Anterior versus Posterior Myotomy during POEM for the Treatment of Achalasia: Systematic Review and Meta-Analysis of Randomized Clinical Trials

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INTRODUCTION

Achalasia is a rare disorder characterized by incomplete swallow-induced relaxation of the lower esophageal sphincter (LES) and impaired peristalsis of the esophageal body. Endoscopic treatment options provide a significant improvement of symptoms and quality of life [1]. The first human case of peroral endoscopic myotomy (POEM) was performed in 2008 [2]. Ten years later, this minimally invasive technique has spread worldwide, and several meta-analyses confirm that POEM is highly effective with a favorable safety profile [3]. Indeed, recent guidelines place POEM as a first-line alternative for achalasia and non-spastic disorders [1, 3].

One of the main advantages over laparoscopic Heller myotomy (LHM) is the possibility to adjust the length and location, anterior or posterior, of the myotomy freely. Before answering the question of whether the location of the myotomy is of clinical importance, some anatomical and pathophysiological parameters must be considered. Manometric studies have reported a significant pressure...
asymmetry within the LES [4, 5]. Macroscopically, the inner muscular layer of the LES is composed of semicircular muscle “clasp” fibers on the lesser curve side, and long oblique gastric “sling” fibers on the left side towards the greater curvature [5]. It seems that both types of fibers respond to different stimuli and play a different role in LES competence [5]. Consequently, several anti-reflux and relaxation mechanisms of the LES are anatomically determined [4, 6]. This explains the importance of myotomy orientation and the growing interest in recent years on this subject. Anterior myotomy (12-3 o’clock in the supine position) was the first approach adopted to mimic traditional LHM and preserve the posterior sling fibers alongside the angle of His [2, 6, 7]. This was the standard of treatment for several years, a fact depicted by an international survey from 2013 where 14 out of 16 centers favored the anterior approach [8]. The posterior myotomy (5-6 o’clock in the supine position) was initially described by Ren et al. [9]. Due to technical advantages, such as a better alignment of the knife during the myotomy [10], posterior myotomy has become the standard of POEM in several centres [10–12]. However, some concerns have been raised regarding the incidence of gastroesophageal reflux disease (GERD) if the posterior sling fibers are disrupted [7, 13]. It is therefore evident that each approach has its “pros” and “cons” and the choice of either one lies mostly in the operator’s preference. The limited sample size of available studies has hindered the detection of relevant differences, if any, between anterior and posterior myotomy [7, 10]. To our knowledge, this is the first meta-analysis aiming to compare posterior and anterior myotomy during POEM for the treatment of achalasia regarding clinical success, safety, and procedure-related outcomes.

METHODS

This study was conducted according to the PRISMA statement [14]. The protocol was registered at PROSPERO (number: CRD42018106142). Our PICOT question was:

- Population: Patients with esophageal achalasia.
- Intervention: POEM.
- Comparison: Anterior vs. posterior myotomy.
- Outcomes: Clinical success, adverse events (AEs), GERD, manometry post-POEM, and procedure-related outcomes.
- Type of study: Randomized clinical trials (RCTs).

Two authors (E.R.S. and N.M.) independently applied the search strategy and performed the study selection, data extraction, and assessed the quality of the RCTs. A third investigator (A.M.) reviewed the extracted data. Discussion with senior authors solved any differences.

Data sources and Search strategy

Pubmed, Embase, Web of Knowledge, the Cochrane Library, and clinicaltrials.gov were screened for eligible RCTs during August 2018. Abstracts from the Digestive Disease Week (DDW) and the United European Gastroenterology Week (UEGW) were also reviewed. In addition, the reference lists of identified articles were examined for additional studies. We applied the Cochrane highly sensitive strategy for identifying RCTs. Since POEM was first described in humans in 2008, we restricted our search to studies published from January 2009 to the 19th August 2018. No language restriction was applied. The search strategy is further detailed in Supporting information (Supplementary material).

Study selection

All titles and abstracts of identified citations were reviewed. Randomized clinical trials comparing posterior and anterior myotomy during POEM for the treatment of esophageal achalasia were selected. Abstracts presented at international congresses and full-length publications (i.e. published in a journal) were considered. Observational, and animal studies were excluded. No restriction criteria regarding age or prior treatments were applied. When overlapping data from the same research were available, the most updated version was included.

Outcomes

The primary outcome was clinical success 3-12 months after POEM. Our primary analysis used the Eckardt score ≤ 3 as a uniform criterion since this threshold is widely accepted for achalasia RCTs [1]. In the study by Khashab et al. [15] this data was not available, and the definition provided by the authors was used instead (Eckardt score < 3). Clinical success was additionally assessed by using the definitions given by the authors and total Eckardt score as a quantitative variable.

Secondary outcomes were: (i) GERD after POEM as assessed by a validated clinical questionnaire, presence of reflux esophagitis at esophagogastroduodenoscopy (EGD), and 24-hour pH monitoring (DeMeester > 14.7 or acid exposure time criterion if unavailable); (ii) total number of adverse events (AEs); (iii) accidental mucosotomy as a separate AE; (iv) median integrated relaxation pressure (IRP) and basal LES pressure (LESP) at high-resolution manometry (HRM) after POEM; (v) total operation, myotomy, and incision closure time (minutes), and length of hospitalization (days).

Data extraction

A predefined data extraction form was used to collect the data. Registration protocols at online platforms (clinical.trials.gov, http://ctri.nic.in, and http://www.chictr.org.cn/) of the included studies were also reviewed. Corresponding authors of the included RCTs were contacted to request unpublished information when deemed appropriate. Intention-to-treat was preferred over per-protocol data if available. The following data were extracted for each study: title, year of publication, first author, study period, number and location of centres, type of publication (conference abstract/ full-length), selection criteria, sample size, baseline characteristics, operator experience, number of endoscopists, type of myotomy (selective/full-thickness), maximum follow-up time, outcomes definitions provided by the authors, and measurements of the primary and secondary outcomes.

