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Efficacy and safety of full-thickness versus circular peroral endoscopic myotomy for treatment of achalasia: a systematic review and meta-analysis

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Abstract

Background Peroral endoscopic myotomy (POEM) is a treatment for esophageal achalasia with 2 variations in myotomy depth: full-thickness myotomy (FTM) and circular myotomy (CM). This systematic review and meta-analysis compares the efficacy and safety of these variations.

Methods Major health databases and registers, including Embase, MEDLINE and Cochrane were searched systematically. The primary outcome was clinical success, while secondary outcomes included change in achalasia severity scores, post-POEM gastroesophageal reflux disease (GERD) measures, procedural time, and adverse events. Meta-analysis was conducted using random-effects models, with risk ratios (RR) and mean differences (MD) calculated for dichotomous and continuous variables, respectively.

Results Nine observational studies compared FTM and CM in 1,203 patients. FTM was performed in more severe achalasia and demonstrated similar clinical success to CM (RR 1.01, 95% confidence interval [CI] 0.98-1.04; P=0.55; n=6) and procedural time (MD 3.49 min, 95%CI -2.79-9.78; P=0.28, I^2=66%; n=3). FTM was associated with increased post-POEM GERD outcomes, post-POEM pain (RR 1.94, 95%CI 1.27-2.95; P=0.002; n=2), and length of stay (LOS) (MD 0.85 days, 95%CI 0.11-1.59; P=0.02; I^2=0%; n=2); however, association with esophagitis disappeared when proton pump inhibitors use was accounted for (RR 1.68, 95%CI 0.89-3.16; P=0.11; I^2=23%; n=4). CM was associated with higher rates of subcutaneous emphysema (RR 0.59, 95%CI 0.43-0.81; P=0.001; n=5).

Conclusions FTM and CM have comparable observed clinical efficacy and procedural time, with minimal differences in complications. FTM may be preferred in more severe achalasia and its association with post-POEM GERD may have been overestimated, but it may increase post-POEM pain and LOS.

Keywords Peroral endoscopic myotomy, myotomy depth, efficacy, safety

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Conflict of Interest: None

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Introduction

Peroral endoscopic myotomy (POEM) is an endoscopic treatment for esophageal achalasia, a condition characterized by ineffective relaxation of the lower esophageal sphincter (LES), which leads to symptoms such as dysphagia, chest pain, and weight loss [1]. POEM involves several steps: making an initial incision, creating a submucosal tunnel, performing the myotomy of the LES and closing the mucosal incision, all to reduce LES pressure [2]. Variations in the procedure exist, including the depth of this myotomy [3].

Circular myotomy (CM) is the original, more common variation [4], where the inner circular muscle at the LES

is dissected [4]. Later, full-thickness myotomy (FTM) was introduced, where the thin outer longitudinal muscle layer is also cut [4]. Both methods have been reported to be similarly effective [5-7], though CM is thought to be associated with a lower incidence of post-POEM gastroesophageal reflux disease (GERD) [6,7], possibly because of the preservation of the outer longitudinal muscle layers [8], but is also associated with longer procedural times [5,7].

It is unclear whether FTM or CM leads to more POEM-related complications. Gas-related complications [9] associated with POEM include subcutaneous emphysema, pneumothorax and pneumoperitoneum. Other complications include mucosal injury [5], bleeding, and perforation. Advocates of CM argue that sparing the outer longitudinal muscle preserves a barrier to the mediastinum, theoretically reducing these gas-related complications [8]. This is contradicted by 2 studies [5,9] showing that CM was associated with more gas-related complications. There is also an association between increased mucosal injury and CM [5].

Recent studies [10,11] have compared FTM and CM outcomes, but no meta-analysis has compared the efficacy and safety between these methods. Therefore, our aim was to carry out a systematic review and meta-analysis (SRMA) to compare the efficacy and safety of FTM and CM in terms of short- and long-term clinical success, procedural time, POEM-related complications, length of hospital stay (LOS) and post-POEM GERD.

