CLINICAL—ALIMENTARY TRACT

Outcomes of Treatment for Achalasia Depend on Manometric Subtype

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this CME exercise, successful learners will be able to predict the clinical outcome of achalasia in view of the manometric subtype.

See Covering the Cover synopsis on page 664; see editorial on page 681.

BACKGROUND & AIMS: Patients with achalasia are treated with either pneumatic dilation (PD) or laparoscopic Heller myotomy (LHM), which have comparable rates of success. We evaluated whether manometric subtype was associated with response to treatment in a large population of patients treated with either PD or LHM (the European achalasia trial). **METHODS:** Esophageal pretreatment manometry data were collected from 176 patients who participated in the European achalasia trial. Symptoms (weight loss, dysphagia, retrosternal pain, and regurgitation) were assessed using the Eckardt score; treatment was considered successful if the Eckardt score was 3 or less. Manometric tracings were classified according to the 3 Chicago subtypes. **RESULTS:** Forty-four patients had achalasia type I (25%), 114 patients had achalasia type II (65%), and 18 patients had achalasia type III (10%). After a minimum follow-up period of 2 years, success rates were significantly higher among patients with type II achalasia (96%) than type I achalasia (81%; $P < .01$, log-rank test) or type III achalasia (66%; $P < .001$, log-rank test). The success rate of PD was significantly higher than that of LHM for patients with type II achalasia (100% vs 93%; $P < .05$), but LHM had a higher success rate than PD for patients with type III achalasia (86% vs 40%; $P = .12$, difference was not statistically significant because of the small number of patients). For type I achalasia, LHM and PD had similar rates of success (81% vs 85%; $P = .84$). **CONCLUSIONS: A higher percentage of patients with type II achalasia (based on manometric tracings) are treated successfully with PD or LHM than patients with types I and III achalasia. Success rates in type II are high for both treatment groups but significantly higher in the PD group. Patients with type III can probably best be treated by LHM. Trialregister.nl number NTR37; ISRCTN56304564.**

Keywords: Esophagus; Motility; Response to Therapy; Surgery.

Achalasia is a rare motility disorder of the esophagus characterized by the absence of peristalsis and a defective relaxation of the lower esophageal sphincter (LES) resulting in an impaired bolus transport and stasis of food in the esophagus.[1] Because its exact etiology still is unknown, current treatment options of achalasia are directed only at relieving the functional obstruction at the level of the LES and consist mainly of endoscopic pneumatic dilation (PD) and laparoscopic Heller myotomy (LHM).[2–6]

It generally is accepted that the loss of enteric neurons, in particular nitric oxide–releasing neurons, is responsible for the lack of peristalsis and impaired relaxation of the LES during swallowing.[1,7,8] Recently, 3 manometric subtypes were identified based on the residual esophageal wave pattern: type I, in which the esophageal body shows minimal contractility; type II, in which there is no peristalsis but intermittent periods of compartmentalized esophageal pressurization; and type III, in which there are spastic contractions in the distal esophagus (Figure 1).[9] Importantly, this study suggested that the efficacy of treatment, mainly consisting of PD, strongly varies depending on the manometric type. Success rates were indeed significantly higher for type II achalasia (96%) compared with type I (56%) and type III

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Abbreviations used in this paper: ANOVA, analysis of variance; HRM, high-resolution manometry; IQR, interquartile range; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; PD, pneumatic dilation.

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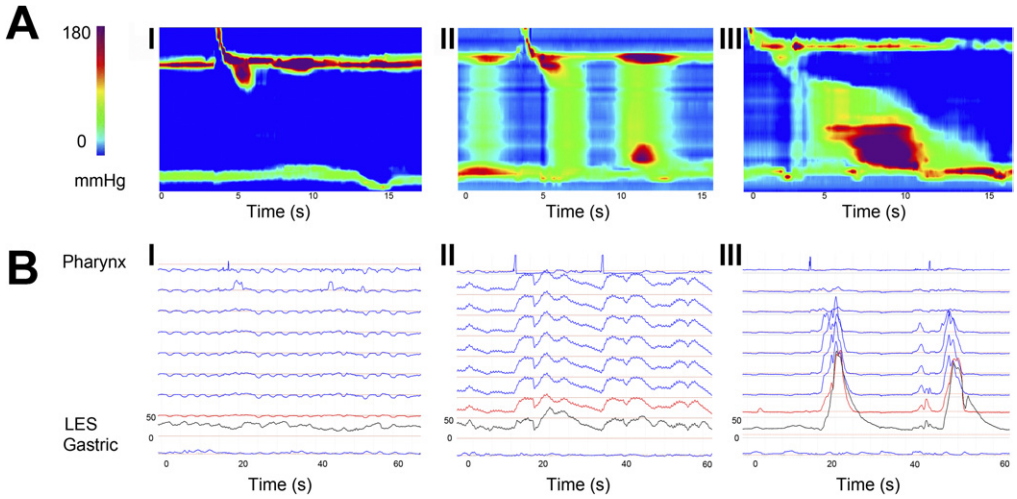

Figure 1. Based on the residual wave type on HRM, 3 subtypes of achalasia can be determined. (*A*) No distal pressurization is observed in type I (*AI*), whereas panesophageal pressurizations and spastic contractions are observed in type II (*AII*) and type III (*AIII*), respectively. (*B*) A similar classification can be made when conventional manometry is used. Note that pressure recordings in type II achalasia are similar in every line tracing, compatible with panesophageal pressurization.