Risk of bias

The risk of bias was assessed with the Cochrane tool [16]. The domains evaluated were: (i) selection bias; (ii) performance bias; (iii) detection bias; (iv) attrition bias; (v) reporting bias and (vi) other potential biases. Funnel plots assessed publication bias.
Statistical analysis

The overall pooled effectiveness of POEM was calculated by the double arcsine transformation [17]. We used inverse-variance weighting random-effects models for our primary analyses. This decision was made beforehand and was not based on heterogeneity. The random-effects model provides more conservative estimations and was deemed to be more realistic in this scenario [18]. For binary outcomes, we estimated pooled relative risks (RR) and their 95% confidence intervals (CI). Differences in means (MD) were calculated for quantitative variables.

Heterogeneity was determined by inspection of forest plots, the Cochrane Q test, and the I² statistic. Q test significance was set at P < 0.10. I² values were interpreted according to the Cochrane Handbook for Systematic Reviews of Interventions: <30% low heterogeneity, 30-50% moderate heterogeneity, >50% substantial heterogeneity, and >75% high heterogeneity [16].

The following sensitivity analyses were performed to assess heterogeneity and test the robustness of our findings: (i) fixed-effects models when heterogeneity was low; (ii) Mantel-Haenszel estimates for binary outcomes; (iii) full-thickness vs. selective myotomy; (iv) full-length articles only; (v) published data only (i.e. excluding data obtained by contacting the authors); (vi) alternative definitions for the primary outcome as detailed above.

Statistical significance was set at p<0.05 except where noted. Revman 5.3 and MetaXL 5.3 software were used.

RESULTS

An initial search yielded 581 citations. A total of 467 were considered for screening after removing duplicates. Four RCTs were finally included (NCT02454335, NCT03228758, CTRI/2016/05/006949, and ChiCTR-ICR-15007211). The PRISMA diagram is outlined in Fig. 1.

Description of the studies

A total of 488 patients with achalasia type I, II, and III [7, 10, 15, 19]. Sample size varied from 60 to 215 patients. Two RCTs were published as full-length papers [7, 10], and the remaining two as abstracts at DDW 2018 [15, 19]. All procedures were performed by experienced operators, although the exact number of prior POEMs per endoscopist was unavailable. Sigmoid anatomy was an exclusion criterion in all but one RCT, where 24 patients with this variant were included [19]. One RCT excluded patients with prior endoscopic or surgical treatment [10], and another one excluded those with prior surgery [15]. Full-thickness myotomy was the preferred method in three of the reports [7, 15, 19], while selective myotomy was used by Yuyong et al. [10]. Follow-up ranged from 3 to 12 months. Selection criteria, number of centers, baseline characteristics, and main outcomes are further detailed in Table I. Funnel plots were not indicative of publication bias for any outcome and are provided in Supporting information. Bias assessment is depicted in Fig. 2.
Table I. Characteristics of individual studies

| Study          | Location and number of centres | Inclusion criteria | Exclusion criteria | N  | Baseline characteristics | Effectiveness     | pH GERD | Adverse events |
|----------------|--------------------------------|--------------------|-------------------|----|--------------------------|-------------------|---------|----------------|
| Khashab 2018   | 3 Asia 2 Europe 1 US           | >18 years Achalasia by HRM | Previous esophagogastric surgery, Sigmoid oesophagus, Hiatal hernia >3 cm, Severe esophagitis, Large lower diverticula, Gastroesophageal malignancy, Major comorbidities, Pregnancy, Coagulopathy | 150 | Age, years, Sex Female, BMI (kg/m²), Achalasia type, I, II, III | Anterior: 51.5  | POSTERIOR: 50.7 | Anterior: 91%  | Posterior: 49%  | Anterior: 11%  | Posterior: 9%  |
| Abstract       |                                |                    |                   |    |                          |                   |         |                |
| Stavropoulos   | 1 USA                          | >18 years Achalasia by HRM | Prior Heller, Esophageal diverticula, Major comorbidities | 215 | Age, years, Sex Female, BMI (kg/m²), Achalasia type, I, II, III | Anterior: 54.2  | POSTERIOR: 54.8 | Anterior: 92%  | Posterior: 92.1% | Anterior: 69.6% | Posterior: 8.9% |
| 2018 Abstract  |                                |                    |                   |    |                          |                   |         |                |
| Ramchandani    | 1 India                        | Primary achalasia  | Hiatal hernia >3 cm, Sigmoid oesophagus, Severe esophagitis, Major cardiopulmonary comorbidities | 60  | Age, years, Sex Female, BMI (kg/m²), Achalasia type, I, II, III | Anterior: 38     | POSTERIOR: 43  | Anterior: 100% | Posterior: 100% | Anterior: 16%  | Posterior: 70% |
| 2018           |                                |                    |                   |    |                          |                   |         |                |
| Yuyong 2018    | 1 China                        | Age: 18-70 years   | Prior surgical/endoscopic treatment, Sigmoid oesophagus | 63  | Age, years, Sex Female, BMI (kg/m²), Achalasia type, I, II, III | Anterior: 45.8   | POSTERIOR: 42.4 | Anterior: 100% | Posterior: 100% | Anterior: 26.7% | Posterior: 12.9% |
|                |                                |                    |                   |    |                          |                   |         |                |

N: Total sample size; GERD: Gastroesophageal reflux disease; HRM: High-resolution manometry; BMI: Body mass index
Clinical success
A total of 4 RCTs with 464 patients were included in this meta-analysis. No differences were detected between posterior and anterior myotomy with a pooled RR of 0.98 (95% CI 0.96-1.01; p= 0.3) (Fig. 3). Heterogeneity was low (I²: 0%). Hence, random and fixed-effect models yielded identical results. Eckardt score after POEM as a quantitative variable was available for three studies and a total of 326 patients. Clinical success was similar between both myotomy alternatives (MD: -0.10; 95% CI (-0.34)-0.14; p= 0.44; I²: 49%). Sensitivity analysis was consistent with these results and is provided in Supporting Information.

