70 mmHg).[19] The Chicago classification was used for the HRM findings, defining achalasia as follows: pattern I when there was no distal esophageal pressurization to > 30 mmHg in ≥ 8/10 swallows; pattern II when at least two test swallows were associated with a panesophageal pressurization > 30 mmHg; and pattern III when patients had at least 20% of premature contractions (distal latency < 4.5 s).[14]

Surgical Technique

The surgical technique for LHD was first described in 1993[5] and has changed little since. The procedure was performed by six staff surgeons. Briefly, a myotomy 7–8 cm long was performed after dissecting only the anterior wall of the esophagus, extending the myotomy 1.5–2 cm on the gastric side. During the procedure, a 30-mm Rigiflex balloon was placed inside the esophageal lumen at the cardia level, using an endoscopically positioned guide wire. The balloon was then gently inflated with air and deflated while the muscle fibers were being cut. If a mucosal perforation was identified intraoperatively, a 4/0 absorbable suture was performed, with 1–3 separate stitches. A partial anterior fundoplication according to the technique described by Dor[20] was performed and sutured to the edges of the myotomy with three stitches on each side. The more proximal suture included the homolateral pillar of the hiatus to keep the fundoplication high around the esophagus. At the end of the procedure, a nasogastric tube was placed in all patients and removed after a water-soluble

contrast swallow (with Gastrografin®, Bracco, Milan, Italy) on the first post-operative day (POD) revealed no leakage from the myotomy. Since mid-2017, due to the minimal number of unrecognized mucosal lesions identified by this study (see below), the nasogastric tube was judged an unnecessary discomfort for patients, and the protocol was amended. After a negative contrast swallow, a liquid diet was allowed and patients were given soft food on the second POD. The length of their hospital stay depended on the distance patients had to travel from home to the hospital. If leakage was identified on post-operative contrast swallow, the nasogastric tube was left in place (or newly inserted) and used for gastric decompression, antibiotics were administered, and the patient was kept on total parenteral nutrition until a new contrast study (usually 7 days later) showed no leakage. If a mucosal lesion was detected and repaired during the surgical procedure, the post-operative contrast swallow was scheduled on the fifth to seventh POD, and the patient was kept on total parenteral nutrition with the nasogastric tube in place.

Follow-up and Outcome

Clinical outcome was assessed by administering the pre-operative questionnaire again 2, 6, and 12 months after surgery, and every 2 years thereafter. If the patient failed to return to the outpatient clinic, a telephone interview was conducted. Endoscopy was performed 12 months after the operation and then recommended every 24 months. Any esophagitis was rated according to the Los Angeles classification. Barium swallow was repeated 2 months after the myotomy and then 2 to 4 years later, and whenever patients had symptoms. Esophageal manometry and 24-h pH monitoring were performed 6 months after the surgical procedure. Twenty-four-hour pH monitoring was performed according to DeMeester. A test was considered abnormal when a composite score of 14.7 or higher was found. Accuracy of reflux detection was checked manually by an expert to distinguish true episodes of gastroesophageal reflux from false reflux due to stasis.[21] Treatment failure was defined as a post-operative symptom score higher than the 10th percentile of the pre-operative score (i.e., > 8.0) of the first 100 patients observed.[22]

Statistical Analysis

Data are expressed as medians and interquartile ranges (IQR) for continuous variables, and as counts or proportions (%) for categorical variables. Nonparametric tests were used to compare groups (Mann-Whitney and Wilcoxon, as appropriate). Fisher's exact test was used to compare categorical data. Disease-free survival estimates were calculated with the Kaplan-Meier method and survival comparisons were performed using the log-rank test. The 10-year probability of being asymptomatic was calculated for the whole population of patients, and the 20-year probability only for patients who had a follow-up of at least 120 months. All independent variables with associations of $p = 0.1$ at univariate analysis then underwent multivariate analysis: logistic regression models were used to identify independent predictors of recurrence and model parameters were estimated using the maximum likelihood method. Odds ratios with 95% confidence intervals were calculated from these estimates. Correlations were analyzed by univariate regression analysis (Pearson) and using Spearman's correlation coefficients. A probability of 5% was assumed to be statistically significant ($p = 0.05$).

Results

Demographic Data, Mortality, and Morbidity

One thousand one patients underwent LHD (536 males and 465 females, with a median age of 46 years [IQR 34–58]). As part of the surgical technique, a partial anterior fundoplication (Dor) was performed in all. The patients' ages showed a perfect Gaussian distribution, with 86 of them over 70 years old (Fig. 1). One hundred eighty-three patients (18.3%) had a history of endoscopic treatments, involving PD in 121 cases, Botox injection in 44, and both in 18 (Table 2).