Materials and methods

Search strategy

A comprehensive search strategy to identify reports of studies comparing FTM and CM myotomy in POEM was constructed in Embase (Embase.com, Elsevier) by an experienced health sciences librarian (WL-S), using truncated keywords, phrases and subject headings (Supplementary Table 1). This strategy was translated to MEDLINE (PubMed platform, National Center for Biotechnology Information, National Library of Medicine), Cochrane Central Register of Controlled Trials (CochraneLibrary.com, Wiley), Web of Science Core Collection, Korean Citation Index (Web of Science platform, Clarivate) and Global Index Medicus (World Health Organization), with an initial search performed January 29, 2024, and updated September 10, 2024 (Supplementary Table 2). No limits were imposed on publication date or language. All results were exported to EndNote 21 citation management software (Clarivate, Philadelphia, PA, USA).

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Study screening

To screen studies, duplicates were removed by successive iterations of EndNote's duplicate detection algorithms and manual inspection. Next, 2 authors (SD and MA) reviewed records and excluded duplicated studies not removed by the software, studies on animals or children, review articles, case reports/series, study protocols, or any studies that did not compare FTM and CM. Experimental and observational studies published in all languages and countries were considered. One manuscript screened by title written exclusively in Mandarin [10] was translated preliminarily by ChatGPT 4.0 and afterwards by a native Mandarin speaker (AZ) to verify the methodology and results section. This resulted in the inclusion of all studies on adult patients who underwent POEM, directly comparing FTM to CM for at least 1 outcome of interest. Any discrepancies in study inclusion/exclusion between SD and MA was resolved by another author (MP). Our study selection process was modeled after the flow diagram recommended by the PRISMA 2020 statement [12] (Fig. 1).

Extraction of data and outcome selection

The baseline patient characteristics in each study included demographics, disease course, prior achalasia treatment and Chicago Classification of achalasia [13] (Table 1). The study methodologies included study type, POEM technique, conditions to perform FTM vs. CM, post-POEM proton pump inhibitor (PPI) treatment, and follow-up periods (Table 2). Clinical success, defined as an Eckardt score <3, was our primary outcome, being the most reported outcome across studies; this score focuses on symptom relief, which is the primary goal of the procedure. Secondary outcomes for efficacy were reduction in lower esophageal sphincter pressure (LESP) measurement and Eckhardt score. Secondary outcomes measuring postprocedural acid reflux included GERD symptoms, esophagitis on esophagogastroduodenoscopy (EGD), pathological acid exposure by pH monitoring, considered abnormal if the DeMeester score was >14.72 [14], and clinically relevant GERD, defined as pathological acid exposure on pH monitoring [6], and either GERD symptoms or esophagitis on EGD [15]. The final set of secondary outcomes included the duration of the procedure, LOS, and peri-POEM adverse events. The first adverse event was recorded as a compilation of reported bleeding, mucosal injury and (mucosal) perforation across studies, termed broadly in this study as "tissue injury". Subcutaneous emphysema, pneumothorax, pneumoperitoneum and postprocedural pain events were also recorded as secondary outcomes. The primary and secondary outcomes collected were recorded in a Microsoft Excel spreadsheet. Clinical success, incidence of periprocedural adverse events, including pain, and all