Pooled overall clinical success was 97% (95% CI 93-100%, I²: 83.7%). The study by Khashab et al. [15], which applied a more restrictive definition for clinical success, accounted for most of the heterogeneity (Fig. 3). Overall clinical success after excluding this study was 98% (95% CI 96.8-100%; I²: 23.8%).

Gastroesophageal reflux disease
Gastroesophageal reflux disease diagnosed via 24-hour pH monitoring was available for a total of 326 patients from the four RCTs. The meta-analysis found no differences between both approaches (RR 0.98, 95% CI 0.75-1.28; p= 0.87; I²: 21%). Furthermore, presence of reflux esophagitis at EGD (RR 1.04, 95% CI 0.78-1.38; p= 0.81; patients: 210; studies: 3; I²: 0%), and GERD symptoms (RR 0.89, 95% CI 0.55-1.42; p= 0.61; patients: 326; studies: 3; I²: 13%) were similar (Fig. 4). Heterogeneity was low for all the estimations. Subgroups analyses endorsed the absence of GERD differences (Supporting information).

Adverse events
The rate of AEs for each arm is detailed in Table I. No procedure-related deaths were recorded. The risk of AEs (RR 0.63, 95% CI 0.42-0.94; p=0.02, patients: 488; studies: 4; I²: 0%) was lower for the posterior approach, with no heterogeneity. The risk of mucosotomy was available for two studies including 275 patients and was significantly reduced during posterior POEM (RR 0.42, 95% CI 0.27-0.66; p<0.001; studies: 2; patients: 275; I²: 0%). These differences remained statistically significant in all sensitivity analyses (Supporting information).

Manometry outcomes
High resolution manometry after POEM was available in three RCTs for a total of 173 patients. Integrated relaxation pressure (MD: -0.39 mmHg, 95% CI -1.40-0.61; p= 0.44; I²: 0%) and LESP (MD: -1.18 mmHg, 95% CI -2.41-0.05; p= 0.06; I²: 0%) did not differ between posterior and anterior myotomy.

Fig. 2. Bias risk assessment.

J Gastrointestin Liver Dis, March 2019 Vol. 28 No 1: 107-115
**Fig. 3.** Anterior versus posterior myotomy. Meta-analysis of primary outcomes.

**Fig. 4.** Gastroesophageal reflux disease after POEM. Anterior versus posterior myotomy.
**Procedure-related outcomes**

Total procedure duration (MD: 3.48 minutes, 95% CI (-8.55)-1.58; p=0.18; patients: 338; studies: 4; F: 0%) and myotomy time (MD: 1.79 minutes, 95% CI -4.06-0.48; p=0.12; studies: 2; patients: 275) were comparable. Mucosal incision closure was faster during posterior POEM (MD = -2.28 minutes, 95% CI -3.46-(-1.10); p<0.001; studies: 2; patients: 275) were comparable. Mucosal incision time (MD: 1.79 minutes, 95% CI -4.06-0.48; p=0.12; studies: 2; patients: 267), while length of hospitalization was more prolonged (MD: 0.31 Days, 95% CI 0.05-0.57; p=0.02; studies: 3; patients: 338). Between-studies heterogeneity was low (I^2: 0%) for all procedure-related outcomes.

**DISCUSSION**

In this meta-analysis, we critically appraised the available RCTs comparing anterior and posterior myotomy for the treatment of achalasia. Our main findings are that both are equally effective, yet posterior myotomy was safer and associated with shorter incision closure time. Heterogeneity was low, a comprehensive sensitivity analysis was consistent with our primary findings, and no publication bias was detected.

Peroral endoscopic myotomy has proven to be highly effective in several meta-analyses of uncontrolled and non-randomized studies [2, 20, 21]. Our analysis, which was based exclusively on RCTs, provides additional evidence supporting that POEM offers excellent results with an overall clinical success of 97%. The efficacy for the anterior and posterior approach was similar regardless of the definition used, type of myotomy, sort of publication, and the statistical method employed to pool the data. The meta-analysis of manometric outcomes, where no significant disparities were detected, further endorsed the lack of any clinical differences between anterior and posterior myotomy.

Another matter of debate is GERD after POEM [22]. Although some reports showed a lower GERD incidence with POEM attributed to the preservation of the phrenoesophageal ligament [23, 24], a recent meta-analysis showed a higher frequency of symptomatic GERD after POEM (19%) compared to LHM (8.8%) [13]. Posterior myotomy was statistically associated with GERD in meta-regression, though it must be remembered that meta-regression is a powerful tool for addressing heterogeneity but not a causal relationship [25]. In the present meta-analysis, the incidence of GERD diagnosed via 24-hour pH monitoring, EGD or symptoms questionnaires was similar. Moreover, 24-hour pH monitoring in two RCTs revealed a non-significant higher incidence of GERD in the anterior group [15, 19].

Some technical refinements have been attempted to decrease the rate of GERD after POEM, such as a selective myotomy of the inner circular muscle [26], performing an endoscopic fundoplication [27, 28] or limiting the length of the gastric myotomy [3]. The proper location of the gastroesophageal junction (GEJ) is critical to ensure the effectiveness of the procedure and may have an impact on GERD [29, 30]. Posterior POEM could provide an additional benefit to this end by enabling the identification of the "Two Penetrating Vessels". Tanaka et al. [31] reported that when making the tunnel at 5 o’clock, two thick vessels can be detected at the right edge of the oblique muscle, the first being located immediately after passing the GEJ and the second 2-3 cm distally towards the gastric side. Despite the value of this landmark, the use of a second scope may be advisable to resear the length of the gastric tunnel [32].

