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Comparison of Endoscopic Dilatation and Heller's Myotomy for Treating Esophageal Achalasia in Children: A Multicenter Study

Short title: Esophageal achalasia treatment in children

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Objective To compare the efficacy of, and complications from the two main treatments for achalasia are endoscopic dilatation and surgical cardiomyotomy (Heller's myotomy). **Study design** We retrospectively collected data on children treated for achalasia over an 11-year period from eight tertiary pediatric centers. A line of treatment was defined as performing either Heller's myotomy or 1–3 sessions of endoscopy dilatation over three months. Treatment success was a priori defined as clinical improvement and no need for new treatment.

Results 97 children (median age: 12 years, 57% boys) were included. Median time-to-diagnosis was 10.5 months, and the median follow-up period was 27 months. Thirty-seven children were treated by Heller's myotomy and 60 by endoscopy dilatation as the first-line treatment. After adjustment for potentially confounding factors, Heller's myotomy was significantly more successful than endoscopy dilatation (hazard ratio, HR 3.93[1.74;8.88], $p=0.001$), with a median survival without failure of 49 and 7 months, respectively, and with no significant difference in the occurrence of complications (35.2% for Heller's myotomy, 29.7% for endoscopy dilatation, $p=0.56$). Hydrostatic dilatation was as successful as pneumatic dilatation (HR 1.35[0.56;3.23], $p=0.50$).

Conclusions Heller's myotomy is more successful than endoscopy dilatation, with no significant difference in the occurrence of serious complications. This raises the potential role of peroral endoscopic myotomy as an alternative treatment to Heller's myotomy.

Achalasia is a rare motor disorder of the esophagus characterized by esophageal aperistalsis and defective relaxation of the lower esophageal sphincter (LES) (1). There is currently no curative treatment, but two main techniques can limit excessive LES pressure: endoscopic dilatation and myotomy, either by surgical route (Heller's myotomy) or more recently by endoscopy (peroral endoscopic myotomy, POEM); however, there is no clear consensus on management. Due to the low incidence of achalasia in pediatrics, between 0.10 and 0.18 per 100,000 children/year (2,3), comparisons of treatment efficacy and complications in this population are usually limited to retrospective, single-center, small sample studies. One systematic literature review found insufficient comparable data to recommend a first-line treatment (4). Thus, our aim herein was to compare success rates and complications with the two techniques (i.e., endoscopy dilatation and Heller's myotomy) currently used most often for first-line pediatric treatment.

Methods

Study Population

We retrospectively collected data on patients followed for achalasia, confirmed by esophageal manometry (aperistalsis of the esophageal body and increased LES tone). Subjects were diagnosed before the age of 18 years and treated for the first time, by either endoscopy dilatation or Heller's myotomy, over an 11-year period at one of the eight French tertiary referral centers. Data were collected from electronic and paper records using data collection sheets.

The main study objective was to compare the success of endoscopy dilatation (pneumatic and hydrostatic, then pneumatic alone) and Heller's myotomy as first-line treatments, by analyzing median survival without recourse to a new treatment. A line of treatment was defined as either performing Heller's myotomy or performing 1–3 endoscopy dilatation sessions, with a maximum period of three months between the first and third sessions.

Treatment success was a priori defined as clinical improvement (improvement of clinical signs and no need for further treatment) and failure as the need for a new treatment (e.g. Heller's myotomy, endoscopy dilatation, or POEM) and/or enteral nutrition support (delivery of nutrition directly to the stomach or jejunum via feeding tube or gastrostomy). Patients who presented with symptom recurrence more than two months after 2–3 dilatations, and who therefore needed more than 3 endoscopy dilatations, were considered treatment failures and were candidates for new treatment (endoscopic dilatation, Heller's myotomy, POEM, or enteral nutrition). The choice between Heller's myotomy and endoscopy dilatation was at the clinician's discretion.

Secondary objectives were to compare complications from these therapeutic methods and to compare the success of pneumatic dilatation and hydrostatic dilatation. A complication was defined as any event occurring during either a procedure or follow-up, which needed an intervention (e.g., perforation or pneumomediastinum).

