Title: Long-term outcomes (5 years or more) after myotomy

Short title: Myotomy: long-term outcomes

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Abstract

Background: Surgical or endoscopic myotomy are good options for treating achalasia, as >80% of patients continue to report no symptoms at medium-term follow-up. Little is known about the long-term natural history of patients who have undergone myotomy, however, in terms of symptom control, need for retreatment, and complications. In this review we examined the long-term results at least 5 years after surgical or endoscopic myotomy.

Methods: A narrative review of all studies reporting the results of surgical or endoscopic myotomy with a follow-up of 5 years or more was conducted. The main focus was on symptom relief, the incidence of GERD, and the need for retreatment.

Results: Transthoracic or laparotomic approaches to Heller myotomy were mainly used in the last century, with long-term studies reporting symptom relief in the range of 73% to 95%, and a 4.4% to 45.5% incidence of GERD. The laparoscopic approach has been the gold standard for the last 20 years, eliminating dysphagia symptoms in 65% to 95% of patients. Per-oral endoscopic myotomy (POEM) is a valid method that achieves long-term symptom relief in up to 92% of patients. GERD remains an issue as it's incidence after POEM exceeds that reported after laparoscopic myotomy.

Conclusion: Surgical and endoscopic myotomy both achieve symptom control that persists for more than 5 years and can be accepted as an effective primary treatment for achalasia. However, the real role of the higher incidence of postoperative reflux carried by POEM should not be underestimated.

Bullet points:

1. The etiology of achalasia is still poorly understood, but myotomy is an effective palliative treatment.

2. Results of myotomy persist over the years, and surgical retreatment is rarely needed.

3. In the last 20 years, laparoscopic and endoscopic myotomy have replaced the open surgical approach and are now the gold standard.

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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 its pathogenesis 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[1]. In the early 1990s, minimally invasive techniques became widespread, and a laparoscopic approach to myotomy was introduced, both without[2] and with an added fundoplication[3]. The laparoscopic Heller myotomy (LHM) rapidly changed the treatment algorithm for achalasia and, with its more limited surgical morbidity, it has become the procedure of choice for this disease[4-6]. More recently, a new endoscopic procedure was introduced, called per-oral endoscopic myotomy (POEM)[7], and is being used more and more worldwide. It has demonstrated good short- to mid-term results and many consider it a candidate for replacing LHM (and PD too) as the first-line therapy for achalasia[8].

The medical literature contains an abundance of papers on the outcome of surgical or endoscopic myotomy, most of them reporting high percentages of good results (>80%), and with a short follow-up (from a few months to 2 years). Little is known about the long-term natural history of patients who have undergone surgical or endoscopic myotomy, in terms of symptom control, need for retreatment, complications (namely reflux), and cancer risk. The aim of the present review was therefore to examine the results of surgical or endoscopic esophageal myotomy at least 5 years after the procedure. A PubMed search on papers reporting the long-term results of myotomy (from 1990 for open surgery, from 2000 for the laparoscopic access and from 2005 for the endoscopic access, respectively) was performed. Only papers with a median follow-up higher than 5 years were considered. The analysis of the collected papers was performed by the two senior authors (RS and MC).

1. Open surgical myotomy

In the last century, surgical myotomy was performed via a transthoracic or a laparotomic approach, with surgeons' preferences nearly equally divided between the

two options[9]. Ellis and the group at the Mayo Clinic championed the transthoracic approach[10], while laparotomic surgery was preferred by surgeons in South America and Europe[11,12].

