Reflux disease and achalasia: Failure of the gatekeeper

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Chapter 10
Outcomes of Treatment for Achalasia depend on Manometric Subtype

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ABSTRACT

Background and aims: Achalasia is currently treated by pneumatic dilation (PD) or laparoscopic Heller myotomy (LHM) with comparable success rates. Recently, a new subtype classification for achalasia has been described associated with different response to treatment. In this study we evaluated the impact of the manometric subtype on therapeutic success in a large study population randomized to PD or LHM (i.e. the European achalasia trial).

Methods: Esophageal pre-treatment manometries were collected from patients included in the European achalasia trial. Symptoms (weight loss, dysphagia, retrosternal pain and regurgitation) were assessed using the Eckardt score, and treatment was considered successful if the Eckardt score ≤ 3. Manometric tracings were classified into the three types according to the Chicago classification.

Results: Manometric tracings of 176 of the 201 randomised patients could be collected and analyzed. Type I, II and III achalasia were observed in 44 (25%), 114 (65%) and 18 (10%) patients respectively. After a minimum follow-up of two years, success rates were significantly higher in patients with type II (96%), compared to type I (81%, \( p<0.01 \) log-rank) and type III achalasia (66%, \( p<0.001 \), log-rank). Treatment success of PD was significantly higher in type II achalasia compared to LHM (100% vs. 93%, \( p<0.05 \)). In type III patients the success rate after LHM was higher than after PD (86% vs. 40%), however, due to the small patient number, statistical significance was not reached \( (p=0.12) \). For type I achalasia, LHM and PD had similar success rates (81% vs. 85%, \( p=0.84 \)).

Conclusion: Achalasia types I and III are important predictors of treatment failure compared to type II. 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.
INTRODUCTION

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. As its exact etiology is still unknown, current treatment options of achalasia are only directed at relieving the functional obstruction at the level of the LES and consist mainly of endoscopic pneumatic dilation (PD) and laparoscopic Heller myotomy (LHM).

Recently, three manometric subtypes were identified based on the residual esophageal wave pattern: Type I, in which the esophageal body exhibits 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. 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 to type I (56%) and type III (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 type I, II and III respectively. However, these studies had a different definition of treatment success and patients were not followed up prospectively, making comparison between PD and LHM impossible.

Figure 1 | Based on the residual wave type on high resolution manometry, 3 subtypes of achalasia can be determined. No distal pressurisation is observed in type I (AI), whereas panesophageal pressurisations and spastic contractions are observed in type II (AII) and type III (AIII) respectively. As demonstrated in figure 1B 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 pressurisation.
Recently, the efficacy of PD and LHM was compared prospectively in a large European multi-centre trial. More than 200 patients were included, randomized and followed up for more than two years (mean follow-up of 43 months). This study showed that LHM was not superior to PD and revealed success rates of 85-95% for both treatments. As esophageal manometry was performed in all patients prior to treatment, this data set is ideally 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 (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.

METHODS

Patients
From February 2003 through February 2008 201 patients with achalasia were enrolled in the European Achalasia Trial. 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 absence of peristalsis and impaired LES relaxation (nadir pressure > 10 mmHg 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, 3 = each meal) and weight loss (0 = no weight loss, 1 = < 5 kg, 2 = 5-10 kg, 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 equally randomized for LHM or PD and stratification was performed for hospital and age. The interventions were performed as described previously. In short, for PD a Rigiflex® balloon (Boston Scientific, Nanterre, France) was positioned at the esophagogastric junction and dilated with 5 PSI during 1 min, followed by 8 PSI during 1 min. During the first PD a 30 mm balloon was used, followed by dilation with a 35 mm balloon after 1 to 3 weeks. If 4 weeks later the Eckardt score was still over 3, a third dilation with a 40 mm balloon was performed. Patients were considered a failure if the Eckardt score remained over 3. Patients with recurrent symptoms during follow up were re-dilated with a 35 mm and if necessary (Eckardt score still >3) with a 40 mm balloon. A third and final series of dilations was only allowed 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 degree fundoplication according to Dor was performed to reduce postoperative gastroesophageal reflux. If symptoms recurred after surgery with an Eckardt score > 3, the patient was considered a failure.