Statistical Analyses

Continuous variables were expressed as mean (standard deviation) when normally distributed, or as median (interquartile range). Categorical variables were expressed as value (percentage). Distribution normality was assessed using histograms and the Shapiro–Wilk test. We estimated the risk of failure at different timepoints using the Kaplan–Meier method by censoring lost to follow-up at the last available follow-up. Failure risks were compared between treatments using a univariate Cox proportional hazard regression model and then adjusting for prespecified factors (age at diagnosis, delay-to-treatment, and triple A syndrome). The same approaches were used to identify baseline characteristics associated with risk of failure. The log-linearity assumption for continuous measures was checked by examining Martingale residual plots and using restricted cubic spline functions, and the proportional hazard assumption for each

potential predictive factor was checked by examining the Schoenfeld residuals. Comparisons of adverse events and complications between first-line treatment groups were performed using generalized linear mixed models (with a binomial distribution and logit function) by including subject as a random effect (i.e., several treatments by subject). Baseline characteristics were compared between first-line treatment groups using Students t-test for Gaussian continuous variables, Mann–Whitney U test for non-Gaussian continuous variables, and Chi-square test (or Fishers exact probability test when expected cell frequency was <5) for categorical variables, as appropriate.

Statistical testing was conducted at the two-tailed α -level of 0.05. Data were analyzed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The study was declared to the French Data Protection Authority (Commission nationale informatique & libertés). All data were anonymized. The study was approved by the Ethics Committees of the Francophone Group of Hepatology, Gastroenterology and Pediatric Nutrition.

Results

Study Sample

Between 2005 and 2016, 97 patients under the age of 18 years (55 boys) with achalasia, confirmed by esophageal manometry, were treated by first-line endoscopy dilatation or Heller's myotomy at one of the eight selected centers. Data were missing for manometry type for 18 patients, and for achalasia subtype for 5 patients who underwent high-resolution manometry (HRM); however, they all had manometric confirmation at diagnosis. Sample characteristics are shown in Table I.

Symptoms and Additional Investigations

The two main clinical signs at diagnosis were dysphagia and regurgitation. All patients had esophageal manometry at diagnosis, confirming achalasia. Clinical characteristics are reported in Table II. Twenty-seven patients (28%) underwent HRM, making it possible to define achalasia type according to the Chicago classification; 30% of these patients had achalasia type I, 48% type II, and 22% type III. The median LES relaxation pressure was 22.8 mmHg, and the median minimal LES pressure at rest was 28.8 mmHg. Manometric metrics are detailed in Table I.

Treatment Groups

Sixty patients (61.9%) were treated by first-line endoscopic dilatation, and 37 (38.1%) by Heller's myotomy (Figure 1). The two treatment groups were comparable (Table II). Nine patients were treated by first-line hydrostatic dilatation and 44 by pneumatic dilatation (7 missing data). Patients treated by hydrostatic dilatation (n=45, 26.0%) were significantly younger than those treated by pneumatic dilatation (n=128, 84.0%) (8.6 [\pm 4.7] years vs. 13.3 [\pm 2.7] years, $p < 0.001$).

Treatment Efficacy

As a first line of treatment, Heller's myotomy was significantly more successful than endoscopy dilatation (risk of failure with Heller's myotomy group as reference, hazard ratio [HR] 3.56[1.73;7.29], $p = 0.0005$) and pneumatic dilatation alone (risk of failure with Heller's myotomy group as reference, HR 3.41[1.62;7.18], $p = 0.0013$) (Figure 2 and 3; available at www.jpeds.com). Similar results were found after adjustment for age at diagnosis, delay-to-treatment, and history of triple A syndrome (risk of failure with Heller's myotomy group as reference, adjusted HR 3.93[1.74;8.88], $p = 0.001$ for comparison with endoscopy dilatation; adjusted HR 3.89[1.59;9.53], $p = 0.003$ for comparison with pneumatic dilatation).