Some reports on the very long-term results of Heller myotomy performed via a traditional open approach have since been published, and their findings are summarized in Table 1[13-18]. It was consistently reported in all series that most patients no longer experienced any symptoms of achalasia after a median follow-up >5 years (and some patients had been followed up for 20 years and more). This result was achieved with percentages of iatrogenic reflux ranging from 5% to 30% or more, depending on how this symptom was assessed. Some studies reported outcomes at different follow-up points. For example, Csendes et al.[16] considered patients with a follow-up of 6 to 10, 10 to 20, or more than 20 years after surgery. They found a gradual overall decline in symptom relief from 93% to 77%, and then 65%, respectively, with a parallel increase in reflux from 15% to 28%, and then 53%, respectively. Other studies[18] reported similar results, concluding that, despite myotomy initially obtaining good results, achalasia patients' clinical symptoms gradually worsen over time. There can be some truth in their conclusions, but it is worth emphasizing that these were not longitudinal studies, only a snapshot of patients with different durations of follow-up, and who were probably treated at different times during the study period. The rate of reoperations was <5% in all but 2 studies, both of which involved patients treated using a transthoracic approach.

2. Laparoscopic Heller myotomy (LHM)

As mentioned earlier, the minimally-invasive surgery revolution in the early 1990s soon led to these techniques being applied to Heller myotomy to treat achalasia[2,3]. Laparoscopic Heller myotomy (LHM) rapidly became the standard of care of achalasia at most centers, with minimal morbidity and excellent functional outcomes. These days, an anterior myotomy of the lower esophagus is performed, extending it 2-3 cm onto the proximal stomach. As the natural antireflux barrier is completely disrupted, postoperative GERD is to be expected following myotomy, so a partial fundoplication is usually performed as well, either anteriorly (Dor, 180°) or posteriorly (Toupet, 270°). The reported early and medium-term success rates with LHM were generally high, just below 90% at a median 3-year follow-up[19]. In recent years, several papers reporting on the long-term results (>5 years) of LHM have appeared in the literature. Table 2 summarizes the findings of some of these studies[20-31]. Jeansonne et al.[20] reported a good result in two-thirds of the 17 patients (65%), they were able to contact for a 10-year follow-up. Albeit in this small sample of patients, they found that the rate of recurrent dysphagia at 10 years was no different from the situation seen at an earlier follow-up (2.2 years): severe dysphagia in 5.9% (vs. 5% at short-term follow-up), moderate dysphagia in 29.4% (vs. 20% at short-term follow-up), mild dysphagia in 17.7% (vs. 45% at short-term follow-up). They successfully treated three of their six patients with recurrent dysphagia (17.7% of the whole cohort of patients) with complementary PD, while they had to reoperate other two. Cowgill et al.[21] reported a much higher rate of good results (92%) in 47 patients followed up for more than 10 years, although six of them required some sort of postoperative endoscopic treatment. Krishnamoham[26] reported on 500 patients, roughly half of whom were contacted at a median 6.5 years after LHM: dysphagia we well controlled in 86% of cases, including 83.2% of those with a follow-up of more than 5 years. Postoperative GERD was not

properly assessed, but the Authors reported that 28% of patients had daily episodes of heartburn. Other series with a median follow-up of more than 5 years indicated similar rates of good results[22-25], and a multicenter European trial comparing LHM with PD reported an 84% success rate at 5 to 10 years after LHM[27]. Intriguingly, this rate was not much lower than at 2-year follow-up (89%). Postoperative GERD was assessed using 24-h pH-monitoring and endoscopy, with 34% of patients revealing abnormal reflux, and 18% had esophagitis.

Our group recently reported on the largest series to date of achalasia patients treated with LHM + Dor (LHD)[28]. The procedure was successful in nearly 90% of a thousand patients with a median follow-up beyond 5 years. When only patients followed up for more than 10 years were considered, the probability of still being symptom-free after 20 years exceeded 80%. These data are reinforced by the fact that nearly all the patients were operated over a 25-year period, and most of them had a follow-up that included both clinical and functional assessments. More than 60% of the patients underwent 24-h pH monitoring, revealing GERD in only 9.1% of them. About 10% of the whole sample required one or more complementary PD, which ameliorated their symptoms in all but 11 patients (1.1%), who eventually required reoperation. Two patients developed a squamous cell carcinoma: one had missed several follow-up visits and endoscopies, and presented with advanced disease 8 years after LHD, dying 14 months later; the other had fully adhered to the routine follow-up, and an early cancer was identified 14 years after LHD, that could be treated curatively.