The surgical procedure was completed laparoscopically in all but eight patients (0.8%), whose conversion to open surgery was due to the following: mucosal perforation in four cases; adhesions in two; an abdominal mass (unexpected ectopic kidney) in one; and spleen damage (requiring splenectomy) in one. Six of these patients were among the first 50 cases treated. These eight patients were included in the final analysis. There was one peri-operative death (0.1%), involving an elderly male with parkinsonism and chronic coronary disease, and a history of unsuccessful endoscopic treatment. He suffered from a cardiac arrest during the night after an uneventful operation. Two patients required reoperation on the first POD (one for bleeding from a trocar site, the other for bleeding from the myotomy site). LHD was completed uneventfully in 976 patients (97.5%), while mucosal perforations occurred in 25 (2.5%). Twenty-two of these perforations were recognized and repaired intraoperatively; only three

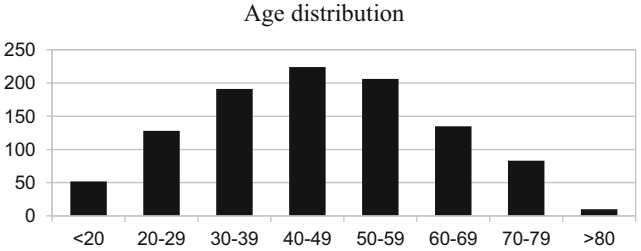

Fig. 1 Distribution of patients who underwent LHD by age. Eighty-six patients were over 70 years old

were detected on routinely performed post-operative water-soluble contrast swallow. In one of these three patients, the first post-operative swallow showed no leakage, and the perforation was detected only on a second X-ray obtained on the third POD. All mucosal lesions healed with conservative treatment, and reoperation was never necessary. Table 1 shows the procedure-related morbidity, which accounted for 4.7% overall.

Follow-up and Early and Late Results

At a median follow-up of 62 months (IQR 18–110), the outcome was positive in 896 patients (89.5%), and the probability to be cured from symptoms (i.e., the probability to have a symptom score ≤ 8) at 10 years after surgery was 84.3% (Fig. 2). A follow-up of more than 120 months was available for 220 patients: the probability to remain cured from symptoms (i.e., the probability to maintain a symptom score ≤ 8) at 20 years remained remarkably stable at 81.4% (Fig. 3). Table 3 shows the characteristics of patients with a positive outcome and those whose achalasia recurred. Only 11 patients were lost to follow-up and 23 died (22 of other unrelated causes, one of esophageal cancer). Overall, only two patients developed a squamous cell cancer of the distal esophagus: one patient missed several follow-up endoscopies, then presented with advanced disease 8 years after LHD, and died 14 months later despite neo-adjuvant therapy and esophageal resection; the other completed the routine follow-up, early cancer was identified 14 years after LHD, and she is currently alive and disease-free 12 months after successful esophageal resection.

Symptoms recurred in 105 patients, during the first year of follow-up in 50%, and after 5 years of follow-up in only a minority of patients (Fig. 4). All 105 patients whose LHD failed subsequently underwent one or more endoscopic PD

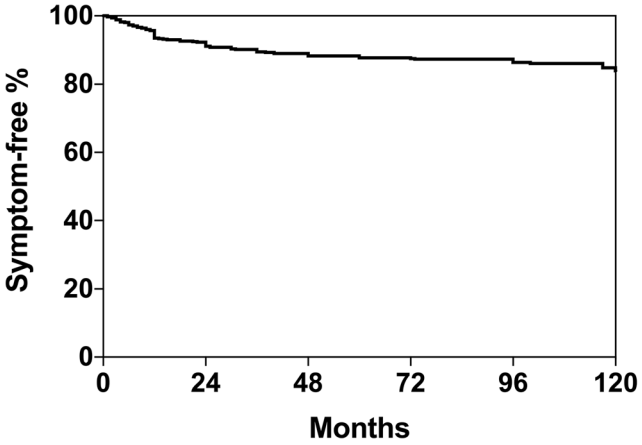

Fig. 2 The Kaplan-Meier curve for symptom control in the whole study population: the probability to maintain a good control of symptoms (i.e., a symptom score ≤ 8) 10 years after the operation was 84.3%

treatments, which ameliorated their symptoms in all but 11, who eventually required reoperation. The overall success rate of LHD and PD combined was therefore 98.4%.

Effect of Previous Endoscopic Treatments

Among the 182 patients who underwent LHD after failed endoscopic treatments (PD in 121 cases, Botox injections in 44, and both in 18; Table 2), the procedure failed in 25/183 (13.6%), whereas there were 80/818 failures (9.8%) in the primary treatment group. This difference was not statistically significant ($p = 0.19$). The timing of recurrences was also similar between the two groups. When the different endoscopic treatments received before surgery were considered separately, a trend towards a higher symptom recurrence rate in Botox-treated patients emerged, but this too failed to reach statistical significance.