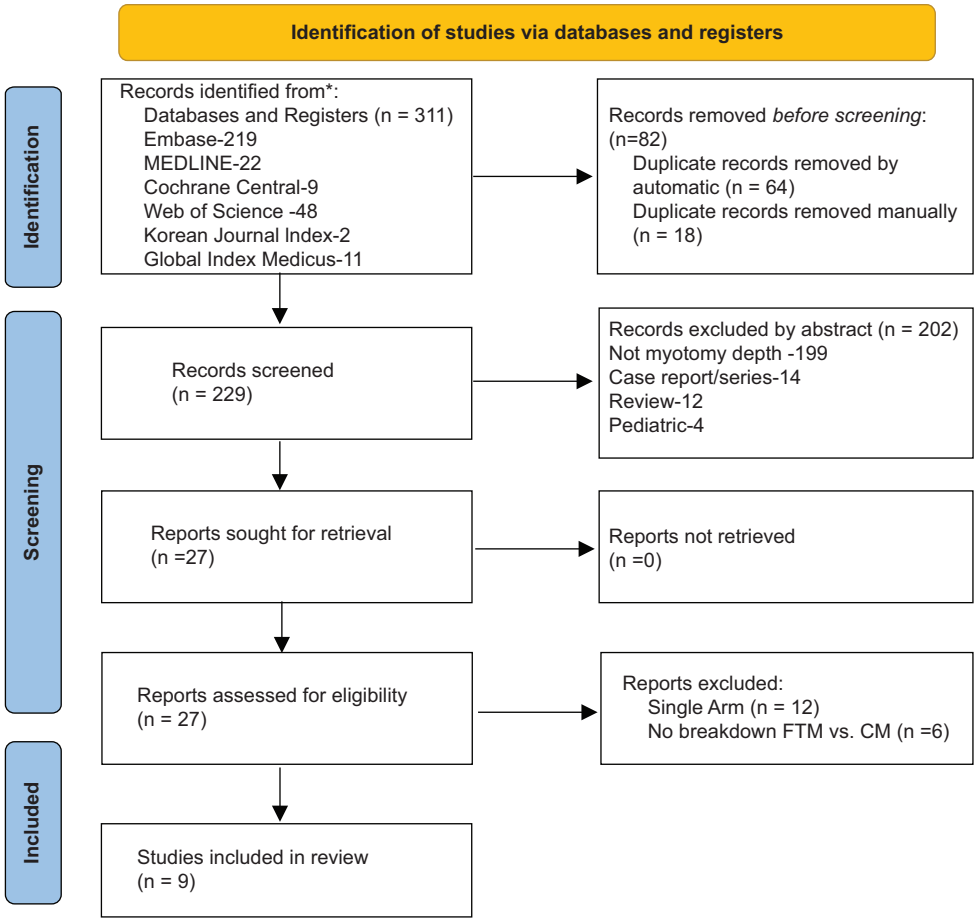

Figure 1 PRISMA 2020 flow diagram for systematic reviews including searches of registrars and databases
CM, circular myotomy; FTM, full-thickness myotomy

post-POEM GERD outcomes were recorded as an incidence over the total sample. Pre and post Eckardt scores and LESP measurements, procedural time and LOS were recorded as a mean ±/- standard deviation (SD).

Meta-analysis

Outcome data were exported to Review Manager 5.4.1 software (Revman) to perform the meta-analysis. The dichotomous variables of clinical success, incidence of periprocedural adverse events, and all acid reflux outcomes were pooled as risk ratios (RR) with confidence intervals (CI) to determine an overall effect size. The continuous outcomes of differences in pre vs. post LESP, pre vs post Eckardt scores, procedural time and LOS were pooled as mean differences (MD) with CI to determine an overall effect size. To determine if there were significant differences between FTM and CM in pre vs. post Eckardt and LESP values, the pre- vs. post-POEM means and SD were pooled to generate an MD for FTM and CM separately. The FTM and CM MDs were then compared by subgroup analysis with chi-square testing to generate a P-value in Revman. In view of the anticipated heterogeneity among studies, the random-effects model was used to calculate all the RRs, MDs and CIs (Table 2). A P-value of <0.05 was considered statistically significant. Statistical heterogeneity was assessed using the Higgins I^2 index calculated by Revman.