Other subsequent papers reporting on the long-term follow-up of patients after LHM[29-31] include a report from Csendes et al.[29], whose series has reached the longest median follow-up published to date (17 years): 79% of patients had good results >10 years after LHD, and 18.7% had GERD symptoms. The Authors also performed 24-h pH-monitoring, finding abnormal acid exposure in 63% of patients; this finding is highly

flawed, however, because the test was performed in only half of the asymptomatic patients, but all of the symptomatic cases. The Authors also identified 3 cases of advanced SCC.

A recent publication from Japan[31] retrospectively reported on 530 patients who were followed up for a median 4.2 years after LHD, and 78 of them for more than 10 years. The results were similar to those of previous reports (dysphagia relief in 81% of patients, 21% with postoperative GERD), and 6 patients (1.2%) developed SCC a median 27 months after LHD. It is worth noting that all these cases were found early, on routine endoscopic follow-up, enabling curative endoscopic submucosal dissection in 5, and esophagectomy in 1; all 6 patients survived and are still being followed up. Finally, out of 15 patients (2.8%) who required retreatment, 10 were successfully treated with POEM, only 3 with PD, and 2 with redo surgery.

3. Per-oral endoscopic myotomy (POEM)

This technique was introduced and popularized by Inoue et al. in 2010[7], and spread rapidly, first in Asia and then in the USA and Europe. A meta-analysis in 2016 reported on 2,373 patients treated with POEM in 12 countries; two-thirds of the cases were in Japan and China[32]; and others followed soon afterwards[33,34]. All the reports published to date indicate that the technique achieves excellent results (>90%) in the short term, but these positive findings come from uncontrolled open-label studies with a short follow-up. It is only recently that some RCTs and comparative studies[35-37] have been published and, with the passing of the years, some reports with a median follow-up beyond 5 years have begun to appear in the literature (Table 3). A recent metanalysis[38] on 11 studies with a median follow up of 4 years reported 87.3% of good results after POEM (with substantial heterogeneity, however) and 22% rate of symptom-based post-procedural reflux. They also found a decrease on the efficacy of

POEM (from 93% after 1-3 years, to 87% at 4-year follow up), albeit this difference did not reach statistical significance.

Teitelbaum et al.[39] were the first to publish their findings on 23 achalasia patients treated between 2010 and 2012, and followed up for at least 5 years, reporting a good outcome in 83% of cases. The Eckardt score was greatly improved at 6 months, and this result was maintained at 2 years; then a small, but significant worsening was reported at 5 years. Only one patient who developed Barrett esophagus (BE) required reintervention (LHM). Though reflux was detected on pH-manometry in 33% of patients at an early F/U, endoscopy at 5 years identified esophagitis in only 2 patients (13%). Three years later, the same group of researchers reported on the Portland experience[40], which involved a larger number of patients with a follow-up of at least 5 years. They confirmed their previous findings (80% of patients with good results) but reported 7 reinterventions (2 redo-POEM, 4 LHM, 1 PD). It is noteworthy that 7 of their 19 failures were considered “early”, while the majority were “late” – underscoring the importance of a long follow-up in these patients. The Authors did not quantify postoperative GERD because they had only conducted telephone interviews. Onimaru et al.[41], from Inoue’s group, later reported on 15 of the 36 patients operated in 2008-2010 that they managed to contact >10 years after the procedure. The long-term success rate was 93.3%, but further treatment with PD had been necessary in 4 patients, so good results were achieved with POEM alone in 67% of cases. A multicenter retrospective study[42] on patients operated in 2010-2012 and with a follow-up of at least 6 years also reported very satisfactory long-term results (89%). Symptomatic GERD and endoscopic esophagitis persisted after 6 years in 37.5% and 31% of patients, respectively. Four patients required further treatment with PD. Modayil et al.[43] recently reported on 10-year outcomes for patients in a large, single-center U.S. series. Albeit with a median follow-up of 2.5 years, they estimated that 92%