Prior to 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 timed barium esophagogram were performed after 1 month and on a yearly basis. Esophageal manometries were retrospectively collected 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 6-10 channel esophageal manometry catheter with a sleeve sensor incorporated at the distal end. After introduction and equilibration, basal pressure was monitored during at least 5 minutes. LES pressure was determined end-expiratory. The esophageal pressure wave amplitude was analysed in the two channels above the LES. These sensors were located at 3 or 4 cm and at 6 or 8 cm above the LES respectively, depending on the design of the manometric catheter used in the participating centres. Swallow-induced relaxation of the sphincter and esophageal pressure wave amplitude are assessed on 10 consecutive 5 ml wet swallows, at least 30 s apart.

**Timed barium esophagogram**

Esophageal stasis was determined on a timed barium esophagogram 1, 2 and 5 minutes after ingestion of the maximal tolerable amount of low density barium sulphate over 30-45 s without regurgitation or aspiration, with the patient upright in a slight left posterior position. 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, USA) or Dynosystem (Memphis, Bologna, Italy) software by two reviewers (WR and RS). We classified the study patients according to their dominant distal esophageal pressurization pattern using modified definitions from Pandolfino et al. 9: Type I achalasia when 9/10 swallows elicited contractions with an amplitude < 30 mm Hg; Type 2 when 2 or more contractions had an amplitude > 30 mm Hg; and Type 3 when at least two spastic waves were detected (lasting > 6.0 sec with an amplitude > 70 mm Hg). These criteria
have been validated for conventional manometry by Salvador et al. Parameters of esophageal function (lower esophageal sphincter pressure, esophageal stasis after 5 minutes and esophageal width on a timed barium esophagogram) were determined before therapy and at 1 months and yearly after therapy.

**Statistical analysis**

Analysis was performed on the modified intention to treat population, as previously described. All patients except those in whom a perforation occurred during PD (censored) or those who were lost to follow up were included. Protocol violations were considered failures in the modified intention-to-treat analysis. Treatment success was defined as drop in Eckardt score to ≤ 3, determined at yearly follow up. (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 patients were still in follow-up.) Data were analysed using SPSS 16.0 (IBM corporation, Somers, NY, United States). Continuous variables are presented as means ± SEM, and non-parametric as median (IQR). If three subtypes were compared, a one-way ANOVA test was used in case of parametric data, and a Kruskal-Wallis test in case of non-parametric data. If there was a statistically significant difference a post-hoc Student’s 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 three subtypes. Repeated measurements of symptom scores and esophageal function after therapy were analysed with a 2-way repeated ANOVA. In case of repeated measurement, data are presented as estimated means ± SEM. All p-values were two-tailed and a p-value <0.05 was considered as statistically significant.

**RESULTS**

**Patient characteristics**

In the present study, pre-treatment manometries of 176 patients were available for analyses. Data of 25 patients (12%) could not be retrieved due to a change of recording system without backup (n = 10), inaccessible data files (n = 4), two centres not participating in this substudy (n = 11). Of the 176 patients included, 44 patients (25%) had achalasia type I, 114 (65%) type II and 18 (10%) type III. No statistically significant differences in age and sex were observed between the three patient groups. Patients were equally distributed over the two treatment protocols. (Table 1.)
| Treatment outcome depends on manometric subtype | CHAPTER 10 |

| Table 1 demonstrates patient demographics, symptom scores and parameters of esophageal function, all before treatment. # \( p < 0.05 \) vs type I and \( p < 0.01 \) vs type II. |