Table 1 Morbidity observed in the whole series of patients (POD = Post-operative day)

Type of complication	Number of occurrences	Treatment
Spleen damage	1	Conversion to open procedure and splenectomy
Bleeding from trocar site	2	1 repeat laparoscopy in POD 1, 1 conservative
Bleeding from myotomy site	1	Repeat laparoscopy in POD 1
Pneumothorax	1	Chest drainage
Transient vocal cord palsy	2	Rehabilitation
Ext. sciatic popliteal nerve palsy	1	Rehabilitation
Unexplained fever	1	Conservative
Gastric bleeding	1	Endoscopic treatment of acute gastric ulcer
Mucosal tears	22	Intraoperative immediate repair: 4 conversions, 18 laparoscopic
Radiological leak	3	3 conservative
Incisional hernias	12	8 surgical treatment, 4 conservative
Total	47	

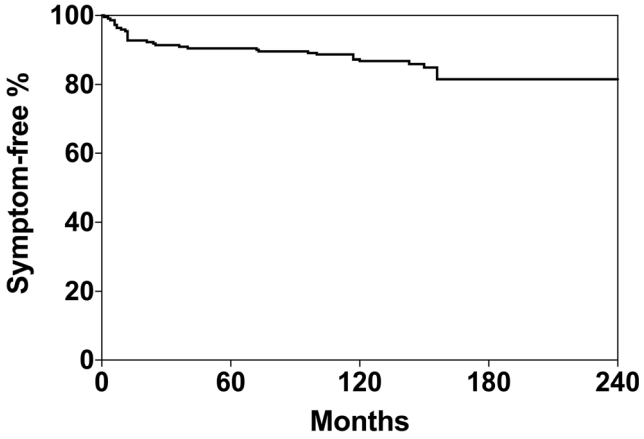

Fig. 3 The Kaplan-Meier curve for symptom control in patients with a follow-up > 10 years: the probability to maintain a good control of symptoms (i.e., a symptom score ≤ 8) 20 years after LHD was still more than 80% (81.4%)

Radiological Stage

Radiological stage could be assessed on pre-operative barium swallow in 883 patients (88.2%): 271 patients had stage I disease, 470 had stage II, 87 had stage III, and 55 had stage IV (sigmoid megaesophagus > 6 cm). The LHD success rate for stage IV patients differed statistically from that of patients with less advanced stages of the disease (76.4% vs 88%, $p = 0.031$; see Table 3, Fig. 5).

Manometric Pattern and LES Parameters

The manometric pattern was assessable in 690 patients and classified as follows: 318 patients (46.1%) had pattern I, 324 (47%) had pattern II, and 48 (6.9%) had pattern III. All patients with a sigmoid megaesophagus had a manometric pattern I. When the outcome was stratified by manometric pattern of achalasia, patients with pattern II had the lowest incidence of failures (4.3%, 14/324), pattern I had a 9.4% failure rate (30/318), and pattern III had a 25% failure rate (12/48), $p < 0.001$ (Table 3, Fig. 6).

Pre- and post-operative LES parameters were available in 469 out of the 615 patients who agreed to undergo post-operative function tests. Only patients who had manometry performed with the same method used for the pre-operative evaluation were considered: 296 had a conventional low-compliance perfused manometry and 173 had HR manometry. For both patients with a positive outcome and patients who recurred, the resting LES pressure and the residual LES pressure during swallowing (or integrated relaxation pressure, IRP, for HRM) significantly decreased after the operation ($p < 0.001$). The post-operative values did not statistically differ between the two groups of patients (Fig. 7). Finally, a partial recovery of peristalsis was observed, after operation, in five patients: all had a pre-operative pattern II and all had a positive outcome. However, this reappearing peristaltic activity was always ineffective.

Predictors of Outcome

At univariate analysis, the manometric pattern ($p < 0.001$), the presence of a sigmoid-shaped megaesophagus ($p < 0.03$), and the presence of chest pain ($p < 0.001$) were the factors that predicted a poor outcome (Table 3). Table 4 shows the independent variables with a significant association ($p < 0.1$) on univariate analysis that entered the multivariate analysis. The three abovementioned factors were independently associated with a poor outcome on multivariate analysis. No correlations emerged between patients' age or sex, symptom duration, symptom score, previous endoscopic treatment, and intraoperative mucosal lesions. Since two different manometric techniques were used during the study period (low-compliance, water-perfused conventional manometry, and solid-state HRM), we opted not to include the manometric findings in the statistical analysis because the values and the parameters of the two techniques differed and were not comparable.