Regarding POEM-related AEs, multicentre studies show that the technique is associated with a low rate of severe AEs (<1%) [12, 33]. Interestingly, we found that the total number of AEs and the risk of mucosotomy were significantly lower with posterior myotomy. This finding is consistent with an international registry of 1,826 cases where anterior myotomy was more frequent than posterior in patients experiencing an AE (70.1 vs. 27%, respectively) [12]. This could be explained by the fact that posterior orientation permits a better alignment of the knife for the myotomy, while the anterior approach requires a steeper angulation of the endoscope and the mucosa may be inadvertently injured. Besides, anterior tunneling runs closer to airway structures and the heart, which could potentially lead to more severe AEs. Also, cardiac arrhythmias and CO2 leaks toward the mediastinum and pleural cavity appear to be more frequent with the anterior approach [10, 12]. Unfortunately, the lack of a uniform definition impeded a stratified analysis by grade or type of AE, other than mucosotomy.

Procedure-related outcomes were also evaluated. As expected from our experience, the closure of the mucosal incision was faster after posterior tunneling. Conversely, the length of hospitalization was slightly increased (MD 0.31 days). It should be highlighted that although a statistically significant difference did exist, the clinical relevance of both findings is likely negligible.

Our meta-analysis has some limitations. The number of studies was low and two RCTs were only presented as abstracts. The latter limitation was overcome by contacting the authors, thoroughly reviewing study protocols, and a sensitivity analysis restricted to articles published in journals supporting our main findings. Besides, achalasia is a rare disease and RCTs evaluating POEM are scarce. Hence, a meta-analysis comprising almost 500 patients seems the best available tool to shed some light on this controversial matter. Finally, long-term differences between posterior and anterior myotomy could not be assessed since the maximum follow-up was one year.

Altogether, it seems that anterior tunneling should be reserved for selected cases where prior treatments or submucosal fibrosis impeded a posterior entry. Recently, we have adopted what we have termed the “modified” posterior POEM. The tunneling is made on the posterior wall and, by meticulous dissection, the posterior sling fibers are identified at the GEJ. At this point, the direction of the myotomy is slightly diverted toward the right-anterior wall (= 4 o’clock) to preserve the posterior sling fibers and potentially decrease the risk of GERD, although the effectiveness of this alternative has not yet been validated.

**CONCLUSION**

Posterior and anterior myotomy are both highly effective for the treatment of achalasia without differences in postprocedural GERD. Posterior myotomy exhibited a superior safety profile and lower incision closure time. Future...
RCTs with more extensive follow-up and addressing POEM refinements intended to decrease the incidence of GERD are awaited.

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Authors’ contribution: E.R. de S. and N.M. independently applied the search strategy and performed the study selection, data extraction, assessed the quality of the RCTs, analyzed the data and drafted the first version of the manuscript. E.R de S. performed the statistical analysis. A.M. reviewed the extracted data. All the authors participated in the: i) conception and design of the study, ii) interpretation of the data, iii) critical revision of the article for important intellectual content and iv) final approval of the article.

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INDEX

1. Search strategy ........................................................................................................................................ 3
2. Sensitivity and subgroup analysis ........................................................................................................... 5
   2.1 Clinical success 3-12 months after POEM ......................................................................................... 5
      2.1.1 Clinical success using only the definitions of the authors ......................................................... 5
      2.1.2 Mantel-Haenszel estimations ..................................................................................................... 6
      2.1.3 Excluding articles published as an abstract version only .......................................................... 6
      2.1.4 Full-thickness myotomy only .................................................................................................... 6
      2.1.5 Published data only .................................................................................................................. 7
   2.2 Gastroesophageal reflux disease after POEM .................................................................................... 8
      2.2.1 Fixed effect models .................................................................................................................... 8
      2.2.2 Mantel-Haenszel estimations ..................................................................................................... 9
      2.2.3 Excluding articles published as an abstract version only .......................................................... 9
      2.2.4 Full-thickness myotomy only .................................................................................................... 10
      2.2.5 Published data only .................................................................................................................. 11
   2.3 Adverse events .................................................................................................................................... 12
      2.3.1 Total adverse events .................................................................................................................. 12
      2.3.2 Mucosotomy ................................................................................................................................ 13
   2.4 Manometry outcomes .......................................................................................................................... 14
      2.4.1 Integrated relaxation pressure .................................................................................................... 14
      2.4.2 Lower esophageal sphincter pressure ........................................................................................ 14
   2.5 Procedure-related outcomes ............................................................................................................... 16
      2.5.1 Total procedure time .................................................................................................................. 16
      2.5.2 Myotomy time ............................................................................................................................ 16
      2.5.3 Mucosal incision closure time .................................................................................................... 17
      2.5.4 Length of hospitalization ........................................................................................................... 17
3. Publication bias ......................................................................................................................................... 18
   3.1 Clinical success .................................................................................................................................... 18
      3.1.1 Pooled relative risks .................................................................................................................. 18
      3.1.2 Eckardt score as quantitative outcome ...................................................................................... 18
   3.2 Gastroesophageal reflux disease ....................................................................................................... 19
      3.2.1 24-hour pH monitoring .............................................................................................................. 19
      3.2.2 Clinical symptoms ..................................................................................................................... 19
3.2.3 Reflux esophagitis at upper gastrointestinal endoscopy .............................................. 19
3.3 Adverse events .................................................................................................................. 20
  3.3.1 Total adverse events .................................................................................................. 20
  3.3.2 Mucosotomy ............................................................................................................. 20
3.4 Manometry outcomes ...................................................................................................... 21
  3.4.1 Integrated relaxation pressure .................................................................................... 21
  3.4.2 Lower esophageal sphincter pressure ....................................................................... 21
3.5 Procedure-related outcomes ............................................................................................ 21
  3.5.1 Total operation time .................................................................................................. 21
  3.5.2 Myotomy time ......................................................................................................... 22
  3.5.3 Mucosal incision closure time .................................................................................... 22
  3.5.4 Length of hospitalization .......................................................................................... 22
1. Search strategy