Clinical heterogeneity was addressed with subgroup and sensitivity analyses. For clinical success, GERD symptoms and esophagitis outcomes, 2 subgroups were defined as studies lasting closer to 1 year [5,11,16] or 3 years [6,7,10], and subgroup differences between groups were calculated in Revman to assess whether clinical success rates varied between FTM and CM depending on the duration of follow up. Three layers of sensitivity analysis were performed. First, when the Higgins I^2 index was 75-100%, demonstrating high heterogeneity [17], studies were individually excluded and the single study that lowered the I^2 index to the lowest extent below 75% was excluded. Second, 2 studies [10,11] assessing clinical success were noted to have statistically higher pre-POEM Eckardt scores, reflecting more severe baseline achalasia in the FTM group, so these studies were pooled separately. Third, 2 studies used PPIs [6,7] only when esophagitis was diagnosed via EGD, so these were excluded from the pooled analysis to assess esophagitis rates when PPIs were given preemptively post-POEM.

No funnel plot was utilized to assess publication bias, since no pooled analysis exceeded 10 outcomes [18]. Quality

Table 1 Baseline characteristics of studies comparing FTM vs. CM in POEM

Author, year [ref.]	N (FTM, CM)	Tx	% Male	Age (years) (mean±SD)	Preprocedural Eckardt Score (Mean±SD)	Preprocedural LESP (Mean±SD)	Chicago achalasia classification (%)			Sigmoid	Prior Heller myotomy (%)	Prior POEM (%)	Other achalasia therapy (i.e. PD, Botox) (%)	Disease course (years) (mean±SD, median range), or (%)	Significant difference in FTM vs. CM (P-value)
							1	2	3						
Li *et al*, 2013 [5]	234 (103, 131)	FTM	43.7	37.6±13.2	7.6±2.0	30.5±14.5	-	-	-	10.7	5.8	0.0	37.9	7.2±7.7	Age (P=0.04)
		CM	51.1	41.5±16.3	8.0±1.9	29.6±11.5	-	-	-	5.3	6.1	0.8	34.4	7.9±9.4	
J Wang *et al*, 2015 [21]	46 (31, 15)	Total	37.0	44.0	8.4±3.2	39.4±10.1	57.0	41.0	2.0	0.2	0.0	2.2	15.2	-	
X Wang *et al*, 2015 [9]	216 (133, 83)	Total	50.5	41.9	6.2±1.7	-	-	-	-	5.1	3.2	0.0	13.0	-	
X Wang *et al*, 2016 [6]	58 (24, 34)	FTM	45.8	44.5±14.5	6.5±1.6	38.3±6.0	15.6	75.0	9.4	14.3	-	-	26.3	6.6±8.4	
		CM	40.6	41.5±10.8	6.4±1.3	39.5±7.1	16.7	75.0	8.3	3.1	-	-	23.1	5.3±7.0	
Duan *et al*, 2017 [7]	123 (70, 53)	FTM	47.1	43.0±14.0	7.3±1.7	35.0±7.3	17.1	72.9	10.0	8.6	20.0	-	16.7	5.0 (0.5-33.0)	
		CM	56.6	41.0±13.0	7.3±1.9	34.0±6.8	12.9	55.7	7.1	9.4	12.5	-	17.8	4.5 (0.5-20.0)	
Kumbari *et al*, 2017 [20]	282 (256, 26)	Total	51.7	49.1±17.4	7.8±2.1	-	17.4	51.8	7.4	5.2	5.0	-	23.5	-	
Li *et al*, 2017 [16]	33 (19, 14)	FTM	-	45.4±12.3	6.7±1.8	27.7±15.6	-	-	-	-	0.0	0.0	21.1	6.4±7.4	
		CM	-	46.1±15.4	6.6±1.9	37.4±17.4	-	-	-	-	0.0	0.0	28.6	5.0±4.2	
Dezhi *et al*, 2018 [10]	53 (32, 21)	FTM	46.9	43.0±13.8	8.1±1.6	34.6±6.9	21.9	63.0	15.6	-	-	-	18.8	5.0 (2.5-10.0)	Pre-POEM Eckart (P=0.023)
		CM	33.3	44.4±14.9	7.4±1.4	35.9±8.3	23.8	61.9	14.3	-	-	-	24.0	4.0 (2.0-8.0)	
Sanavio *et al*, 2024 [11]	158 (33, 125)	FTM	45.4	63.7+/-18.8	8.03 (±1.71)	-	12.1	60.6	27.3	-	0	-	-	-	Pre-POEM Eckart (P=0.027)
		CM	57.6	61.8+/-16.1	7.04 (±2.30)	-	8.0	69.6	16.8	-	0	-	-	-	