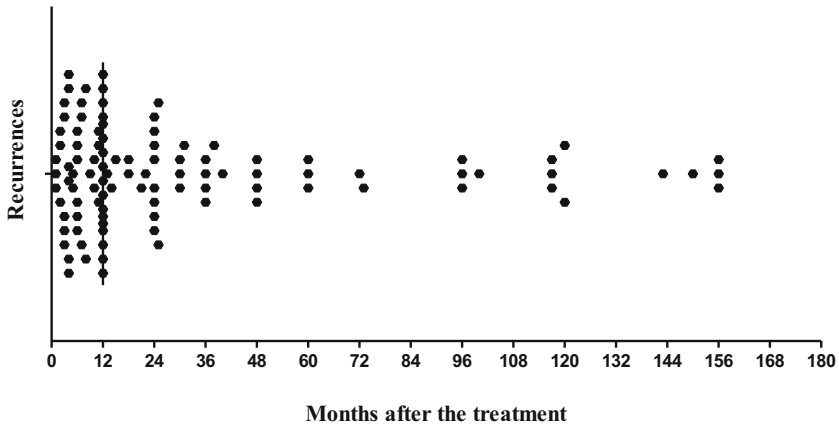

Fig. 4 Scatter plot of the timing of recurrences: 50% of failures were detected within the first year of follow-up, and only a minority later on

Table 2 Distribution of previous treatments in patients who underwent LHD

Previous treatment	Good outcome	Failures	*p* value
Naïve (818 patients)	738 (90.2%)	80 (9.8%)	$p = 0.19$
Previous endoscopic treatment (183 patients)	158 (86.3%)	25 (13.7%)	
Pneumatic dilation (121 patients)	107 (88.4%)	14 (11.6%)	
Botox injection (44 patients)	36 (81.8%)	8 (18.2%)	
PD + Botox (18 patients)	15 (83.3%)	3 (16.7%)	

Post-operative Gastroesophageal Reflux

During the follow-up, 615 patients (61.5%) agreed to undergo manometry and 24-h pH monitoring 6 months after LHD, 396 patients refused. Considering only the patients who submitted to post-operative 24-h pH monitoring, pH acid exposure of the distal esophagus was normal in 560 patients (90.9%), and pathological (with a DeMeester score > 14.7) in 55 (9.1%). False reflux due to stasis came to light in 16 patients (2.6%).

At endoscopy (performed off-therapy), the percentage of esophagitis of any grade did not differ between patients with normal pH findings (26/237, 11%) and those found to have abnormal pH monitoring (4/21, 19%) ($p = 0.28$), though the latter showed a trend towards a higher frequency of esophagitis.

Discussion

In 1999, we reported our experience with the first 100 LHD operations[23] at the 40th Annual Meeting of the Society for Surgery of the Alimentary Tract, SSAT (Orlando, FL). In 2008, we published the results obtained with our first 400 procedures.[8] In the intervening 10 years, another 600 patients underwent LHD, and this follow-up study reports on our whole experience of 1001 consecutive patients treated for achalasia with LHD at our referral center over a period spanning 25 years. To our knowledge, this is the largest series from a single center ever reported in the literature.

The version of LHD performed worldwide nowadays was first described by our group in 1993,[5] after Shimi et al.[3] reported on the first laparoscopic Heller myotomy in 1991. One of the strengths of the present study lies in that the operation had changed very little since, and all patients underwent exactly the same procedure, performed by a relatively small number of surgeons, and the more expert among them passed on the technical details of the operation to the less expert. All patents followed the same pre-operative and follow-up protocol, and were assessed using the same symptom scales and morphological and functional studies (and the majority of patients completed all the tests). We believe that the results obtained in this homogeneous and comprehensive group of

Table 3 Demographic and clinical data for the study population (univariate analysis)

	Good outcome ($n = 896$)	Failure ($n = 105$)	*p* value
Sex (M:F)	480:416	56:49	1
Age	46 (34–58)	45 (32–57)	0.42
Duration of symptoms	24 (12–48)	24 (12–36)	0.14
Symptom score	18 (14–20)	19 (16–20)	0.16
Chest pain score	4 (0–8)	7 (0–10)	< 0.001
Chest pain	50.1%	66.7%	0.004
Diameter of esophagus (mm)	35 (30–45)	38 (30–50)	0.006
Sigmoid esophagus (yes:no)	4.7%	12.3%	0.005
Mucosal lesion (yes:no)	2.3%	3.8%	0.29
Previous endoscopic treatment	17.6%	23%	0.19
Radiological stage			
Stage I (271 patients)	241 (88.9%)	30 (11.1%)	
Stage II (470 patients)	425 (90.4%)	45 (9.6%)	0.031
Stage III (87 patients)	79 (90.8%)	8 (9.2%)	
Stage IV (55 patients) (sigmoid megaesophagus)	42 (76.4%)	13 (23.6%)	
Manometric pattern			
Pattern I (318 patients)	288 (90.6%)	30(9.4%)	
Pattern II (324 patients)	310 (95.7%)	14 (4.3%)	< 0.001
Pattern III (48 patients)	36 (75%)	12 (25%)	