Search strategy for Pubmed:

((("esophageal achalasia"[MeSH Terms] OR achalasia[tiab]) AND ("POEM"[All Fields] OR "Per-oral endoscopic myotomy"[All Fields] OR (esophageal[All Fields] AND ("myotomy"[MeSH Terms] OR "myotomy"[All Fields])))) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))) AND ("2009(01/01"[PDAT] : "3000"[PDAT]))

Web of Knowledge:

TOPIC: ("POEM" OR "Peroral endoscopic myotomy" OR "Esophageal myotomy" OR "Per-oral endoscopic myotomy") AND TOPIC: (anterior OR posterior OR modified) AND TOPIC: ("randomized controlled trial" OR "controlled clinical trial" OR randomized OR randomly OR trial)

Timespan: 2009-2018.

Search language=Auto

Embase:

(‘poem’ OR ‘peroral endoscopic myotomy’ OR ‘per-oral endoscopic myotomy’) AND (achalasia OR ‘oesophagus achalasia’/exp) AND [2009-2018]/py AND (‘crossover procedure’:de OR ‘double-blind procedure’:de OR ‘randomized controlled trial’:de OR ‘single-blind procedure’:de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*:de,ab,ti) OR placebo*:de,ab,ti OR ((double* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti)

Clinicaltrials.gov:
POEM OR peroral endoscopic myotomy OR per-oral endoscopic myotomy

Filter: Completed/withdrawn/suspended/terminated.

**Cochrane library:**

"POEM" OR "Peroral endoscopic myotomy" OR "esophageal myotomy" OR “Per-oral endoscopic myotomy”, Publication Year from 2009 to August 19th in Trials and Cochrane reviews.
2. Sensitivity and subgroup analyses

To strengthen our analysis, we performed several subgroup analyses. Relative risks with their 95% confidence interval, Cochran’s Q test and $I^2$ of the following meta-analysis are embedded in the Figures. When $I^2$ was equal to zero, fixed-effect model subanalyses are not presented, since random-effects models provide identical results.

2.1 Clinical success 3-12 months after POEM

2.1.1 Clinical success using only the definitions of the authors

The trial by Ramchandani et al. did not provide Eckardt score as a qualitative variable.

When using the definition of Eckardt score ≤ 3 for this RCT:

Excluding the RCT without a qualitative definition for clinical success:
2.1.2 Mantel-Haenzsel estimations

| Study or Subgroup | Posterior | Anterior |
|-------------------|-----------|----------|
|                   | Events    | Total    | Events    | Total    |
| Slavropoulos 2018 | 110       | 114      | 93        | 100      |
| Khaskah 2019      | 83        | 71       | 62        | 66       |
| Vuong 2018        | 30        | 30       | 30        | 30       |
| Ramchandani 2018  | 27        | 27       | 26        | 26       |
| Total (5%) CI     | 57        | 55       | 100.00    | 100.00   |

Heterogeneity: $\tau^2 = 0.00$, $CH^2 = 0.00$, $df = 1$ ($P = 1.00$), $I^2 = 0$
Test for overall effect: $Z = 0.00$ ($P = 1.00$)

2.1.3 Excluding articles published as an abstract version only

| Study or Subgroup | Posterior | Anterior |
|-------------------|-----------|----------|
|                   | Events    | Total    | Events    | Total    |
| Slavropoulos 2018 | 110       | 114      | 93        | 100      |
| Khaskah 2019      | 83        | 71       | 62        | 66       |
| Vuong 2018        | 30        | 30       | 30        | 30       |
| Ramchandani 2018  | 27        | 27       | 26        | 26       |
| Total (5%) CI     | 57        | 55       | 100.00    | 100.00   |

Heterogeneity: $\tau^2 = 0.00$, $CH^2 = 0.00$, $df = 1$ ($P = 1.00$), $I^2 = 0$
Test for overall effect: $Z = 0.00$ ($P = 1.00$)

2.1.4 Full-thickness myotomy only

| Study or Subgroup | Posterior | Anterior |
|-------------------|-----------|----------|
|                   | Events    | Total    | Events    | Total    |
| Slavropoulos 2018 | 110       | 114      | 93        | 100      |
| Khaskah 2019      | 83        | 71       | 62        | 66       |
| Vuong 2018        | 30        | 30       | 30        | 30       |
| Ramchandani 2018  | 27        | 27       | 26        | 26       |
| Total (5%) CI     | 212       | 191      | 100.00    | 100.00   |

Heterogeneity: $\tau^2 = 0.00$, $CH^2 = 0.37$, $df = 2$ ($P = 0.63$), $I^2 = 0$
Test for overall effect: $Z = 1.17$ ($P = 0.24$)
2.1.5 Published data only

| Study or Subgroup | Posterior | Anterior | Risk Ratio |
|-------------------|-----------|----------|------------|
|                   | Events    | Total    | Weight     | IV, Random, 95% CI |
| Ishaqah 2018      | 63        | 71       | 60         | 18.2% 0.59 [0.37, 1.00] |
| Liuang 2018       | 30        | 30       | 30         | 50.7% 1.00 [0.84, 1.19] |
| Stavropoulos 2019 | 105       | 114      | 92         | 33.1% 1.00 [0.83, 1.20] |
| **Total (95% CI)**| **215**   | **196**  | 100.0%     | 1.00 [0.95, 1.04] |