(29%) achalasia. Also, in patients treated by LHM, differences in treatment success between the subtypes were confirmed, with success rates of 85%, 95%, and 70% for types I, II, and III, respectively.[9–11] However, these studies had a different definition of treatment success and patients were not followed up prospectively, making comparison between PD and LHM impossible.

Recently, the efficacy of PD and LHM was compared prospectively in a large European multicenter trial. More than 200 patients were included, randomized, and followed up for more than 2 years (mean follow-up period, 43 mo). This study showed that LHM was not superior to PD and revealed success rates of 85%–95% for both treatments.[12] Because esophageal manometry was performed in all patients before treatment, this data set ideally is suited to identify the impact of the manometric subtype on clinical outcome in both treatment arms in a prospective manner using the same criteria of treatment success. Therefore, we reviewed the tracings of the European Achalasia Trial to evaluate the following: (1) whether the manometric subtype indeed determines the success rate of treatment, (2) whether the subtype should dictate the choice of treatment, and (3) whether specific symptoms or functional data could explain the differences in success rates.

Materials and Methods

Patients

From February 2003 through February 2008 there were 201 patients with achalasia enrolled in the European Achalasia Trial.[12] Patients between 18 and 75 years of age were included at 14 hospitals in 5 European countries and randomized for PD or LHM. The diagnosis of achalasia was based on esophageal manometry showing the absence of peristalsis and impaired LES relaxation (nadir pressure of ≥10 mm Hg during swallow-induced relaxation). In addition, patients had to have an Eckhardt symptom score of more than 3. The Eckardt score (maximum score, 12) is the sum of the symptom scores for dysphagia, regurgitation, and chest pain (0, absent; 1, occasional; 2, daily; and 3, each meal), and weight loss (0, no weight loss; 1, <5 kg; 2, 5–10 kg; and 3, >10 kg). Patients with an esophageal diameter of more than 7 cm were excluded. The study was approved by the Medical Ethics Committee of the Academic Medical Center. Written informed consent was obtained from all subjects before enrolment in the study.

Study Design

Patients were randomized equally for LHM or PD and stratification was performed for hospital and age. The interventions were performed as described previously.[12] In short, for PD a Rigiflex balloon (Boston Scientific, Nanterre, France) was positioned at the esophagogastric junction and dilated with 5 psi for 1 minute, followed by 8 psi for 1 minute. During the first PD a 30-mm balloon was used, followed by dilation with a 35-mm balloon after 1–3 weeks. If 4 weeks later the Eckardt score still was greater than 3, a third dilation with a 40-mm balloon was performed. Patients were considered a failure if the Eckardt score remained greater than 3. Patients with recurrent symptoms during follow-up evaluation were re-dilated with a 35-mm balloon, and, if necessary (Eckardt score still >3), with a 40-mm balloon. A third and final series of dilations was allowed only if symptoms recurred at least 2 years after this second series of dilations.

In patients randomized for LHM, a myotomy was performed extending at least 6 cm over the esophagus above the junction and at least 1–1.5 cm over the stomach. Thereafter, an anterior 180° fundoplication according to Dor[13] was performed to reduce postoperative gastroesophageal reflux. If symptoms recurred after surgery with an Eckardt score greater than 3, the patient was considered to have had treatment failure.

Before treatment, esophageal manometry was performed for the diagnosis of achalasia and to determine LES pressure. Furthermore, a timed barium esophagogram was conducted to quantify esophageal stasis. After treatment, symptom scores were assessed and esophageal manometry and a timed barium esophagogram were performed after 1 month and on a yearly basis. Esophageal manometries were collected retrospectively to determine the type of achalasia. All authors had access to the study data and reviewed and approved the final manuscript.

Manometry

Esophageal manometry was performed using a pneumohydraulic perfusion system and a 6- to 10-channel esophageal manometry catheter with a sleeve sensor incorporated at the distal end. After introduction and equilibration, basal pressure was monitored for at least 5 minutes. LES pressure was determined end-expiratory. The esophageal pressure wave amplitude

was analyzed in the 2 channels above the LES. These sensors were located at 3 or 4 cm and at 6 or 8 cm above the LES, depending on the design of the manometric catheter used in the participating centers. Swallow-induced relaxation of the sphincter and esophageal pressure wave amplitude were assessed on 10 consecutive 5-mL wet swallows, at least 30 seconds apart.