FTM, full-thickness myotomy; CM, circular myotomy; POEM, per-oral endoscopic myotomy; Tx, treatment; SD, standard deviation; sigmoid, sigmoid esophagus; LESP, lower esophageal sphincter pressure; PD, pneumatic dilation; stenting, esophageal stenting

Table 2 Study methodologies for FTM vs. CM in POEM

			POEM Landmarks							
Author, Year [ref.]	Type of study	Mean overall follow up time period (months) (Mean±SD or (range))	Initial incision/ injection	Myotomy start	Myotomy extension	Myotomy length (cm) (mean±SD or (range) or %) P if<0.05	Orientation	Notes on condition (s) to perform FTM	PPI use post-POEM (weeks)	Exclusion criteria
Li *et al*, 2013 [5]	Retro Cohort	FTM: 6.1±4.3 CM: 10.5±3.8	10 cm above EGJ	2 cm distal to ME or 6-8 cm above EGJ	2-3 cm into stomach	Esophagus: FTM: 8.1±1.3 CM: 7.9±1.3 Gastric: FTM: 2.2±0.6 CM: 2.3±0.5	Posterior (5-6 o'clock)	"Inadvertent" FTM performed in 37/103 FTM patients	4-8	• Severe cardiopulmonary disease, other systemic disease with unacceptable procedural risk • Pseudoachalasia • Megaesophagus (>7 cm) • Hiatal hernia (>2 cm)
J. Wang *et al*, 2015 [21]	Prosp Cohort	Overall: 3.0	-	1-2 cm distal to ME	1-2 cm into cardia	5.4 (3.4-7.5)	Right lateral (2-3 o'clock)	Endoscope difficult to pass through narrowed LES	4	• Prior esophageal or gastric surgery (except POEM/PD) • Malignant or precancerous esophageal lesions
X. Wang *et al*, 2015 [9]	Retro-Analysis	Overall: 16.8 (6.0-33.0)	10 cm above EGJ	2-3 cm distal to ME	3 cm distal to EGJ	Value NR	Right posterior	-	Not given	NR
X. Wang *et al*, 2016 [6]	Retro Cohort	FTM: 38.6±1.8 CM: 39.8±4.2	8-10 cm above EGJ	2-3 cm distal to ME	3 cm into stomach	Standard length, Value NR	Posterior (5 o'clock)	Less satisfactory results from CM	Only in response to esophagitis	• Patients with incomplete 24hr pH monitoring, manometry, GERD evaluation, or lost to follow up
Duan *et al*, 2017 [7]	Retro Cohort	Overall: 30.0 (24.0-46.0)	10 cm above EGJ	2-3 cm distal to ME	3 cm distal to EGJ	FTM: 10.5±1.3 CM: 10.5±1.2	Right posterior	-	Only in response to esophagitis	• Active esophagitis • Giant ulcer at EGJ • Pseudoachalasia • Severe coagulopathy • Severe cardiopulmonary disease or other systemic disease with unacceptable procedural risk
Kumbari *et al*, 2017 [20]	Retro Case–control	Overall: 12.0	NR	NR	2-3 cm into cardia	Esophagus: 8.6±2.4 Gastric: 3.2±1.0	Anterior (97.2) Posterior (2.8)	-	2	• Altered Upper GI anatomy (except HM) • No 24-h pH study or upper GI endoscopy≥3 months post-procedure