of patients would probably be symptom-free at 5 years, and 91% at 7 years; the number of patients at risk was only 126 (out of 610) at 5 years, however, and 28 at 7 years. The Authors reported that 24-h pH-manometry confirmed GERD in 57.5% of patients at an early follow-up (and 50% of patients had endoscopic evidence of esophagitis). They were able to assess 21 patients 5 months and 5 years after POEM, and found a significant decrease in the number of patients with abnormal reflux (from 67% to 43%). In their whole series they reported 27 reinterventions (4.4%), roughly half of which were performed after 4 years. Most were redo-POEM (15), and some were PD (7); LHM was performed in only one patient. It is worth mentioning that Percutaneous Endoscopic Gastrostomy (PEG) was required for 4 patients, who were all very old or mentally ill, raising some doubts as to the real indications for the primary procedure. Finally, a very large series of patients treated with POEM and followed up for at least 5 years was recently published by an Indian group[44]. They reported a success rate of 92.6%, with 30% of patients experiencing symptomatic GERD, and 35% revealing esophagitis on endoscopy. Using intention-to-treat analysis, the clinical success rate was 82.1%, however.

Unlike the case for surgical myotomy, none of these papers reported on the development of esophageal carcinomas; only one case of short BE was reported. This is presumably related to the relatively short follow-up, even though it was more than 5 years in all, because carcinoma usually develops late in the course of the disease. On the other hand, some cases of new-onset (short) BE were identified already 2 years after POEM in a well-conducted multicenter study[45], and one case of esophageal adenocarcinoma 4 years after POEM has been reported too[46].

Discussion

Despite the lack of knowledge in the etiology of esophageal achalasia, the good news is that, judging from this narrative review, the palliative treatment of this disease achieves good symptom relief in most patients. Our review also shows that this benefit persists over the years – an aspect of paramount importance for a benign functional disease that frequently occurs in young, active, and otherwise healthy adults. The treatment involves disrupting the unrelaxing LES so that the esophagus is emptied by gravity, since no treatment can effectively restore esophageal peristalsis. Some treatments (medication, botulinum toxin injections) have failed the test of time and are very seldom used nowadays, and only in very frail patients[1]. The most effective treatments that can be offered to patients today are PD, LHM and, more recently, POEM. It is very difficult to analyze and compare the results reported by the different papers we reviewed, since they belong to different timeframes, they mostly are retrospective case series and the definitions, the methods of assessing the outcome and failure are very vague and non-homogeneous, and the evaluation of post-treatment GERD very variable as well. Moreover, the strict comparison of the different techniques was beside the purpose of this paper, which aimed to describe what we can reasonably expect by the different modalities of performing myotomy on the long run.

That said, LHM rapidly replaced the open laparotomic or thoracotomic approaches of the 1990s, becoming the treatment of choice for achalasia. Three decades on, we can now draw more or less definitive conclusions on the value of this treatment, drawing on reports regarding the very long-term follow-up of patients who underwent LHM in its early days. These studies suggest that long-term symptom relief can be achieved in more than two in three patients, with most papers reporting good results in 80% or more. This is achieved with an acceptable incidence of postoperative GERD (10-20%) and reintervention rate (around 10% or less), most of these

reinterventions involving complementary PD. Barring a few exceptions[28,29], a common flaw of the long-term follow-up studies lies in the large proportion of patients lost to follow-up, and differences in the patient assessment methods (based in most cases on symptom scores alone, with endoscopic or pH-manometry findings reported in only a minority of studies). We know from experience, however, that it is very difficult to get patients to return for visits or tests, since most of them fare well. We can nonetheless conclude that LHM is a very valid treatment for esophageal achalasia and remains the reference standard with which any other treatment should be compared.