Timed Barium Esophagogram

Esophageal stasis was determined on a timed barium esophagogram at 1, 2, and 5 minutes after ingestion of the maximal tolerable amount of low-density barium sulphate over 30–45 seconds without regurgitation or aspiration, with the patient upright in a slight left posterior position.[14] The distance from the tapered distal esophagus to the top of the barium column and the maximal diameter of the esophagus were measured.

Data Analysis

Manometric tracings were reviewed using MMS (Medical Measurements Systems, Enschede, The Netherlands), Medtronic (Medtronic, Minneapolis, MN), or Dynosystem (Memphis, Bologna, Italy) software by 2 reviewers (W.O.R. and R.S.).

We classified the study patients according to their dominant distal esophageal pressurization pattern using modified definitions by Pandolfino et al.[9] Type I achalasia was when 9 of 10 swallows elicited contractions with an amplitude less than 30 mm Hg; type 2 achalasia was when 2 or more contractions had an amplitude greater than 30 mm Hg; and type 3 achalasia was when at least 2 spastic waves were detected (lasting $>$ 6.0 s with an amplitude $>$ 70 mm Hg). These criteria were validated for conventional manometry by Salvador et al.[10]

Parameters of esophageal function (LES pressure, esophageal stasis after 5 minutes, and esophageal width on a timed barium esophagogram) were determined before therapy and at 1 month and yearly after therapy.

Statistical Analysis

Analysis was performed on the modified intention-to-treat population, as previously described.[12] All patients except those in whom a perforation occurred during PD (censored) or those who were lost to follow-up evaluation were included. Protocol violations were considered failures in the modified intention-to-treat analysis. Treatment success was defined as a decrease in Eckardt score to 3 or less, determined at yearly follow-up evaluation. The time to treatment failure was calculated from the day of surgery and the first dilation session until the closing visit or the last visit that was considered part of the follow-up period.

Data were analyzed using SPSS 16.0 (IBM Corporation, Somers, NY). Parametric data are presented as mean ± standard error of the mean, and nonparametric data are presented as median (interquartile range [IQR]). If 3 subtypes were compared, a 1-way analysis of variance (ANOVA) test was used in case of parametric data, and a Kruskal–Wallis test was used in case of nonparametric data. If there was a statistically significant difference a post hoc Student *t* test or a Mann–Whitney *U* test was performed with Bonferroni correction. To compare success rates, log-rank tests on Kaplan–Meier estimates were used. A Cox regression model was used to determine risk factors for treatment failure in the 3 subtypes. Repeated measurements of symptom scores and esophageal function after therapy were analyzed with a 2-way repeated-measurements ANOVA. In case of repeated measurement, data are presented as estimated means ± standard error of the mean. All *P* values were 2-tailed and a *P* value less than .05 was considered statistically significant.

Results

Patient Characteristics

In the present study, pretreatment manometries of 176 patients were available for analyses. Data from 25

Table 1. Patient Demographics, Symptom Scores, and Parameters of Esophageal Function, All Before Treatment

	Type I	Type II	Type III	*P* value
Number of patients, n (%)	44 (25)	114 (65)	18 (10)	
Age, *y*	44 ± 2.4	46 ± 1.4	49 ± 3.4	.43
Sex, n				.58
Male	25	65	8	
Female	19	49	10	
Treatment protocol, n				.76
PD	22	53	10	
LHM	22	61	8	
Symptoms				
Total Eckardt score	7.3 ± 0.28	7.1 ± 0.19	7.4 ± 0.49	.68
Chest pain	1 (1–1)	1 (0–1)	2 (1–2)[a]	<.01
Dysphagia	3 (3–3)	3 (3–3)	3 (3–3)	.81
Regurgitation	2 (1–2)	2 (1–3)	1 (1–3)	.74
Weight loss	2 (1–3)	1 (0–2)	1 (0–2)	.46
Esophageal function				
LES pressure, *mm Hg*	28 ± 2.3	31 ± 1.4	34 ± 5.3	.17
Mean distal esophageal pressure wave amplitude, *mm Hg*	17 ± 1.0	38 ± 1.7	81 ± 8.3	<.0001
Timed barium esophagogram–height of stasis, *cm*				
1 min	16 ± 1.1	14 ± 0.7	14 ± 1.6	.39
2 min	16 ± 1.1	13 ± 0.7	12 ± 1.6	.17
5 min	14 ± 1.1	12 ± 0.7	10 ± 1.7	.15
Esophageal width	4.5 ± 0.23	4.0 ± 0.12	3.1 ± 0.30	<.01

[a]$P < .05$ vs type I and $P < .01$ vs type II.