(*Contd...*)

Table 2 (*Continued*)

					POEM Landmarks					
Author, Year [ref.]	Type of study	Mean overall follow up time period (months) (Mean±SD or (range))	Initial incision/ injection	Myotomy start	Myotomy extension	Myotomy length (cm) (mean±SD or (range) or %) P if<0.05	Orientation	Notes on condition (s) to perform FTM	PPI use post-POEM (weeks)	Exclusion criteria
Li *et al*, 2017 [16]	Retro Cohort	Overall: 12.0	10 cm above EGJ	2 cm distal to ME	2-3 cm into stomach (FTM was partial from 2 cm above EGJ to fundus)	FTM: 10.3±0.9 CM: 9.9±1.7	Posterior (6 o'clock)	-	4-5	• Recent anticoagulants or hormonal drug • Severe cardiopulmonary disease or other systemic disease with unacceptable procedural risk • Severe erosion or fibrosis in lower segment or severe sigmoid shaped esophagus
Dezhi *et al*, 2018 [10]	Retro Cohort	FTM: 44.0 (32.0-50.8) CM: 35.5 (32.0-42.6)	10 cm above EGJ	2-3 cm distal to ME	2-3 cm below EGJ	-	Right posterior	Less satisfactory results from CM	4-6	• Patients with incomplete 24-h pH monitoring, manometry, or lost to follow up
Sanavio *et al*, 2024 [11]	Retro Cohort	FTM: 12.7±NR CM: 11.3±NR P=0.529	10 cm above EGJ	6 cm above EGJ	2 into cardia	FTM: 8.97±3.57 CM: 7.74±2.72 (P=0.021)	Posterior	Different centers performed FTM vs. CM	56	• Patients with mediastinal or esophagogastric neoplasia. • Patients with evidence of esophagitis prior to or during the POEM procedure. • Patients with a history of anti-reflux surgery

CM, circular myotomy; FTM, full-thickness myotomy; POEM, peroral endoscopic myotomy; Retro, retrospective; Prosp, prospective; SD, standard deviation; EGJ, esophagogastroesophageal junction; cm, centimeter; LES, lower esophageal sphincter; PPI, proton-pump inhibitor; PD, pneumatic dilation; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HM, Heller myotomy; ME, mucosal entry, NR, not reported

assessment was performed using the Methodological Index for Non-Randomized Studies (MINORS) criteria [19]. The aims, methods, results and clinical implications detailed in our manuscript are reported in accordance with the 2020 PRISMA Checklist (Supplementary Table 3) [12].

Results

Systematic review

The systematic review process (Fig. 1) yielded 9 comparative observational studies with 987 patients who underwent either FTM or CM, with a male proportion of 45.2% and an average age of 45.3 years [5-7,10,11,16,20,21]. Most patients had Type 2 achalasia according to the Chicago classification. Baseline characteristics and study methodologies are outlined in Tables 1 and 2, respectively.

Efficacy outcomes

Our meta-analysis revealed no difference between FTM and CM in terms of clinical success rates over follow-up times of approximately 1 and 3 years (RR 1.01, 95%CI 0.98-1.04; P=0.55; I^2=0%, subgroup difference P=0.80; n=6; Fig. 2A). Similar degrees of reduction in LESP measurements and Eckardt score were seen in both the FTM and CM groups (Fig. 2B,C).