Pre-treatment Eckardt 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 type I, II and III respectively. Type III achalasia patients had a significantly higher median chest pain score of 2 (IQR 1-2) compared to type I (median 1 (IQR 1-1) \( p = 0.03 \)) and type II patients (median 1 (IQR 0-1) \( p < 0.01 \)). Other symptoms (dysphagia, regurgitation and weight loss) were similar in the 3 treatment groups. Prior to treatment, LES pressure and the height of the barium column (assessed after 5 minutes) were comparable in the three 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 to type I (\( p < 0.001 \)) and type II (\( p < 0.001 \)). Lastly, esophageal width was significantly larger in type I patients (4.5 ± 0.23 cm) compared to type II (4.0 ± 0.12 cm, \( p = 0.02 \)) and type III (3.1 ± 0.30 cm, \( p < 0.001 \)).

<table>
<thead>
<tr>
<th>Number of patients (no.%)</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44 ± 2.4</td>
<td>46 ± 1.4</td>
<td>49 ± 3.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Sex (no.)</td>
<td>25</td>
<td>65</td>
<td>8</td>
<td>0.58</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>49</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Treatment protocol (no.)</td>
<td>0.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>22</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>LHM</td>
<td>22</td>
<td>61</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Eckardt score</td>
<td>7.3 ± 0.28</td>
<td>7.1 ± 0.19</td>
<td>7.4 ± 0.49</td>
<td>0.68</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (1-1)</td>
<td>1 (0-1)</td>
<td>2 (1-2) *</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3 (3-3)</td>
<td>3 (3-3)</td>
<td>3 (3-3)</td>
<td>0.81</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>2 (1-2)</td>
<td>2 (1-3)</td>
<td>1 (1-3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (1-2)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
<td>0.46</td>
</tr>
<tr>
<td>Esophageal function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LES pressure (mmHg)</td>
<td>28 ± 2.3</td>
<td>31 ± 1.4</td>
<td>34 ± 5.3</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean distal esophageal pressure wave amplitude (mmHg)</td>
<td>17 ± 1.0</td>
<td>38 ± 1.7</td>
<td>81 ± 8.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Timed barium esophagogram – Height of stasis (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>16 ± 1.1</td>
<td>14 ± 0.7</td>
<td>14 ± 1.6</td>
<td>0.39</td>
</tr>
<tr>
<td>2 min</td>
<td>16 ± 1.1</td>
<td>13 ± 0.7</td>
<td>12 ± 1.6</td>
<td>0.17</td>
</tr>
<tr>
<td>5 min</td>
<td>14 ± 1.1</td>
<td>12 ± 0.7</td>
<td>10 ± 1.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Esophageal width</td>
<td>4.5 ± 0.23</td>
<td>4.0 ± 0.12</td>
<td>3.1 ± 0.30</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 1
Figure 2 | Esophageal stasis, LES pressure and esophageal width are demonstrated for Type I, II and III before and after treatment. Data are presented as mean ± SEM and tested between the three subtypes before and after therapy separately, using a one-way ANOVA with a post-hoc Student’s t-test with Bonferroni correction in case of statistically significant differences. * P<0.05  ** P<0.01 ***P<0.001

Figure 3 | Type II achalasia has a higher success rate compared to type I achalasia (p<0.01) and type III achalasia (p<0.001), as demonstrated in a Kaplan Meier curve.

Figure 4 | Kaplan Meier curves comparing PD and LHM are shown for the three subtypes for up to 60 months after treatment. Success rates are comparable in type I achalasia (p=0.84). Pneumodilation has a significantly higher success rate in type II achalasia (p=0.03). Success rates are however high for both treatments. In type III patients the largest difference is observed, which is however not statistically significant (p=0.12).
Treatment outcome depends on manometric subtype