Hydrostatic dilatation was as successful as pneumatic expansion within first-line treatment (risk of failure with Heller's myotomy group as reference, HR 1.35[0.56;3.23], $p=0.50$), with new treatment-free survival medians of 7 and 3 months, respectively (Figure 4; available at www.jpeds.com).

Treatment Complications

The overall complication frequency, early (before 48 hours) or late, and severe or not, including all treatment lines, did not differ significantly after endoscopy dilatation or Heller's myotomy (29.7% and 35.2%, respectively, $p=0.56$)(Table III; available at www.jpeds.com). The frequency of serious complications, early or late, including all treatment lines, did not differ after endoscopy dilatation or Heller's myotomy (2.6% and 9.6%, respectively, $p=0.080$). Serious complications were discontinuation of the operation, conversion to laparotomy, in-process transfusion, esophageal or gastric perforation, cervical emphysema, pneumomediastinum, peritonitis, esophageal fistula, and gastric volvulus with hiatal hernia. No death occurred among this sample. The frequency of early complications, whether serious or not, including all treatment lines, did not differ after endoscopy dilatation or Heller's myotomy (18.4% and 16.7%, respectively, $p=0.79$), nor did the frequency of late complications, whether serious or not, including all treatment lines (10.8% and 21.8%, respectively, $p=0.092$). Gastroesophageal reflux disease (GERD) was suspected in 21.3% of patients after endoscopy dilatation and 20.6% after Heller's myotomy; this was confirmed by pH manometry in 0% and 8.8% of patients, respectively. GERD was considered a mild complication, as no patient needed fundoplication. Mucosal breach after endoscopy dilatation and Heller's myotomy was found in 8.9% and 13.0% of patients, respectively, and esophageal perforation in 1.6% and 3.7% of patients, respectively.

Discussion

Endoscopic dilatation and Heller's myotomy are both successful and safe treatments (5,6), yet the optimal treatment of achalasia in pediatric patients remains debated and findings are conflicting (2,4,6,7). A systematic literature review of seven pediatric studies showed a lack of comparable data to recommend a first-line treatment (4); two studies recommended Heller's myotomy as the first-line treatment (8,9), one recommended pneumatic dilatation (10), one found comparable efficacy between the two treatments (11), and three recommended that therapeutic choice should be according to the age of the child(12–14). Herein, we report children with achalasia whose characteristics are similar to the few published pediatric series (2–5,15,16). In our study, as in most studies, endoscopy dilatation was most often the first-line treatment (2,4,17).

Our analyses indicate that Heller's myotomy as the first-line treatment may be more successful than endoscopy dilatation, whether using pneumatic alone or pneumatic and hydrostatic. Other studies have also found that Heller's myotomy is a superior first-line treatment (2,8,11,17), including retrospective studies with smaller samples (7). This is in contrast to a large randomized trial in adults showing that Heller's myotomy and endoscopy dilatation symptom-based outcomes are similar at posttreatment years one, two, and five (18,20). A major difference in time-to-relapse was found, of a few months after endoscopy dilatation and more than four years after Heller's myotomy. This superiority can be understood because there is a more complete dissection of the LES muscle fibers and therefore greater efficacy. We found no age-based difference in outcomes between techniques, indicating that age need not be a criterion for choosing one over the other.

Our study is consistent with data from adults showing that Heller's myotomy is more successful in young people than in older people. The success rate of endoscopy dilatation as a first-line treatment was relatively low in our study (20%) compared with previous studies (60–90%) (6,10,12), but higher than the study by Smits et al (10%) (2). Our lower rate can be