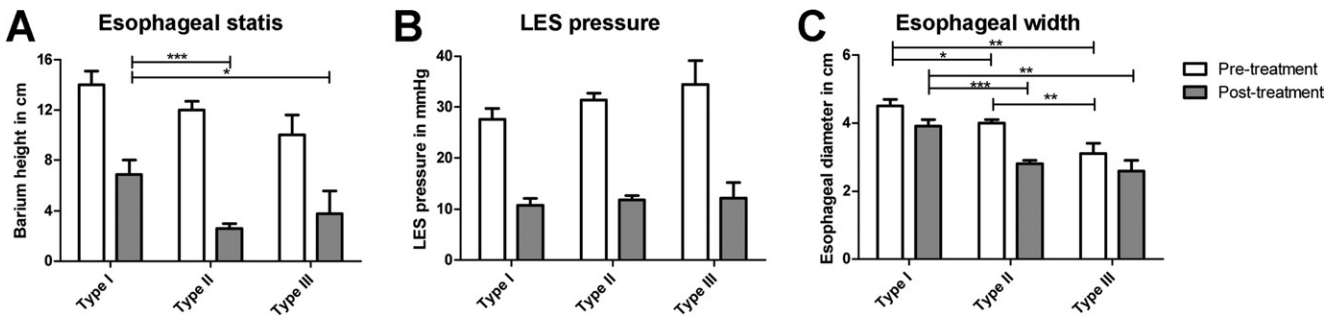

Figure 2. (*A*) Esophageal stasis, (*B*) LES pressure, and (*C*) esophageal width are shown for types I, II, and III before and after treatment. Data are presented as mean ± standard error of the mean and tested between the 3 subtypes before and after therapy separately, using a one-way ANOVA with a post hoc Student *t* test with Bonferroni correction in case of statistically significant differences. *$P < .05$, **$P < .01$, and ***$P < .001$.

patients (12%) could not be retrieved because of a change of recording system without a back-up (n = 10), inaccessible data files (n = 4), and because 2 centers did not participate in this substudy (n = 11).

Of the 176 patients included, 44 patients (25%) had achalasia type I, 114 patients (65%) had achalasia type II, and 18 patients (10%) had achalasia type III. No statistically significant differences in age and sex were observed between the 3 patient groups. Patients were distributed equally over the 2 treatment protocols (Table 1).

Pretreatment Eckhardt symptom scores were similar for all types, with mean values of 7.3 ± 0.3, 7.1 ± 0.2, and 7.4 ± 0.5 for types I, II, and II, respectively. Type III achalasia patients had a significantly higher median chest pain score of 2 (IQR, 1–2) compared with type I achalasia patients (median, 1; IQR, 1–1; $P = .03$) and type II achalasia patients (median, 1; IQR, 0–1; $P < .01$). Other symptoms (dysphagia, regurgitation, and weight loss) were similar in the 3 treatment groups.

Before treatment, LES pressure and the height of the barium column (assessed after 5 minutes) were comparable in the 3 treatment groups (Figure 2). The mean amplitude measured by the pressure sensors in the distal esophagus during wet swallows was higher in type III achalasia, compared with type I ($P < .001$) and type II ($P < .001$). Finally, esophageal width was significantly larger in type I patients (4.5 ± 0.23 cm) compared with type II (4.0 ± 0.12 cm; $P = .02$) and type III patients (3.1 ± 0.30 cm; $P < .001$).

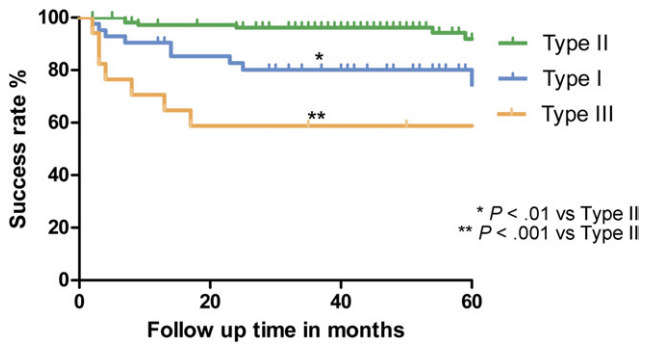

Figure 3. Type II achalasia has a higher success rate compared with type I achalasia ($P < .01$) and type III achalasia ($P < .001$), as shown in a Kaplan–Meier curve.

Treatment Success

Irrespective of treatment arm, success rate after a mean follow-up period of 43 months (IQR, 29–62 mo) was significantly higher in patients with type II compared with type I ($P < .01$, log-rank) and type III ($P < .001$, log-rank) (Figure 3). After 2 years of follow-up evaluation, the success rates were 81%, 96%, and 66% for types I, II, and III, respectively. In comparison with type II, type I (hazard ratio, 4.0; 95% confidence interval, 1.5–11) and type III (hazard ratio, 6.8; 95% confidence interval, 2.3–20) were highly predictive of treatment failure in a Cox regression analysis model.