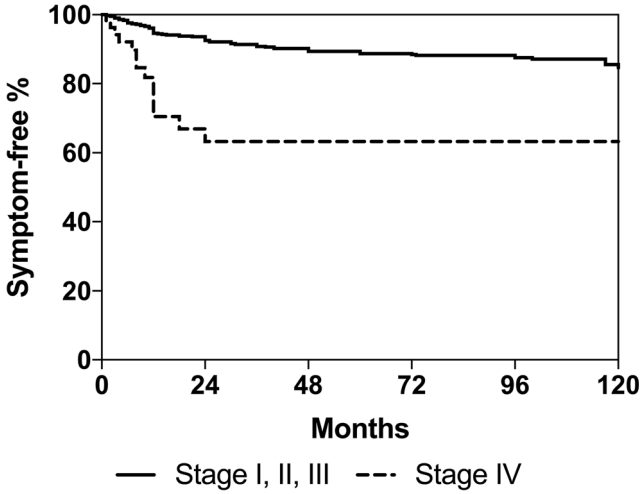

Fig. 5 The Kaplan-Meier curve for positive outcome (i.e., a symptom score ≤ 8) by radiological stage (stages I, II, III versus stage IV). Log-rank test ($p < 0.001$). The success rate for stage IV patients differed statistically from that of patients with less advanced stages of the disease. Durable good outcome was obtained in about 65% of these patients, however

thoroughly studied patients enable us to confirm or confute previous conclusions reported in the literature, by our own or other groups.

First, LHD is a very good, durable one-shot treatment for esophageal achalasia. That laparoscopic myotomy is a good option for relieving esophageal symptoms in achalasia is well known: several series have reported good results in 77–100% of patients treated after an average follow-up of about 3 years.[24] The 5-year follow-up study of the European trial found an 84% success rate for LHM[2] and, in a previous study of ours, we reported good results in 85% of 71 patients who completed a minimum 6-year follow-up.[25] Our present study further confirms these earlier results, showing that the procedure was successful in nearly 90% of a thousand patients with

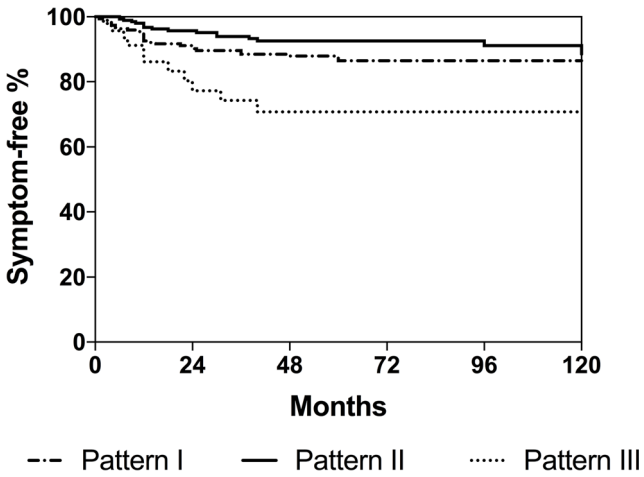

Fig. 6 The Kaplan-Meier curve for positive outcome (i.e., a symptom score ≤ 8) by manometric pattern: patients with pattern II had the lowest incidence of failures, whereas pattern III patients the highest. Log-rank test ($p < 0.001$)

a median follow-up of more than 5 years (62 months). Among our patients with at least 10 years of follow-up, the probability of being symptom-free after 20 years still exceeded 80%. Others[26,27] had reported similarly good results at a 10-year follow-up, albeit in smaller groups of patients. Krishnamoham recently reported on 500 patients in their series: roughly half of them were contacted and they reported good dysphagia control in 86% of cases at a median 77-month follow-up.[28] Our data are reinforced by the fact that we managed to contact nearly all of the thousand patients we treated over a quarter of a century (only 11, i.e., 0.1%, were lost), and that most of them had a follow-up that included both clinical and functional assessments.

LHD is a surgical procedure performed under general anesthesia, so careful patient selection is mandatory. The procedure carries a mortality risk, albeit small. We recorded one peri-operative death (0.1%) due to a cardiac arrest during the night after an uneventful operation. This was an elderly male with Parkinson's disease and chronic coronary disease, who had previously submitted to endoscopic treatment without success. The patient was given CPR in the ward, but the brain damage was so devastating that the patient died a few days later at the ICU. Post-operative monitoring in the ICU might have saved his life, and this should be borne in mind when performing even "minor" surgical procedures in patients at risk. Mortality has been very seldom reported in achalasia patients who undergo laparoscopic myotomy, probably partly due to the small numbers of patients treated. Our figure is lower than the one reported by Rosemurgy in a large series of 505 patients treated with LHD (0.6%).[29] It is similar to those reported in a cumulative review by Lynch[30] (0.15%) and in a retrospective US National review by Wang et al.[31] concerning 1117 patients who underwent (presumably laparoscopic) Heller myotomy from 2003 to 2005 (0.09%). It is noteworthy that this latter mortality rate was unrelated to the annual number of procedures performed by a given hospital. A more recent US National review[32] reported a 30-day mortality rate of 0.3%, which was replicated by two other US National analyses,[33,34] one of which also reported a 0.5% mortality rate after PD.[33] The bottom line is that mortality after LHD is low, but not nil, so careful patient selection, appropriate surgical technique, and watchful peri- and post-operative patient management are of paramount importance.