explained by different definitions of success and failure across studies, and that previous studies were monocentric or bicentric and included small samples. Hydrostatic dilatations have not been validated for the treatment of achalasia but are the only ones available for infants and small children. It did not seem appropriate to exclude them given their frequent use in pediatrics (a quarter of dilatations in our study). Because the minimal diameter of pneumatic balloons is 30 mm, it is unusable in patients younger than 6 years or those weighing <20 kg. Herein, patients treated by hydrostatic dilatation were significantly younger and had lower weight than those treated by pneumatic dilatation. Distinctions between hydrostatic and pneumatic dilatation in previous pediatric studies are often lacking, making comparisons with their results difficult. We did not find any difference in the efficacy of hydrostatic dilatations compared with pneumatic dilatations. This may be due to a true absence of difference, which may help validate their use in achalasia with confirmation by other studies, or a lack of statistical power. Our poorer endoscopy dilatation results might also be explained by differences in dilatation protocols and technical characteristics (e.g., balloon sizes, pressures, times, and number of dilatations per session). Our dilatation protocol is similar to that reported by Boeckxstaens et al, the standard in adults (18). The main difference herein regards the second part of their protocol, which deals with the management of patients whose symptoms recur during follow-up. Indeed, were we to adhere strictly to the Boeckxstaens' protocol, our success rate with balloon dilatations would have been much higher: 55%. Overall, the relatively low success rates of the two treatment types confirm the difficulties with achalasia management, with 60% of patients requiring a minimum of two lines of treatment.

The frequency of complications overall was similar in the two treatment groups, giving even greater importance to Heller's myotomy, which is often associated with more complications (2). The complication rates seemed high for both treatment types (~30%), but mucosal breaches—often minor—and suspected GERD were most common. However,

although nonsignificant, more serious complications might be associated with Heller's myotomy. Posttreatment GERD frequency is difficult to compare across studies, as its definition is not uniform. The difference in GERD frequency confirmed by pH measurement between the two groups was worse with surgery—nearly 9% vs. 0%—with anti-reflux surgery performed for 90% of Heller's myotomy. Performing systematic anti-reflux surgery during Heller's myotomy remains controversial, with some studies showing low rates of GERD without fundoplication. Routine fundoplication might have little benefit while placing the patient at risk of a too tight anti-reflux procedure resulting in dysphagia (16,19). Also, dysphagia following Heller's myotomy with fundoplication makes it difficult to know whether it is a sign of recurring achalasia, and therefore a treatment failure, or if it is because of an anti-reflux device that is too tight. Thus, Heller's myotomy failures were probably overestimated, as any new treatment was considered a relapse. According to some teams, concomitant anti-reflux surgery should be determined on a case-by-case basis, depending on personal history and GERD risk factors.

A similar rate of esophageal perforation after endoscopy dilatation (1–2%) is found in most pediatric studies (2,8), though this rate is 2–5% in adults (18,20). This difference can be explained by the use of smaller diameter balloons in pediatrics, as the perforation rate increases with balloon size (2,18). However, there may also be a modifying factor, as larger diameter balloons are also more effective in pediatrics (2). Regardless, a low perforation rate is even more attractive following endoscopy dilatation, as surgery negates the benefit of the endoscopic procedure (4).

One strength of our study was its multicenter character. Our relatively large pediatric sample allowed us to evaluate achalasia treatments using multivariate analysis, whereas most previous studies have relied on cohorts of 10–40 patients (6,8–12). A main study limitation was its retrospective nature. The fact that dilation technique (pneumatic vs. hydrostatic) likely

differed among institutions may otherwise have influenced the results. The choice between endoscopy dilatation and Heller's myotomy was not recorded herein. This may have led to selection and information biases, center- and/or doctor-dependent, with likely differences between surgeons and pediatric gastroenterologists. However, children treated by endoscopy dilatation or Heller's myotomy did not differ at diagnosis, especially according to weight loss and nutritional status, which are good surrogates for disease severity. Our manometric inclusion criteria are open to criticism: with associated aperistalsis and increased LES tone, but without LES cutoff values. This choice is justified by the manometric definition of complex achalasia in pediatrics, by diagnostic heterogeneity with conventional manometry and HRM comprising different thresholds of pathological LES relaxation pressure, by pathological thresholds of relaxation pressure varying according to the HRM system, and by missing data (LES pressure is not always recorded).