Subsequently, we compared treatment success rates of PD with that of LHM for the different manometric subtypes. For type I, no significant difference in success rate between PD (n = 22) and LHM (n = 22) was observed at the end of the entire follow-up period (mean, 43 mo; $P = .84$, log-rank) or after 2 years (81% vs 85% for LHM and PD, respectively) (Figure 4). In contrast, in type II, the success rate for PD (n = 53) was significantly higher than that of LHM (n = 61) ($P = .03$, log-rank), with 100% treatment success in the PD group, compared with 93% in the LHM group after 2 years (Figure 4). To achieve this success rate, 7 patients (13%) in the PD group needed redilation. The largest difference in success rates was observed in type III, with success rates of 86% and 40% for LHM (n = 8) and PD (n = 10), respectively (Figure 4). However, because of the low number of patients in this subgroup, this difference was not statistically significant ($P = .12$, log-rank).

Symptom Control and Esophageal Function After Treatment

To identify the symptoms contributing to the differences in success rate, we compared individual symptom scores during the follow-up period. The dysphagia score of type I and III patients was significantly higher compared with type II patients ($P = .03$ and $P = .001$, respectively) (Table 2). Yet, dysphagia was the main symptom in all 3 subgroups. In contrast, chest pain and regurgitation

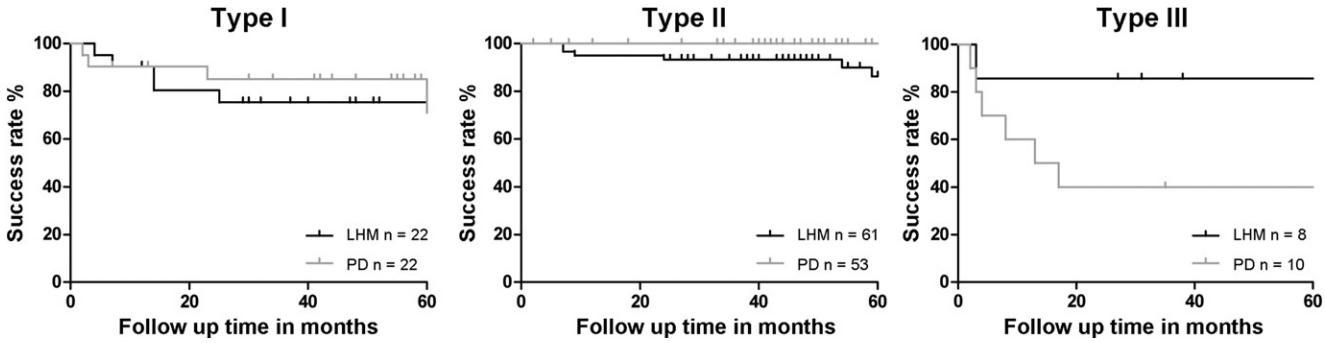

Figure 4. Kaplan–Meier curves comparing PD and LHM are shown for the 3 subtypes for up to 60 months after treatment. Success rates are comparable in type I achalasia ($P = .84$). Pneumodilation has a significantly higher success rate in type II achalasia ($P = .03$). Success rates, however, are high for both treatments. In type III patients the largest difference is observed, which, however, is not statistically significant ($P = .12$).

scores in type III patients were higher compared with type I and II patients (chest pain: $P < .01$ and $P < .001$; regurgitation; $P < .05$ and $P < .01$). Weight loss was uncommon in all subtypes after therapy and therefore no differences were observed between the 3 types. These data indicate that the main persisting symptom in all 3 subtypes was dysphagia, whereas mainly chest pain and regurgitation were reported more frequently by type III patients.

Assuming that symptoms are generated by impaired emptying and/or dilation of the esophagus, we anticipated that the height and/width of the contrast column on timed barium esophagogram would be higher in type III patients. Surprisingly, esophageal stasis and width in type III patients were comparable with those in type II patients. In contrast, barium height was highest in type I achalasia (6.2 ± 0.74 cm) and significantly higher compared with type II (3.1 ± 0.33; $P < .001$) and type III (4.0 ± 1.1; $P < .05$). In addition, type I patients had a significantly wider esophagus compared with patients with type II (3.6 ± 0.21 cm vs 2.8 ± 0.10 cm; $P < .001$) (Figure 2). No differences were observed between the subgroups with respect to LES pressure after treatment.