POEM is a relatively new technique (only 12 years old), so it is not yet possible to assess its long-term. The plethora of retrospective reports and meta-analyses that have appeared in the last decade consistently indicate that POEM can achieve outcomes as good as LHM, in the short and medium term at least. Physicians may nonetheless still have their doubts about the procedure. This is partly because the high efficacy of POEM coincided with a higher GERD rate than in the case of LHM (up to one in two patients), whatever the assessment method used[47]. Other doubts essentially concern the efficacy of POEM in the long run, since some studies[48] found that the number of patients with good results decreased rapidly over 2 years, from 98% to 78%. This was confirmed by a multicenter RCT[37], which found that: POEM is as good as LHM, the reported success rates at 2 years being 83% for POEM and 82% for LHD (somewhat lower than previously reported by several papers, but more likely); and the incidence of reflux esophagitis is higher after POEM than after LHD, at both 3 months and 2 years of follow-up.

With time, various retrospective studies with a median follow-up exceeding 5 years were published. Like LHM, POEM provided good long-term symptom control in more than two-thirds of patients, and sometimes even more than 90% (with most papers reporting rates in the 80-90% range). This means that any doubts about the

long-term efficacy of this technique can be reasonably put aside. These studies also confirmed the persistence of post-POEM GERD over time, however, reporting rates from 28% to 50% and more, depending on the assessment method used. Even if post-POEM (or post-LHM) GERD does not lead to relevant complications (such as severe esophagitis or BE[43]) in most cases, it still demands long-term PPI use and dietary restrictions for up to half of the patients treated with POEM. A recently-published case of esophageal adenocarcinoma (AC), 4 years after POEM also casts a worrisome shadow over this procedure[46].

Based on the reported evidence, we can conclude that LHM and POEM have a similar profile in terms of long-term efficacy, with the proportion of patients obtaining good clinical results tending to decrease slightly over time, settling at around 80% for both techniques. LHM and POEM are also both very safe in terms of complications, adverse events, and mortality. It is worth emphasizing, however, that POEM, like LHM, is an invasive procedure (even though it is managed endoscopically) and requires general anesthesia. Both techniques also demand skilled surgeons and endoscopists, and should only be performed at high-volume centers to ensure the best overall results. The need for reinterventions is low for both techniques, even in the longer term, and most relapsing patients can be managed with complementary PD, so further surgery is seldom necessary. Either LHM or POEM can therefore be proposed as the initial treatment for most achalasia patients – but there are some caveats. Based on what has been said about post-treatment GERD, we believe POEM should not be offered to young adults (<40 years old), and especially teenagers or children, because of their long-life expectancy - until the real clinical relevance of a post-treatment GERD has been fully addressed, at least. On the other side, POEM may be best suited to treating longer-segment disorders of esophageal peristalsis, like type III achalasia, which are reportedly somewhat refractory to other forms of treatment, LHM included. Studies on

POEM performed specifically for type III achalasia reported symptom relief in more than 90% of cases[49]. POEM could therefore be the first-line approach to such patients, even if long-term results prove to be not as good as those hitherto reported. Some studies have also shown that satisfactory results can be obtained with LHM in such patients by elongating the myotomy[50].

The risk of esophageal cancer after myotomy must be considered, even if the procedure is effective in controlling dysphagia. These cancers may develop several years after treatment, so they should be expected in the coming years after POEM as well. We have already recalled the case of AC arising 4 years after POEM[46]. When dysphagia is caused by cancer in an achalasia patient with a somewhat dilated esophagus and a long habit of swallowing difficulties, it is usually discovered too late. Most such cancers are detected at an advanced stage, and effective therapy is no longer possible. It is somewhat reassuring that all cases reported in a recent study[32] were early, and could be treated effectively, and endoscopically in most cases. This was also true of the previously-mentioned adenocarcinoma after POEM. The importance of endoscopic follow-up in these patients must therefore be strongly emphasized.

In conclusion, both surgical and endoscopic myotomies for achalasia provide good symptom control at 5 years and more, and can be considered as primary and effective treatments for this disease. In our opinion, POEM should be offered to young patients and children with some caution, but it might be the best treatment for type III achalasia. A center specializing in achalasia should have both techniques (and PD as well) in its armamentarium, so that it can choose the most appropriate treatment for a given patient.

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