Type-II childhood achalasia was the most highly represented in our study, though at a lower rate than among adults (48% vs. 70% in adults) (21). Studies on adults show that therapeutic choice can be guided by achalasia type (20,22) but given the low HRM use—one-third of patients—we could not correlate treatment success with achalasia type using the Chicago classification. Indeed, our results may have been impacted by the fact that achalasia treatment is centralized to specialized centers in the national French network CRACMO (Centre de Référence des Affections Chroniques et Malformatives de l'Oesophage).

Information bias may have been caused by missing data, leading to difficulties in interpreting the results and lower statistical power. Though the Eckardt score was not used as a primary endpoint, due to its low use in pediatric practice, we defined strict a priori criteria for failure. That our study showed the superiority of Heller's myotomy over endoscopy dilatation supports additional studies on POEM, which allows the same myotomy type but is less invasive (23–28). Only one patient herein was treated by POEM, after the failure of two pneumatic

dilatation treatment lines. The efficacy of POEM in the medium- and long-term remains to be determined, compared with Heller's myotomy, as does its safety, because questions remain as to the long-term frequency of GERD (24,27,28).

Future studies should address safety and long-term outcomes using a prospective randomized trial design.

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Table I. Population characteristics, n=97

General characteristics	Values (%)
Male	55/97 (56.7)
Age at the beginning of symptoms (years), median [IQR]	10.5 [6.5;13.0] ^a
Age at diagnosis (years), median [IQR]	12.0 [8.5;14.5] ^b
Diagnostic delay (months), median [IQR]	10.5 [4.0;21.0] ^c
Delay between diagnosis and first treatment (months), median [IQR]	1.0 [1.0;3.0] ^d
Delay to follow-up (months), median [IQR]	27.0 [13.0;50.0]
Personal history	
Triple A syndrome	16/88 (18.2)
Initial psychiatric hypothesis	3/88 (3.4)
Down's syndrome	1/88 (1.1)
Hirschsprung disease	1/88 (1.1)
Congenital central hypoventilation syndrome	1/88 (1.1)
Family history	
Achalasia	11/56 (19.6)
Triple A syndrome	5/56 (8.9)
Clinical data	Values
Dysphagia	86/89 (96.6)
Regurgitation	71/89 (79.8)
Weight loss or stagnation	56/89 (62.9)
Thoracic pain	42/89 (47.2)
Respiratory signs	34/51 (66.7)
Cough	32/52 (61.6)
Repeated respiratory infections	7/28 (25.0)
Denutrition at diagnosis	18/62 (29.0)
BMI ² Median Z-score [IQR]	- 0.94 [-2.36;0.15]
Manometry	97/97 (100.0)
Conventional manometry	47/97 (48.5)
HRM ^e	32/97 (33.0)
Type I	8/27 (29.6)
Type II	13/27 (48.1)
Type III	6/27 (22.2)
LES Relaxation pressure (mmHg)^f	
Median [IQR]	22.8 [14.3;31.3]
Minimum	4.4
Maximum	82.0
LES minimal rest pressure (mmHg)^g	
Median [IQR]	28.8 [18.2-35.0]
Minimum	5.6
Maximum	87.0

Values are expressed as number (percentage) unless otherwise indicated. Numbers of missing data: ^a 15, ^b 3, ^c 19, ^d 7, ^e 5, ^f 69, ^g 51;;BMI: body mass index;[IQR]: Interquartile range; HRM: high-resolution manometry

Table II. Comparison of both groups at diagnosis

Parameters	Heller's myotomy (n=37)	Endoscopic dilatation (n=60)	p-value
Male	22/37 (59.5)	33/60 (55.0)	0.67
Median age (years), median [IQR]	12.8 [9.3;14.5] ^a	11.8 [8.5;14.0] ^b	0.30
Median diagnostic delay (months), median [IQR]	13.0 [2.0;24.0] ^c	9.0 [4.0;18.0] ^d	0.50
Personal history of Triple A syndrome	4/35 (11.4)	12/53 (22.6)	0.18
Weight loss/stagnation	20/31 (64.5)	36/58 (62.1)	0.82
Dysphagia	30/31 (96.7)	56/58 (96.6)	N/A
Thoracic pain	18/31 (58.1)	24/58 (41.4)	0.13
Regurgitation	27/31 (87.1)	44/58 (75.9)	0.21
Median BMI Z-score, median [IQR]	-0.8 [-1.6;0.1] ^e	-1.2 [-2.7;0.3] ^f	0.24