Comparing PD with LHM, we found that type III patients treated by PD did have significantly more esophageal stasis compared with type III patients treated by LHM (6.2 ± 2.1 cm vs 1.1 ± 1.1 cm; $P < .05$) (Figure 5). Moreover, there is a trend for a larger esophageal width (3.1 ± 0.54 cm vs 1.9 ± 0.20 cm; $P = .06$) and a higher LES pressure (17 ± 4.1 mm Hg vs 9.0 ± 3.2 mm Hg; $P = .12$) in patients treated with PD compared with patients treated by LHM. In line with this, patients who underwent PD had a significantly higher dysphagia score (1.6 ± 0.3 vs 0.7 ± 0.4; $P < .05$) whereas the regurgitation score (0.7 ± 0.3 vs 0.1 ± 0.1; $P = .07$) tended to be higher compared with patients after LHM. Chest pain was similar after PD and LHM (1.1 ± 0.3 vs 0.6 ± 0.2; $P = .20$).

Table 2. Total and Individual Symptom Scores After Treatment

Symptoms	Type I	Type II	Type III	*P* value
Total Eckardt score	1.6 ± 0.2	1.2 ± 0.1	2.8 ± 0.6	<.001
Chest pain	0.4 ± 0.1	0.4 ± 0.1	0.9 ± 0.2	<.001
Dysphagia	1.0 ± 0.1	0.7 ± 0.1	1.3 ± 0.2	<.001
Regurgitation	0.2 ± 0.2	0.1 ± 0.02	0.5 ± 0.2	<.01
Weight loss	0.04 ± 0.02	0.03 ± 0.02	0.1 ± 0.04	.47

NOTE. Type III patients have higher chest pain and regurgitation scores compared with type I and type II patients, whereas dysphagia is reported more frequently in type I and type III patients compared with type II patients. Weight loss is an infrequently reported symptom in all types.

Evolution of Subtypes After Treatment

It is hypothesized that the 3 types of achalasia represent a different stage of achalasia.[9,15] To define the course of the subtypes after treatment, we collected 397 post-treatment manometries from 107 patients (median, 2 post-treatment manometries; range, 1–8 post-treatment manometries). During the follow-up period, the mean contraction amplitude remained the lowest in type I patients (type I, 17 ± 0.9 mm Hg; type II, 37 ± 1.5 mm Hg; and type III, 78 ± 7.6 mm Hg; $P < .0001$, 1-way ANOVA). After therapy, most patients with type I achalasia were classified as having absent peristalsis (n = 16; 89%), whereas simultaneous contractions (with an amplitude of >30 mm Hg) were observed in 11% of patients (n = 2), classified as having esophageal spasm in the context of treated achalasia. In contrast, in patients with type II achalasia, only 7% of patients were classified as having absent peristalsis. In these patients this pattern was observed starting after a mean of 2.6 years after treatment. Spastic or simultaneous contractions were observed in follow-up manometries in 83% of type II patients, and weak peristalsis was observed in follow-up manometries in 10% of patients. All type III patients were classified as having esophageal spasms during the entire follow-up period.

Discussion

Different success rates have been reported for the 3 manometric subtypes of achalasia, suggesting that classification by manometry may be useful to determine the treatment of choice.[9–11] In the present study we confirmed that the manometric subtype is indeed an important