Irrespective of treatment arm, success rate after a mean follow up of 43 (IQR 29-62) months was significantly higher in patients with type II compared to type I (p<0.01 log-rank) and type III (p<0.001, log-rank). (Figure 3.) After 2 years of follow up, the success rates were 81%, 96% and 66% for type I, II and III respectively. In comparison to type II, type I (HR 4.0 95% CI 1.5-11) and type III (HR 6.8 95% CI 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 months, p=0.84, log-rank) or after two 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=0.03, log-rank), with 100% treatment success in the PD group, compared to 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 is observed in type III, with success rates of 86% and 40% for LHM (n = 8) and PD (n = 10) respectively (Figure 4). However, due to the low number of patients in this subgroup, this difference is not statistically significant (p=0.12, 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 follow up. The dysphagia score of type I and III patients was significantly higher compared to type II patients (p<0.03 and p<0.001 respectively) (Table 2). Yet, dysphagia was the main symptom in all three subgroups. In contrast, chest pain and regurgitation scores in type III patients were higher compared to type I and II patients (Chest pain: p<0.01 and p<0.001; Regurgitation: p<0.05 and p<0.01). 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 three subtypes was dysphagia, whereas mainly chest pain and regurgitation were more frequently reported by type III patients.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Eckardt score</td>
<td>1.6 ± 0.2</td>
<td>1.2 ± 0.1</td>
<td>2.8 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.4 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.9 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1.0 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>0.2 ± 0.2</td>
<td>0.1 ± 0.02</td>
<td>0.5 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.04 ± 0.02</td>
<td>0.03 ± 0.02</td>
<td>0.1 ± 0.04</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Table 2 | Total and individual symptom scores after treatment. Type III patients have higher chest pain and regurgitation scores compared to type I and type II patients, while dysphagia is more frequently reported in type I and type III patients compared to type II patients. Weight loss is an infrequently reported symptom in all types.
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 to those in type II patients. In contrast, barium height was highest in type I achalasia (6.2 ± 0.74 cm) and significantly higher compared to type II (3.1 ± 0.33 p<0.001) and type III (4.0 ± 1.1 p<0.05). In addition, type I patients had a significantly wider esophagus compared to patients with type II (3.6 ± 0.21 cm vs. 2.8 ± 0.10 cm, p<0.001). (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 to type III patients treated by LHM (6.2 ± 2.1 cm vs. 1.1 ± 1.1 cm, p<0.05). (Figure 5.) Moreover, there is a trend for a larger esophageal width (3.1 ± 0.54 cm vs. 1.9 ± 0.20 cm, p=0.06) and a higher LES pressure (17 ± 4.1 mmHg vs. 9.0 ± 3.2 mmHg, p=0.12) in patients treated with PD compared to patients treated by LHM. In line with this, patients that underwent PD had a significantly higher dysphagia score (1.6 ± 0.3 vs. 0.7 ± 0.4, p<0.05) while the regurgitation score (0.7 ± 0.3 vs. 0.1 ± 0.1, p=0.07) tended to be higher compared to patients after LHM. Chest pain was similar after PD and LHM (1.1 ± 0.3 vs. 0.6 ± 0.2, p=0.20).