Heterogeneity: Tau² = 0.000, Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect Z = 0.15 (P = 0.88)

| Study or Subgroup | Posterior | Anterior | Mean Difference |
|-------------------|-----------|----------|-----------------|
|                   | Mean     | SD       | Total           | Weight |
| Ramchandani 2017  | 0.51     | 0.59     | 27              | 0.62   | 25 53.6% -0.17 [-0.50, 0.18] |
| Stavropoulos 2019 | 0.24     | 0.65     | 114             | 0.26   | 101 86.0% 0.08 [-0.14, 0.22] |
| Liuang 2018       | 0.55     | 0.57     | 90              | 0.89   | 59 48.4% -0.30 [-0.65, 0.05] |
| **Total (95% CI)**| **57**   | **55**   | **100.0%**      |        |

Heterogeneity: Tau² = 0.000, Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect Z = 1.69 (P = 0.09)
2.2 Gastroesophageal reflux disease after POEM

2.2.1 Fixed effect models

2.2.1.1 24-hour pH monitoring

| Study or Subgroup | Posterior Events | Anterior Events | Total Events | Weight | Risk Ratio IV, Fixed, 95% CI |
|-------------------|------------------|-----------------|-------------|--------|-----------------------------|
| Kinoshita 2016    | 25               | 60              | 23          | 59     | 1.05 [0.57, 1.28]           |
| Ramchandani 2018  | 10               | 27              | 4           | 25     | 4.5 [0.83, 8.45]            |
| Stavropoulos 2019 | 81               | 49              | 32          | 48     | 57.9 [0.91, 1.12]           |
| Yueyong 2016      | 10               | 30              | 8           | 30     | 25.25 [0.57, 2.73]          |
| Total (95% CI)    | 166              | 150             | 100%        | 0.95   | 0.77, 1.18                  |
| Total events      | 78               | 73              |             |        |                             |
| Heterogeneity: Chisq = 9.78, df = 3 (P = 0.29); I² = 21% |
| Test for overall effect: Z = 0.44 (P = 0.66) |

2.2.1.2 Clinical symptoms

| Study or Subgroup | Posterior Events | Anterior Events | Total Events | Weight | Risk Ratio IV, Fixed, 95% CI |
|-------------------|------------------|-----------------|-------------|--------|-----------------------------|
| Ramchandani 2018  | 7                | 27              | 5           | 25     | 18.79 [0.64, 3.56]          |
| Stavropoulos 2018 | 21               | 114             | 27          | 183    | 37.54 [0.41, 1.13]          |
| Yueyong 2016      | 7                | 30              | 5           | 30     | 18.60 [0.50, 3.92]          |
| Total (95% CI)    | 47               | 155             | 100%        | 0.85   | 0.56, 1.29                  |
| Total events      | 35               | 37              |             |        |                             |
| Heterogeneity: Chisq = 2.30, df = 2 (P = 0.33); I² = 13% |
| Test for overall effect: Z = 0.70 (P = 0.48) |

2.2.1.3 Reflux esophagitis at upper gastrointestinal endoscopy

| Study or Subgroup | Posterior Events | Anterior Events | Total Events | Weight | Risk Ratio IV, Fixed, 95% CI |
|-------------------|------------------|-----------------|-------------|--------|-----------------------------|
| Ramchandani 2018  | 9                | 27              | 6           | 25     | 18.79 [0.59, 3.34]          |
| Stavropoulos 2018 | 39               | 49              | 30          | 48     | 82.81 [0.10, 1.37]          |
| Yueyong 2016      | 5                | 30              | 5           | 30     | 8.40 [0.32, 1.10]           |
| Total (95% CI)    | 106              | 104             | 100%        | 1.04   | 0.78, 1.38                  |
| Total events      | 44               | 41              |             |        |                             |
| Heterogeneity: Chisq = 0.41, df = 2 (P = 0.79); I² = 0% |
| Test for overall effect: Z = 0.24 (P = 0.99) |
2.2.2 Mantel-Haenzsel estimations

2.2.2.1 24-hour pH monitoring

| Study or Subgroup        | Posterior Events | Anterior Events | Weight | Risk Ratio |
|--------------------------|------------------|-----------------|--------|------------|
|                          | Events           | Total           |        | M-H, Random, 95% CI |
| Kharechko 2018           | 25               | 60              | 0.0%   | 0.85 [0.67, 1.26] |
| Ramachandran 2018        | 10               | 27              | 4      | 2.31 [0.63, 8.45] |
| Stavropoulos 2018        | 21               | 48              | 32     | 0.51 [0.30, 0.88] |
| Yupang 2018              | 10               | 30              | 6      | 1.25 [0.57, 2.73] |
| Total (95% CI)           | 106              | 180             | 100.0% | 0.98 [0.74, 1.30] |

Total events: 75 - 73
Heterogeneity: Tau² = 0.02; Chi² = 3.98, df = 3 (P = 0.28); I² = 25%
Test for overall effect: Z = 0.11 (P = 0.91)

2.2.2.2 Clinical symptoms

| Study or Subgroup        | Posterior Events | Anterior Events | Weight | Risk Ratio |
|--------------------------|------------------|-----------------|--------|------------|
|                          | Events           | Total           |        | M-H, Random, 95% CI |
| Ramachandran 2018        | 7                | 27              | 6      | 1.30 [0.47, 3.56] |
| Stavropoulos 2018        | 21               | 114             | 27     | 0.60 [0.41, 1.13] |
| Yupang 2018              | 7                | 30              | 5      | 1.40 [0.50, 3.62] |
| Total (95% CI)           | 171              | 155             | 100.0% | 0.89 [0.55, 1.42] |

Total events: 35 - 37
Heterogeneity: Tau² = 0.03; Chi² = 2.31, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 0.50 (P = 0.81)

2.2.2.3 Reflux esophagitis at upper gastrointestinal endoscopy

| Study or Subgroup        | Posterior Events | Anterior Events | Weight | Risk Ratio |
|--------------------------|------------------|-----------------|--------|------------|
|                          | Events           | Total           |        | M-H, Random, 95% CI |
| Ramachandran 2018        | 6                | 27              | 6      | 1.30 [0.58, 3.54] |
| Stavropoulos 2018        | 30               | 49              | 30     | 1.09 [0.73, 1.37] |
| Yupang 2018              | 5                | 30              | 5      | 1.10 [0.32, 3.10] |
| Total (95% CI)           | 106              | 194             | 100.0% | 1.04 [0.78, 1.38] |