Values are expressed as number (percentage) unless otherwise indicated. Number of missing data but manometric confirmation performed in all patients: ^a 1, ^b 2, ^c 10, ^d 9, ^e 14, ^f 21; N/A: Not applicable; [IQR]: Interquartile range; BMI: body mass index

Figure 1. Study flow chart

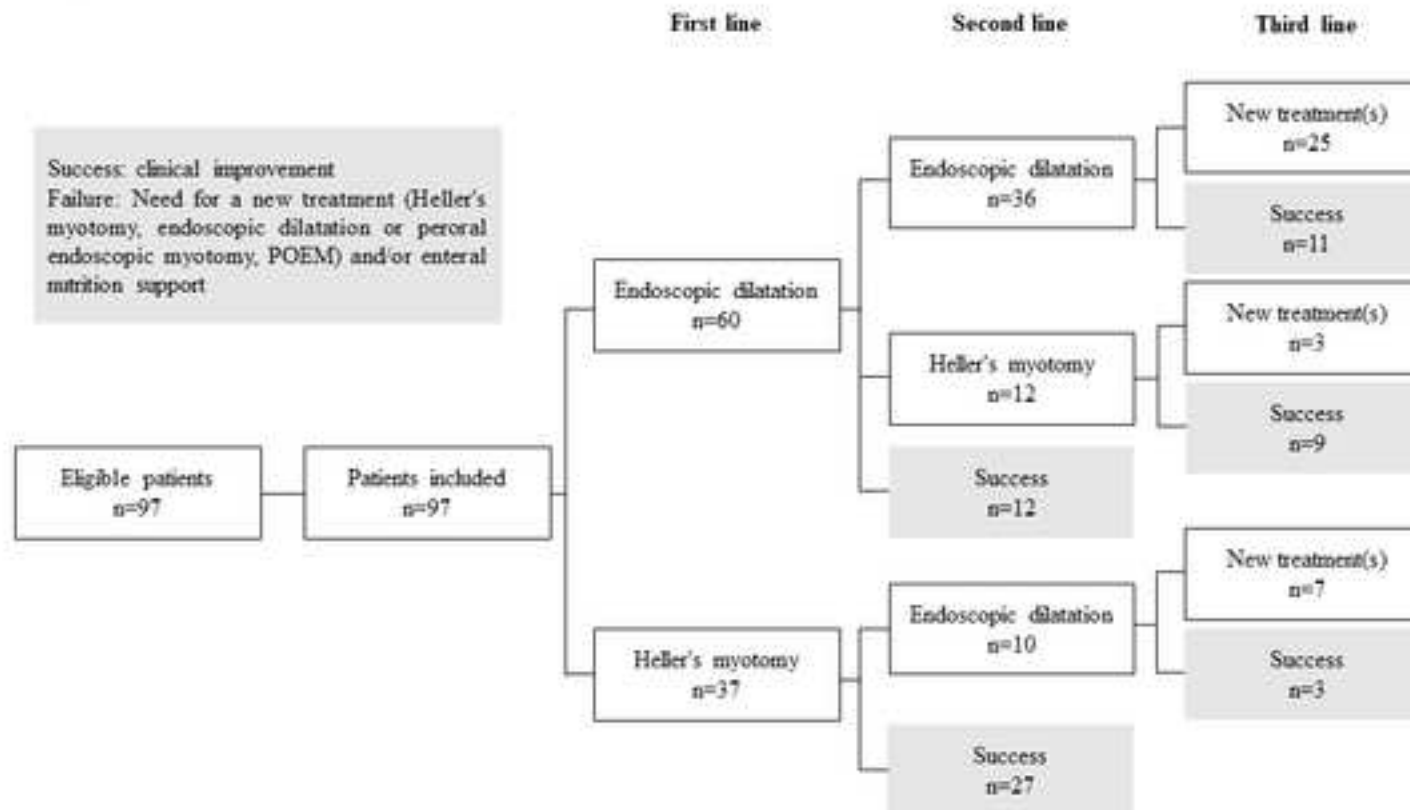


Figure 2. Survival curves after first-line treatment

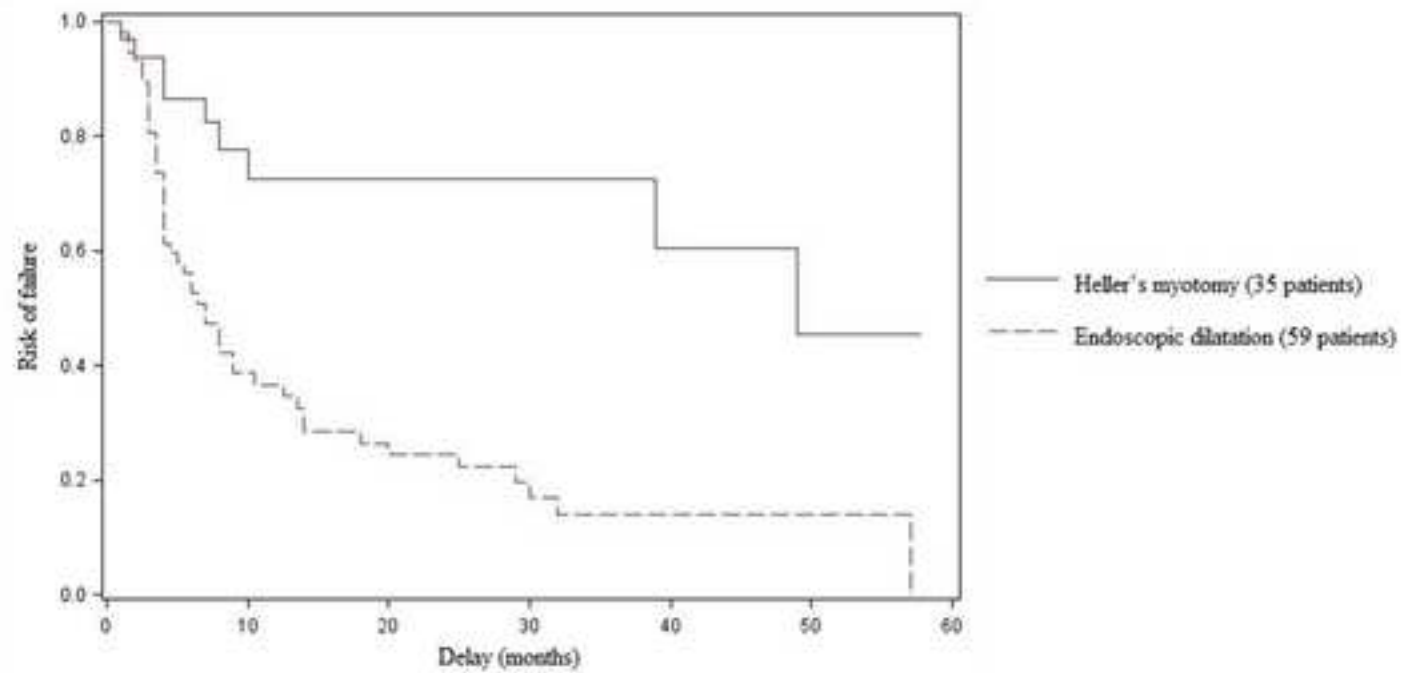


Table III. Early and late serious complications according to endoscopic dilatation or Heller Myotomy.