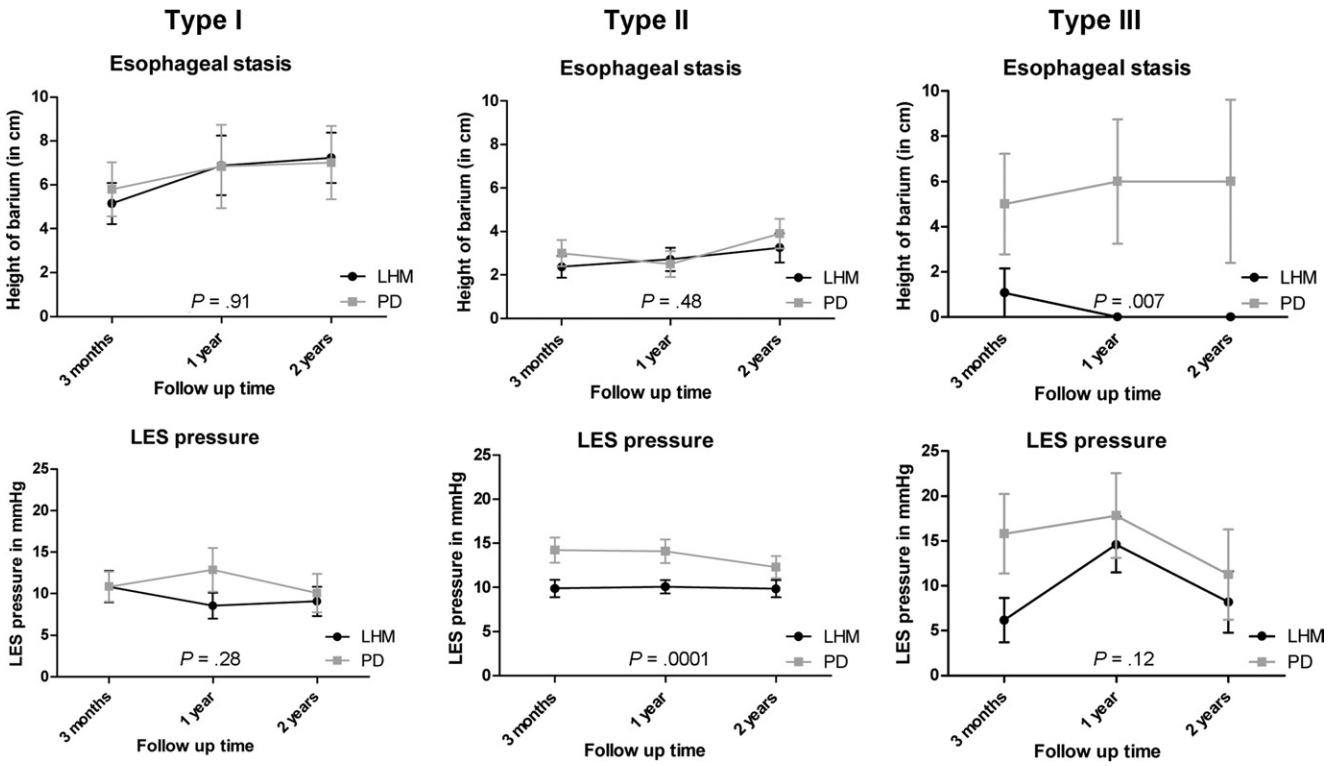

Figure 5. Esophageal stasis and LES pressure are shown for PD and LHM in the 3 subtypes for 3 months, 1 year, and 2 years after treatment. Data are tested using a 2-way ANOVA. Patients with type III achalasia treated by PD have significantly more stasis compared with patients with type II achalasia during 2 years of follow-up evaluation.

determinant of clinical success, with type I and especially type III achalasia having an increased odds rate for treatment failure compared with type II. The main symptoms for treatment failure are dysphagia in type I, and dysphagia, chest pain, and regurgitation in type III. Of note, type I and II patients, representing the majority (90%) of achalasia patients, had an excellent response to both LHM and PD during a mean follow-up period of 43 months, with only a small difference in success rate between PD and LHM in type II patients (100% vs 93%, respectively). Mainly patients with type III have an impaired response rate to PD, but because of the small patient number, there was no significant difference compared with LHM. Based on our current data, we conclude that achalasia subtyping is clinically helpful to estimate the success rate irrespective of the treatment (LHM or PD) used, but may prove relevant only to determine the most optimal treatment option in type III patients.

In achalasia, substantial variability in residual esophageal pressure patterns and dynamics is observed using high-resolution manometry. Based on the residual dominant distal esophageal pressurization pattern, Pandolfino et al[9] classified achalasia into 3 types (type I, no pressurization; type II, panesophageal pressurization; and type III, rapidly propagating contractions). Interestingly, after a follow-up period of at least 1 year, the treatment success rate of type II patients (96%) was significantly higher compared with type I (56%) and type III (29%) patients. Moreover, the number of interventions (PD, LHM, and Botox combined) was twice as high in type III compared with type II patients, suggesting that patients with type II respond better to treatment. Because of the low number, no comparison could be made between the different treatments used. In the same line, Salvador et al[10] reported better clinical response to LHM (n = 246) for type II patients (success rates of type I: 85%, 82 of 96; type II: 95%, 121 of 127; and type III: 70%, 16 of 23; $P = .0007$). Although the follow-up period in our study was longer (median, 43 mo) compared with the previous 2 studies (range, 6–31 mo), our results are largely comparable, confirming that the highest success rate was observed in type II achalasia (96% after 2 years) compared with type I (81%; $P < .01$) and type III (66%; $P < .001$). Also, in a Cox regression analysis model, type I and type III were identified as risk factors for treatment failure with a hazard ratio of 4.0 and 6.8, respectively. Taken together, we confirmed that type I and in particular type III achalasia are important predictors of treatment failure.

In this study we provide more insight into the functional differences and the symptoms underlying treatment failure in the different subtypes. Chest pain scores before as well as after treatment are higher in patients with type III achalasia compared with types I and II. Although chest pain has been shown repeatedly to be an independent predictor of therapeutic failure, the mechanisms leading to this symptom are incompletely understood.[3,12] It is hypothesized that chest pain is evoked mainly by high-amplitude esophageal contractions rather