LHD-related morbidity is usually minimal and not very important. It accounted for only 4.7% in our series. Other authors reported similar or higher rates (5.2–9%).[24,28,29] The previously cited recent National review[32] reported 1.8% of general complications and 2.4% of major complications. Most of the patients selected for LHD are young and fit, so general complications (pneumonia, embolism) tend to be uncommon. To avoid aspiration during the induction of anesthesia, we always position a naso-esophageal tube to empty esophageal contents. Patients with a particularly large

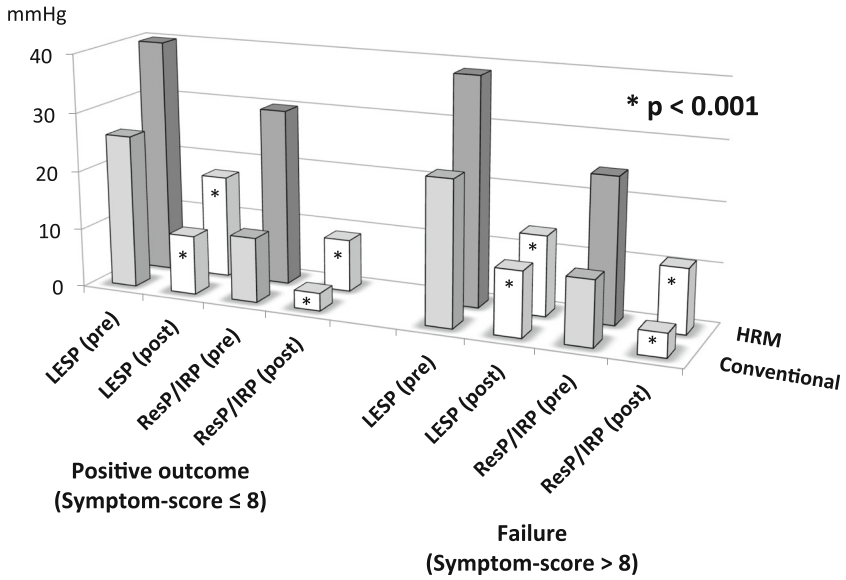

Fig. 7 Manometric characteristics of the LES before and after LHD. Data obtained with conventional low-compliance perfused manometry (front row, $n = 296$) are separated from data obtained with HR manometry (back row, $n = 173$). Patients who had the pre- and post-operative test performed with different methods were not considered. All the post-operative values statistically differed from the pre-operative corresponding values ($p < 0.001$), both in patients with positive outcome and patients who recurred. Moreover, there were no differences in the post-operative values between the two groups of patients. HRM high-resolution manometry, LESP resetting LES pressure, ResP residual LES pressure at swallowing, IRP integrated relaxation pressure

megaesophagus are also asked to stay on a liquid diet for a few days before the operation. Thrombo-embolic prophylaxis with LMW heparin and early mobilization after surgery are also essential.

It is worth emphasizing that 86 of our patients (8.6%) were more than 70 years old. Older age should not be seen as a factor when considering surgery as a primary therapy for achalasia. Our group[15] and others[35,36] have already demonstrated that good results can be achieved with LHM in elderly patients too, with no increase in morbidity (or mortality). Some authors[36] even found that older age predicted a better symptom control.

One of the most common complications of LHM (and somewhat worrisome for the surgeon) is mucosal damage caused while performing the myotomy. This happened in 2.5% of patients in our series. Most of these lesions (2.1%) were detected and repaired during the operation, while 0.4% were revealed by contrast studies post-operatively. This figure is somewhat higher than in other studies:[33] a perforation rate of 0.8% was reported in a series of 871 patients treated from 2009 to 2014, but this was a retrospective study based on administrative charts, whereas complications were collected prospectively in our study. Our figure compares favorably, on the other hand, with other recent reports on large series,[28–30] which had perforation rates of 2–10.4% of operations. The classical meta-analysis conducted by Campos et al.[24] found a median rate of 6.9% among 39 published series concerning 3086 patients. This complication is normally recognized and repaired immediately, while the LHD procedure is underway (with or without converting to open surgery), as in our series and in other reports.[28] It does not usually affect the course and outcome of the patients affected.[24,37] One group reported a death when a leak occurred after a patient's discharge from hospital,[29] but the median post-operative hospital stay for their patients' was just 1 day, far less than the 3–4 days routinely adopted for our patients. Had that particular patient still been in hospital when the leakage became manifest, the outcome might have been different.