Total events: 44 - 41
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

2.2.3 Excluding articles published as an abstract version only

2.2.3.1 24-hour pH monitoring

| Study or Subgroup        | Posterior Events | Anterior Events | Weight | Risk Ratio |
|--------------------------|------------------|-----------------|--------|------------|
|                          | Events           | Total           |        | IV, Random, 95% CI |
| Kharechko 2018           | 25               | 69              | 0.0%   | 0.85 [0.57, 1.26] |
| Ramachandran 2018        | 10               | 27              | 5      | 2.31 [0.63, 8.45] |
| Stavropoulos 2018        | 21               | 48              | 32     | 0.91 [0.68, 1.21] |
| Yupang 2018              | 10               | 30              | 8      | 1.25 [0.57, 2.73] |
| Total (95% CI)           | 57               | 110             | 100.0% | 1.57 [0.84, 2.91] |

Total events: 30 - 12
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.15)
2.2.3.2 Clinical symptoms

| Study or Subgroup | Posterior Events | Anterior Events | Risk Ratio IV, Random, 95% CI |
|-------------------|-----------------|----------------|-------------------------------|
| Ramchandani 2018  | 7               | 27             | 0.33 [0.14, 0.78]             |
| Yang 2018         | 7               | 28             | 1.00 [0.50, 2.00]             |

Total (95% CI) 57 55 1.00 [0.65, 2.77]

Test for overall effect: Z = 0.81 (P = 0.42)

2.2.3.3 Reflux esophagitis at upper gastrointestinal endoscopy

| Study or Subgroup | Posterior Events | Anterior Events | Risk Ratio IV, Random, 95% CI |
|-------------------|-----------------|----------------|-------------------------------|
| Ramchandani 2018  | 8               | 27             | 1.38 [0.58, 3.32]             |
| Yang 2018         | 5               | 10             | 1.60 [0.92, 2.79]             |

Total (95% CI) 57 55 1.23 [0.81, 2.46]

Test for overall effect: Z = 0.33 (P = 0.39)

2.2.4 Full-thickness myotomy only

2.2.4.1 24-hour pH monitoring

| Study or Subgroup | Posterior Events | Anterior Events | Risk Ratio IV, Random, 95% CI |
|-------------------|-----------------|----------------|-------------------------------|
| Kasaih 2018       | 25              | 50             | 0.86 [0.57, 1.29]             |
| Yang 2018         | 10              | 20             | 2.31 [0.83, 6.49]             |

Total (95% CI) 135 130 0.97 [0.69, 1.35]

Test for overall effect: Z = 0.20 (P = 0.84)

2.2.4.2 Clinical symptoms

| Study or Subgroup | Posterior Events | Anterior Events | Risk Ratio IV, Random, 95% CI |
|-------------------|-----------------|----------------|-------------------------------|
| Ramchandani 2018  | 7               | 27             | 1.30 [0.47, 3.66]             |
| Yang 2018         | 7               | 30             | 1.40 [0.50, 3.92]             |

Total (95% CI) 141 125 0.80 [0.46, 1.39]

Test for overall effect: Z = 0.77 (P = 0.44)
2.2.4.3 Reflux esophagitis at upper gastrointestinal endoscopy

2.2.5 Published data only

2.2.5.1 24-hour pH monitoring

2.2.5.2 Clinical symptoms

2.2.5.3 Reflux esophagitis at upper gastrointestinal endoscopy
2.3 Adverse events

2.3.1 Total adverse events

2.3.1.1 Mantel-Haenzsel estimations

2.3.1.2 Excluding articles published as an abstract version only

2.3.1.3 Full-thickness myotomy only

2.3.1.4 Published data only
2.3.2 Mucosotomy

2.3.2.1 Mantel-Haenzsel estimations

Not estimable.

2.3.2.2 Excluding articles published as an abstract version only

Not estimable.

2.3.2.3 Full-thickness myotomy only

2.3.2.4 Published data only
2.4 Manometry outcomes

2.4.1 Integrated relaxation pressure

2.4.1.1 Excluding articles published as an abstract version only

2.4.1.2 Full-thickness myotomy only

2.4.1.3 Published data only

2.4.2 Lower esophageal sphincter pressure

2.4.2.1 Excluding articles published as an abstract version only

2.4.2.2 Full-thickness myotomy only
### Table

| Study or Subgroup | Posterior Mean [mmHg] | SD [mmHg] | Total Mean [mmHg] | Anterior Mean [mmHg] | SD [mmHg] | Total | Weight | IV, Random, 95% CI [mmHg] | Mean Difference | IV, Random, 95% CI [mmHg] |
|-------------------|-----------------------|-----------|-------------------|----------------------|-----------|-------|--------|---------------------------|-----------------|---------------------------|
| Ramsahandi 2018   | 11.68                 | 4.37      | 27                | 13.82                | 5.3       | 25    | 20.9%  | -2.14 [4.91, 0.63]         | -2.14 [4.91, 0.63] |
| Stamnopolitis 2018| 12.1                  | 3.4       | 30                | 20.9                 | 9.7       | 31    | 0.9%   | -0.20 [4.45, 0.03]         | -0.20 [4.45, 0.03] |
| Yang 2018         | 12.3                  | 1.9       | 30                | 13.3                 | 3.5       | 30    | 79.1%  | -1.00 [2.43, 0.43]         | -1.00 [2.43, 0.43] |
| Total (95% CI)    | 12.3                  | 1.9       | 57                | 13.3                 | 3.5       | 55    | 100.0% | -1.24 [2.51, 0.03]         | -1.24 [2.51, 0.03] |