than esophageal widening.[9] Our data are in line with this hypothesis because type III patients have the narrowest esophagus and the highest contraction amplitude, associated with the highest chest pain score. It also should be noted, however, that patients with type III achalasia reported more symptoms of dysphagia and regurgitation than patients with types I and II. Patients with type I achalasia had a higher dysphagia score after treatment compared with patients with type II achalasia. The higher dysphagia score was associated with impaired esophageal emptying on timed barium esophagogram in type I patients. Moreover, type I patients had a significantly wider esophagus. Esophageal stasis and a wide esophagus have been identified as risk factors for treatment failure in multiple earlier studies.[3,16,17] For instance, Vaezi et al[16] showed that 90% of patients with persistent stasis but without symptoms failed therapy within 1 year after initial treatment. Furthermore, Zaninotto et al showed that a wider esophagus is an important risk factor for treatment failure in a large study with patients treated by LHM.[18] Combined high-resolution manometry (HRM) and impedance measurements have shown that esophageal emptying in achalasia mainly occurs during panesophageal pressurizations.[15] The absence of esophageal pressurization in type I achalasia therefore might explain differences in esophageal stasis levels and thereby contribute to higher dysphagia scores and impaired success rates.

Accepting that the manometric subtype is indeed an important predictor of clinical success, the main clinical question that remains is to what extent the choice of treatment (ie, PD or LHM) can be guided by the manometric subtype. For this purpose, we compared success rates for PD and LHM in the 3 subtypes. For type I achalasia, LHM and PD had similar success rates (81% vs 85%, respectively), whereas only a small difference was observed for type II achalasia (93% vs 100% for LHM and PD, respectively). Of note, our success rates for LHM were comparable with those reported previously, however, we obtained higher success rates in patients with type I undergoing PD (56%–63% vs 85%).[9,11] One explanation could be the fact that patients with mega-esophagus (esophageal diameter, >7 cm), known to be more difficult to treat and to present with type I achalasia, were excluded from our study.[9,10,18] It should be emphasized, however, that only one patient was excluded in our series based on this criterion. Alternatively, this difference may be explained by the more rigorous distension protocol we used, our protocol allowed redilation during the first years of follow-up evaluation, which was performed in 7 type I patient (23%) and 5 type II patients (13%). Based on our findings, we conclude that when a graded distension protocol allowing redilation is used, PD and LHM are both appropriate treatment options for type I and type II achalasia, at least until longer follow-up data are available.[19,20]

The largest difference was observed in type III patients, in whom the success rate after LHM was higher than after PD (86% vs 40%, respectively). Because of the small patient number (n = 18), this difference was not statistically significant ($P = .12$). The success rates are in line with the available literature (LHM of 70% vs PD of 33%–38%), although the number of patients with type III achalasia in previous studies is rather small as well (47 in total: 14 PD, 24 LHM, and 9 Botox).[9–11] It was interesting to note that dysphagia was especially high in type III patients treated with PD, a finding that was associated with impaired emptying and a wider esophagus. As shown by Pandolfino et al,[9] type III patients have a functional obstruction not only encompassing the esophagogastric junction but also the distal smooth muscle segment of the esophagus.[10] In the European Achalasia Trial, the myotomy was extended 6 cm above the esophagogastric junction, which may account for the differences in esophageal emptying, dysphagia, and regurgitation, and thereby to the higher success rates compared with PD. Therefore, in combination with the large difference in success rates both in our study and in the literature, we suggest that LHM may be the preferred treatment option in type III patients. Still, an additional study focusing on patients with type III achalasia seems indicated. Because of the very limited incidence of type III achalasia, additional studies probably need to be performed in multicenter studies to provide sufficient patient numbers.

The strength of our study is the prospective randomized trial design and the relatively large number of patients. In 12 centers in 5 European countries, patients were randomized and evaluated in a regular follow-up protocol with validated and objective outcome measures, both symptoms as well as functional outcome measures. As a result, we were able to compare the effect of the 2 standard treatments in 3 different manometric subtypes. In addition, this study provided more insight in functional differences and symptoms of treatment failure in the different subtypes. A possible limitation of our study was the use of conventional manometry instead of HRM, for which the classification was designed. However, during the initiation of the study in 2003, HRM was not available in the participating centers, and diagnosis was based on conventional manometry with a sleeve sensor. Of note, Salvador et al[10] reported 100% agreement between the classification of subtypes based on conventional pressure line tracings vs HRM plots. Although classification of subtypes based on conventional pressure line tracings might be less precise than the sophisticated HRM-based classification, our 3 patient groups were similar to those reported by Pandolfino et al,[9] in terms of both clinical features and outcome after therapy. Therefore, we are confident that our conclusions are of clinical significance.

In conclusion, achalasia types I and III are important predictors of treatment failure compared with type II, and therefore achalasia subtyping is useful to determine the risk for treatment failure. Success rates in types I and II are high for both treatment groups, whereas patients with type III have an impaired treatment response, primarily after PD. This implies that patients with type III achalasia may better be treated by LHM, or be included in a more rigorous follow-up protocol.

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Conflicts of interest

The authors disclose no conflicts.

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