Another possible strength of our study lies in that patients were followed up not only with symptom assessments, but also with morphological and functional tests. In particular, we managed to perform manometry and 24-h pH monitoring of the distal esophagus in nearly two in three of our patients (61.5%), finding an abnormal exposure of the distal esophagus in 9.1% of them. Reflux after myotomy had long been a "vexata quaestio" among experts,[38] initially debated by those advocating the addition of antireflux fundoplication and those

Table 4 Multivariate analysis of predictors of failure. Only independent variables with a significant association on univariate analysis ($p < 0.1$) were considered

	p value	OR	CI (95%)
Sigmoid esophagus	0.018	2.5	1.13–5.20
Pattern II	0.054	0.50	0.24–0.99
Pattern III	0.013	2.84	1.20–6.38
Chest pain score	< 0.001	1.10	1.04–1.16

who preferred a simple myotomy.[6,39,40] More recently, the debate moved between supporters of surgical myotomy and proponents of the new POEM technique.[41] Post-operative reflux is an inevitable complication of any achalasia therapy aiming to reduce the barrier of an unrelaxing sphincter, be it PD, laparoscopic myotomy, POEM, or even Botox injections. The real incidence and severity of GERD in patients who undergo surgical or endoscopic treatment for achalasia is probably over- or underestimated, however, because many studies judged the presence of reflux only from patients' symptoms, or from signs of esophagitis on post-treatment endoscopy.[24,42,43] Very few groups used 24-h pH monitoring to objectively establish any presence of GERD after achalasia treatment with surgical or endoscopic myotomy, or PD.[44–46] Novais and Lemme analyzed 24-h pH patterns after LHD and PD in their randomized trial and, after a careful review of the false-positive results due to fermentation, they showed that the incidence of genuine post-treatment reflux was higher after dilation (31%) than after LHD (4.7%).[44] In a collective review, post-operative reflux was reported in 8.8% of patients after myotomy and fundoplication, and up to 31.5% of those undergoing a simple myotomy.[24] Richards et al.[47] performed a prospective, randomized trial comparing the incidence of post-operative reflux after a myotomy alone or after a myotomy with a Dor fundoplication: pH monitoring showed abnormal reflux in 48% of the former patients and only 9% of the latter; then a follow-up study after 10 years[48] found that the two groups' GERD symptoms did not differ, however (no pH studies were performed). A different picture emerged from the multicenter study by Rawlings et al.[49] The authors compared the Dor versus the Toupet fundoplication after Heller myotomy, reporting a very high incidence of post-operative reflux after myotomy: in particular, they found abnormal acid reflux in 10 out of 24 patients with Dor (41.7%), as compared to 4 out of 19 with Toupet (21.1%). The reason for such a reported high incidence of pH-proven GERD after LHD is difficult to speculate. A different surgical technique with a more extensive isolation of the cardia region (by dividing the gastrophrenic ligament and the short and posterior gastric vessels) may be one possible explanation, together with the small number of patients who accepted to undergo pH studies (24/49 and 19/36 in the Dor and Toupet group, respectively). Also in the European achalasia randomized trial comparing PD with LHD, in which we also participated,[2] the incidence of post-procedural reflux was higher than in the present study. After a 5-year follow-up, the incidence of GERD was 23% after LHD, and this was higher, though not to a statistically significant degree, than after PD (15%). Together with the reportedly high rate of intraoperative mucosal tears (12%), this may point to a suboptimal surgical expertise at some of the participating centers. We have already reported that it takes about 20 procedures to complete the learning curve for LHD,[23] and another group recently confirmed as much, setting the number at 16 operations at least.[50] Given the rarity of achalasia, some of the surgeons involved in the trial may not have had so much experience. Multicenter studies are useful for demonstrating the reproducibility of a technique or method, but the end results may differ greatly from one center to another due to different levels of local expertise, especially when a relatively "new" or particular procedure is involved.

To date, no randomized studies in the literature have compared the outcome of LHM with the newly introduced POEM for achalasia, and the real prevalence of GERD after POEM remains to be clearly documented. Many studies considered the incidence of GERD after POEM merely by assessing GERD symptoms, reporting percentages in the range of 20–40%.[51,52] A very few studies rated the incidence of GERD after POEM by means of a thorough, objective, and comprehensive assessment, including endoscopy and pH monitoring. In a recent review, Patel et al. analyzed the five studies that employed pH monitoring published in the literature so far, finding abnormal acid exposure in 43% of patients after POEM.[53] Familiari et al. described an altered esophageal acid exposure after POEM in 50.5% of cases, though only 20% of their patients had heartburn or esophagitis.[45] These latter authors also found that the overall incidence of clinically relevant GERD due to abnormal acid exposure associated with symptoms or esophagitis was only 29%. A recent meta-analysis[54] comparing the outcome of LHM and POEM showed a clear difference in GERD (as detected by pH monitoring) between the two methods, with a 16% random-effects pooled rate estimated for LHM as opposed to 39% for POEM. If the presence of esophagitis was chosen as a marker, these figures became 6% versus 35.3%, respectively. The incidence of pathological acid reflux after different treatments is an important parameter to consider when offering a therapy for a functional disease like achalasia—especially in younger patients, whose post-operative reflux might warrant chronic therapy with PPI or antacids.[38,46] The risk of developing esophageal cancer in patients with achalasia is linked more to the disease itself than to any related GERD, because food and saliva retained in the gullet can cause bacterial overgrowth and a greater production of nitrosamine, leading to mucosal inflammation, dysplasia, and (eventually) squamous cell cancer.[55–57] Some authors have reported the onset of Barrett's esophagus in achalasia patients, however, and adenocarcinoma too.[58,59] Prophylaxis with antireflux drugs is therefore a necessity, especially in young patients, to reduce these risks. A laparoscopic fundoplication may also be considered, after effective POEM has led to severe reflux.