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

It is hypothesized that the three types represent a different stage of achalasia. To define the course of the subtypes after treatment, we collected 397 post-treatment manometries of 107 patients (median 2 post-treatment manometries [range 1-8]). During follow up, the mean contraction amplitude remained the lowest in type I patients (type I: 17 ± 0.9 mmHg, type II: 37 ± 1.5 mmHg and type III: 78 ± 7.6 mmHg, p<0.0001, one way anova). After therapy, most patients with type I achalasia were classified as having absent peristalsis (n=16, 89%), while simultaneous contractions (with an amplitude of >30mmHg) 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 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 three manometric subtypes of achalasia suggesting that classification by manometry may be useful to determine the treatment of choice. In the present study we confirmed that the manometric subtype is indeed an important determinant of clinical success with type I and especially type III achalasia having an increased odds rate for treatment failure compared to 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, respond excellent to both LHM and PD during a mean follow-up 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 due to small patient number, there was no significant difference compared to 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 only prove relevant 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, Pandolfini et al. classified achalasia into 3 types (type I: No pressurization, type II: panesophageal pressurization and type III: rapidly propagating contractions). Interestingly, after a follow period of at least one year, the treatment success rate of type II patients (96%) was
significantly higher compared to 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 to type II, suggesting that patients with type II respond better to treatment. Due to the low number, no comparison could be made between the different treatments used. In the same line, Salvador et al reported better clinical response to LHM (n=246) for type II patients (success rates type I=85% (82/96), type II= 95% (121/127), and type III=70% (16/23; p=0.0007) [10]. Although the follow-up period in our study was longer (median of 43 months) compared to the previous two studies (ranging between 6 and 31 months), our results are largely comparable, confirming that the highest success rate was observed in type II achalasia (96% after 2 years) compared to type I (81%, p<0.01) and type III (66%, p<0.001). Also in a Cox regression analysis model, type I and type III were identified as risk factor 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 in 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 to type I and II. Although chest pain has repeatedly been shown 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 mainly evoked by high amplitude esophageal contractions rather than esophageal widening. [9] Our data are in line with this hypothesis as type III patients have the narrowest esophagus and the highest contraction amplitude, associated with the highest chest pain score. It should also be noted though that patients with type III achalasia reported more symptoms of dysphagia and regurgitation than patients with type I and II. Patients with type I achalasia had a higher dysphagia score after treatment compared to 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, 15, 16] For instance, Vaezi et al demonstrated that 90% of patients with persistent stasis but without symptoms failed therapy within one year after initial treatment. Furthermore, Zaninotto et al demonstrated that a wider esophagus is an important risk factor for treatment failure in a large study with patients treated by LHM. Combined high resolution manometry (HRM) and impedance measurements have demonstrated that esophageal emptying in achalasia mainly occurs during panesophageal pressurizations. [14] The absence of esophageal pressurization in type I achalasia might therefore 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, i.e. PD or LHM, can be guided by the manometric subtype. For this purpose, we compared success rates for PD and LHM in the three subtypes. For type I achalasia LHM and PD had similar success rates (81% vs. 85%), 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 to those reported previously, however we obtained higher success rates in patients with type I undergoing PD (56-63% vs 85%)

One explanation could be the fact that patients with mega-esophagus (esophageal diameter of >7cm), known to be more difficult to treat and to present with type I achalasia, were excluded from our study. It should be emphasized though 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, i.e. our protocol allowed redilation during the first years of follow up, 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.

The largest difference was observed in type III patients, in whom the success rate after LHM was higher than after PD (86% vs. 40%). Due to the small patient number (n= 18), this difference was however not statistically significant (p=0.12). The success rates are in line with the available literature (LHM 70% vs. PD 33-38%), though 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)). 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 demonstrated by Pandolfini et al, type III patients have a functional obstruction not only encompassing the esophagogastric junction (EGJ) but also the distal smooth muscle segment of the esophagus. In the European Achalasia Trial, the myotomy was extended 6 cm above the EGJ, which may account for the differences in esophageal emptying, dysphagia and regurgitation, and thereby to the higher success rates compared to PD. Therefore, in combination with the large difference in success rates both in our study and in literature, we suggest that LHM may be the preferred treatment option in type III patients. Still, an additional study focussing on patients with type III achalasia seems indicated. Due to the very limited incidence of type III achalasia, additional studies probably need to be performed in multi-center 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 centres 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 two standard treatments in three 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 is 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 centres, and diagnosis was based on conventional manometry with a sleeve sensor. Of note, Salvador et al. reported 100% agreement between the classification of subtypes based on conventional pressure line tracings versus HRM plots. Although classification of subtypes based on conventional might be less precise than the sophisticated HRM-based classification, our three patient groups were similar to those reported by Pandolfino, 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 to 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.
Treatment outcome depends on manometric subtype | CHAPTER 10

REFERENCE LIST