**Heterogeneity:** Test for heterogeneity: $Q = 0.00, df = 1, P = 0.47; I^2 = 0$

**Test for overall effect:** $Z = 1.91 (P = 0.06)$
2.5 Procedure-related outcomes

2.5.1 Total procedure time

2.5.1.1 Excluding articles published as an abstract version only

2.5.1.2 Full-thickness myotomy only

2.5.1.3 Published data only

2.5.2 Myotomy time

2.5.2.1 Excluding articles published as an abstract version only

Not estimable

2.5.2.2 Full-thickness myotomy only
2.5.2.3 Published data only
Not estimable

2.5.3 Mucosal incision closure time

2.5.3.1 Excluding articles published as an abstract version only
Not estimable

2.5.3.2 Full-thickness myotomy only

| Study or Subgroup | Posterior | Anterior | Mean Difference | Mean Difference |
|-------------------|-----------|----------|----------------|----------------|
|                   | [Min:Max] | [Min:Max]| Total [Min:Max]| Total [Min:Max]|
|                   | SD [Min:Max] | SD [Min:Max]|                   |                   |
|                   | Total [Min:Max]| Total [Min:Max]|                   |                   |
|                   | Weight | Weight |                  |                  |
|                   | IV, Random, 95% CI [Min:Max] | IV, Random, 95% CI [Min:Max] |                  |                  |
|                   |                   |                   |                  |                  |
| Ranmarchandani 2018 | 6.46 | 3.44 | 77 | 8.15 | 4.01 | 25 | 41.8% | 1.63 [1.51, 1.75] | -2.70 [-4.24, -1.16] |
| Stempouil 2018 | 5.5 | 3.5 | 114 | 8.2 | 7.2 | 101 | 50.2% | -2.26 [-3.46, -1.07] |
| Total (95% CI) | 126 | 100.0% |                   |                  |
| Heterogeneity: Tau² = 0.00, CH² = 3.81, df = 1, p = 0.14, I² = 0% |
| Test for overall effect: Z = 3.78, p = 0.0002 |

2.5.3.3 Published data only

2.5.4 Length of hospitalization

2.5.4.1 Excluding articles published as an abstract version only

| Study or Subgroup | Posterior | Anterior | Mean Difference | Mean Difference |
|-------------------|-----------|----------|----------------|----------------|
|                   | [Min:Max] | [Min:Max]| Total [Min:Max]| Total [Min:Max]|
|                   | SD [Min:Max] | SD [Min:Max]|                   |                   |
|                   | Total [Min:Max]| Total [Min:Max]|                   |                   |
|                   | Weight | Weight |                  |                  |
|                   | IV, Random, 95% CI [Min:Max] | IV, Random, 95% CI [Min:Max] |                  |                  |
|                   |                   |                   |                  |                  |
| Stempouil 2018 | 2.4 | 3.6 | 114 | 2.1 | 2.5 | 101 | 12.2% | 0.30 [0.02, 0.38] | 0.25 [0.05, 0.46] |
| Yaping 2018 | 7.1 | 3.6 | 32 | 6.5 | 1.6 | 31 | 10.6% | 0.00 [0.0, 0.24] | 0.31 [0.04, 0.59] |
| Ranmarchandani 2018 | 4.31 | 0.82 | 30 | 4.06 | 0.24 | 30 | 81.6% | 0.25 [0.05, 0.46] |                   |
| Total (95% CI) | 60 | 100.0% |                   |                  |
| Heterogeneity: Tau² = 0.00, CH² = 0.50, df = 1, p = 0.34, I² = 0% |
| Test for overall effect: Z = 2.23, p = 0.03 |

2.5.4.2 Full-thickness myotomy only

| Study or Subgroup | Posterior | Anterior | Mean Difference | Mean Difference |
|-------------------|-----------|----------|----------------|----------------|
|                   | [Min:Max] | [Min:Max]| Total [Min:Max]| Total [Min:Max]|
|                   | SD [Min:Max] | SD [Min:Max]|                   |                   |
|                   | Total [Min:Max]| Total [Min:Max]|                   |                   |
|                   | Weight | Weight |                  |                  |
|                   | IV, Random, 95% CI [Min:Max] | IV, Random, 95% CI [Min:Max] |                  |                  |
|                   |                   |                   |                  |                  |
| Stempouil 2018 | 2.4 | 3.6 | 114 | 2.1 | 2.5 | 101 | 0.0% | 0.30 [0.02, 0.38] | 0.25 [0.05, 0.46] |
| Yaping 2018 | 7.1 | 3.6 | 32 | 6.5 | 1.6 | 31 | 0.0% | 0.00 [0.0, 0.24] | 0.31 [0.04, 0.59] |
| Ranmarchandani 2018 | 4.31 | 0.82 | 30 | 4.06 | 0.24 | 30 | 81.6% | 0.25 [0.05, 0.46] |                   |
| Total (95% CI) | 62 | 100.0% |                   |                  |
| Heterogeneity: Tau² = 0.00, CH² = 0.01, df = 1, p = 0.91, I² = 0% |
| Test for overall effect: Z = 1.72, p = 0.09 |

2.5.4.3 Published data only
3. Publication bias

3.1 Clinical success

3.1.1 Pooled relative risks

3.1.2 Eckardt score as quantitative outcome
3.2 Gastroesophageal reflux disease

3.2.1 24-hour pH monitoring

3.2.2 Clinical symptoms

3.2.3 Reflux esophagitis at upper gastrointestinal endoscopy
3.3 Adverse events

3.3.1 Total adverse events

3.3.2 Mucosotomy
3.4 Manometry outcomes

3.4.1 Integrated relaxation pressure

3.4.2 Lower esophageal sphincter pressure

3.5 Procedure-related outcomes

3.5.1 Total operation time
3.5.2 Myotomy time

3.5.3 Mucosal incision closure time

3.5.4 Length of hospitalization