As in previous reports from our own and other groups, the presence of a stage IV, decompensated megaesophagus is a strong predictor of a less satisfactory outcome than for other, less advanced stages of achalasia.[7,8,60] Several studies have also seen significant improvements in dysphagia after a

Heller's myotomy in patients with stage IV disease. In a recent review,[61] outcomes were excellent or good in a mean 79% of cases (range 54–100%), with little morbidity and no mortality. In our series, good results were achieved in more than 75% of the stage IV patients (Table 3), and these results have been durable in about 65% (Fig. 5). Heller's myotomy in patients with more severe achalasia is technically not very different or more difficult than in patients with milder disease. A more extensive dissection of the mediastinal esophagus may be necessary to straighten its axis and is recommended by some.[60,62] A laparoscopic Heller's myotomy is therefore a good option and should be offered to patients with stage IV achalasia too, since dysphagia is relieved in a significant number of cases and the procedure does not preclude esophagectomy later on, if necessary.[60]

The "spastic" manometric subtype of achalasia (pattern III) was first described by Pandolfino et al.[63] as a form of achalasia with a far worse outcome than the other subtypes. This was confirmed by a previous study of ours,[19] in which 30.4% of patients with pattern III had recurrent symptoms after LHD, as compared with 14.6 and 4.7% for patterns I and II. Analyzing manometric tracings from patients participating in the European trial confirmed as much:[64] only 66% of patients with pattern III achalasia had a satisfactory outcome after 2 years. LHD had a higher success rate than PD in this particular subset of patients, however (86% vs 40%). Luckily, pattern III is the least common subtype of achalasia. It may represent an early stage of the disease[65] as it is characterized by the shortest duration of symptoms and the lowest degree of gullet dilation of all the subtypes. In a previous study,[19] we also found that pattern III is associated with a longer LES, and this prompted us to adapt our protocol slightly, extending the length of the myotomy both upwards and downwards in patients with this pattern. Since then, our results in these particular patients have further improved: in a group of 32 patients with pattern III achalasia, treated with this "extended" myotomy, the outcome was satisfactory in 90% of cases, as compared with 67% in 24 patients operated with a standard myotomy (personal data, presented at the DDW 2018). These albeit preliminary data compare well with those of a recent study,[66] in which the outcome in pattern III patients was comparable with that obtained in the other subgroups of patients, when the myotomy was extended onto the stomach. It has to be said that these results only refer to five such patients, however. With its lengthy extension in the esophageal body, the POEM technique would seem to be the ideal solution for this subtype of achalasia, but its rarity means that published data are still scarce. One recent report on 32 pattern III patients undergoing POEM described a good outcome in 90.6% of cases at 2-year follow-up.[67] In a retrospective study that compared 49 patients who underwent POEM for pattern III achalasia across eight centers with 26 patients who underwent LHM at a single institution, a clinical response was significantly more common in the POEM cohort (98.0% vs 80.8%; $p = 0.01$).[68] These enthusiastic reports need to be confirmed by further, more carefully designed studies, however, and with a longer follow-up. For the time being, we can only say that—for pattern III achalasia—LHD and, probably, POEM are the first treatment options to offer patients, leaving the less effective PD to those unfit for general anesthesia.

Finally, our experience clearly demonstrates that previous endoscopic treatment with PD, Botox, or both does not affect the outcome of LHD. This had been another issue hotly debated among surgeons: some reported that such previous treatments made it difficult to perform the myotomy, raised the complication rate, and/or negatively influenced the final outcome;[69–72] others denied any such effects of previous treatments.[73–76] In a previous study of ours,[77] we found no influence of previous, failed PD on the outcome of LHD, while we did see a link with Botox injections. Judging from the results of the present large series, however, we can safely say that earlier treatments with PD, Botox injections, and/or combinations of the two do not influence the final outcome of LHD, even if a trend towards rather less satisfactory results can be seen after Botox treatment.

In conclusion, LHD can durably relieve achalasia symptoms in about 85% of patients, and the probability of being symptom-free remains more than 80% 20 years later. Complications of surgery are rare, and postoperative reflux occurs in less than 10% of patients. Recurrences can be treated successfully with dilations in nearly all cases. The pre-operative manometric pattern, the presence or absence of a sigmoid esophagus, and the chest pain score represent the strongest predictors of outcome.

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