Complications	%Endoscopic dilatation (n=60)	%Heller Myotomy (n=37)	p-value
<i>Early complications</i>			N/A
Discontinuation of the operation	0	0	N/A
Conversion to laparotomy	0	1.9	N/A
In-process transfusion	0	0	N/A
Esophageal perforation	1.6	3.7	N/A
Gastric perforation	0	1.9	N/A
Cervical emphysema	0.8	0	N/A
Pneumomediastinum	0.8	3.7	N/A
<i>Late complications</i>			
Peritonitis	0	1.8	N/A
Esophageal fistula	0	1.8	N/A
Gastric volvulus with hiatus hernia	0	1.8	N/A

N/A: Not Applicable

Figure 3. Survival curves after first lines of treatment, hydrostatic dilatations excluded

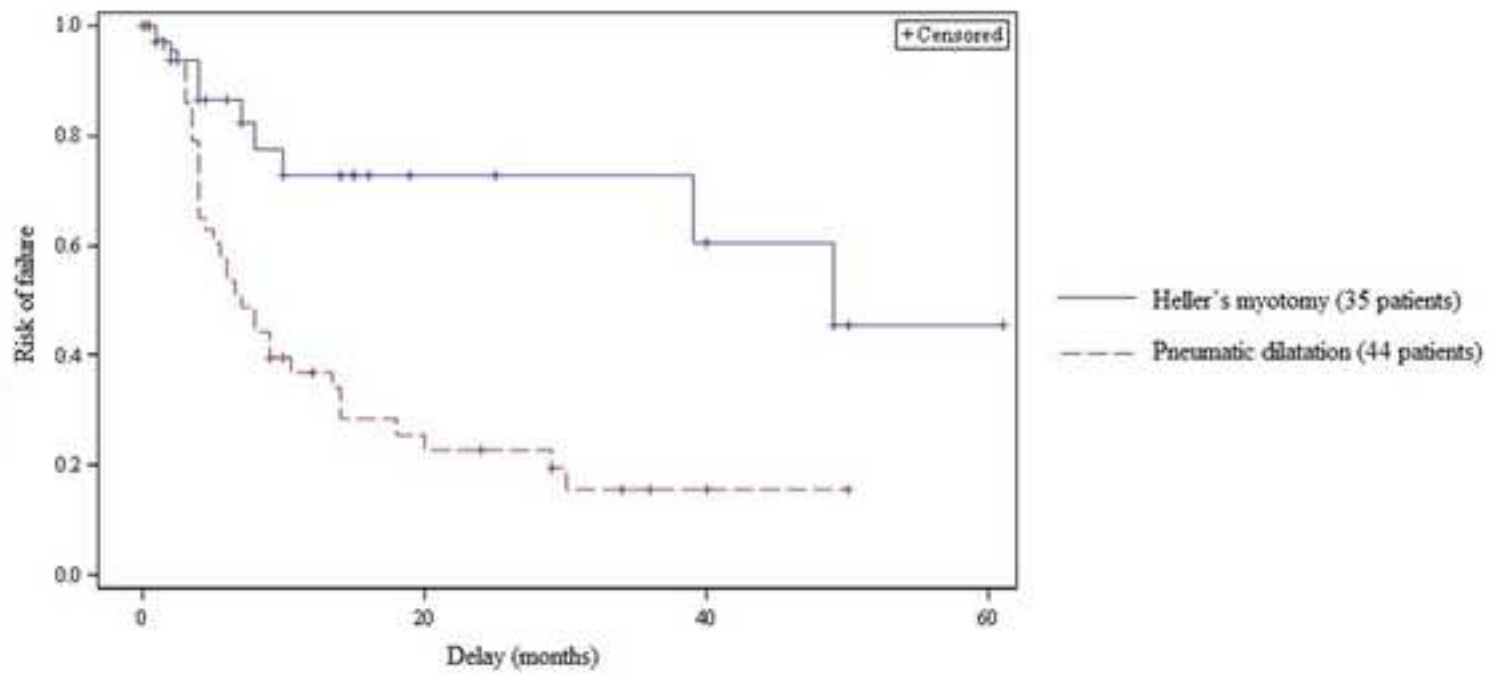


Figure 4. Survival curves after first-line treatment endoscopic dilatation