Periprocedural and safety outcomes

CM was associated with no significant difference in procedure time (MD 7.07 min, 95%CI 1.56-15.69; P=0.11; I^2=80%; n=4; Fig. 3A). In terms of adverse events, FTM led to no significant difference in tissue injury (RR 0.70, 95%CI 0.43-1.14; P=0.16; I^2=0%; n=4; Fig. 3B), pneumoperitoneum (RR 0.96, 95%CI 0.71-1.31; P=0.81; I^2=2%; n=4; Fig. 3C), or pneumothorax (RR 0.80, 95%CI 0.50-1.27; P=0.34; I^2=0%; n=3; Fig. 3D). FTM was associated with a significantly lower incidence of subcutaneous emphysema (RR 0.59, 95%CI 0.43-0.81; P=0.001; I^2=0%; n=5; Fig. 3E). FTM showed no difference from CM in terms of LOS (MD 0.22 days, 95%CI -1.13-1.56; P=0.75; I^2=86%; n=3; Fig. 3F), but was associated with a significantly greater incidence of post-POEM pain (RR 1.94, 95%CI 1.27-2.95; P=0.002; I^2=0%; n=2; Fig. 3G).

Post-POEM GERD outcomes

In terms of post-POEM GERD, FTM was associated with no difference in GERD symptoms (RR 1.18, 95%CI 0.81-1.73; P=0.38; I^2=0%; n=6; Fig. 4A), with subgroup analysis by follow-up times revealing a trend towards more symptoms over longer follow-up times (Fig. 4A). There was no difference in abnormal acid exposure (RR 1.15, 95%CI 0.79-1.66; P=0.47; I^2=43%; n=4; Fig. 4B). FTM was associated with a significantly greater incidence of esophagitis on endoscopy (RR 1.79, 95%CI 1.09-2.76; P=0.02; I^2=0%; n=6; Fig. 4C) with subgroup analysis revealing a higher esophagitis incidence in studies with longer follow-up times (RR 2.19, 95%CI 1.11-4.35; P=0.02; I^2=0%; n=3; Fig. 4C). FTM was also associated with a greater incidence of clinically relevant GERD (RR 3.03, 95%CI 1.53-6.02; P=0.002; I^2=0%; n=3; Fig. 4D).

Sensitivity analysis

First, isolating studies where the FTM group's pre-POEM Eckart scores were statistically higher than those for CM led to a trend towards greater clinical success in FTM (RR 1.11, 95%CI 0.96-1.27; P=0.15; I^2=0%; n=2; Supplementary Fig. 1A). Second, excluding studies that led to high statistical heterogeneity again revealed no difference in procedure time (MD 3.49 min, 95%CI -2.79-9.78; P=0.28; I^2=66%; n=3; Supplementary Fig. 1B) but a significantly longer LOS for FTM (MD 0.85 days, 95%CI 0.11-1.59; P=0.02; I^2=0%; n=2; Supplementary Fig. 1C). Third, excluding studies without preemptive post-POEM PPI eliminated the statistical significance of the greater risk of esophagitis in FTM (RR 1.68, 95%CI 0.89-3.16; P=0.11; I^2=23%; n=4; Supplementary Fig. 1D).

Quality assessment

The MINORS quality assessment tool revealed a mean score of 15.9±1.55 of a total score of 24. There were concerns because none of the studies calculated prospective sample size and most had inadequate contemporary and control groups, with some studies having more severe achalasia in the FTM group (Supplementary Table 4).

Discussion

FTM and CM were associated with comparable rates of clinical success over shorter (1 year) and longer (3 years) follow-up durations, and achieved similar reductions in LESP and Eckardt scores. When studies with more severe achalasia symptoms were assessed in the FTM group, there was a statistically insignificant trend favoring the clinical success of FTM. Excluding outliers in the sensitivity analysis led to significantly longer LOS for FTM. FTM was also associated with more post-POEM pain, esophagitis and clinically relevant GERD. The frequencies of GERD symptoms and esophagitis were higher in studies that measured outcomes over longer follow-up periods; however, when studies that used PPIs preemptively after POEM were taken into account, FTM's higher esophagitis rate was no longer statistically significant. CM did not lead to a difference in procedural times, but did lead to higher rates of subcutaneous emphysema, with

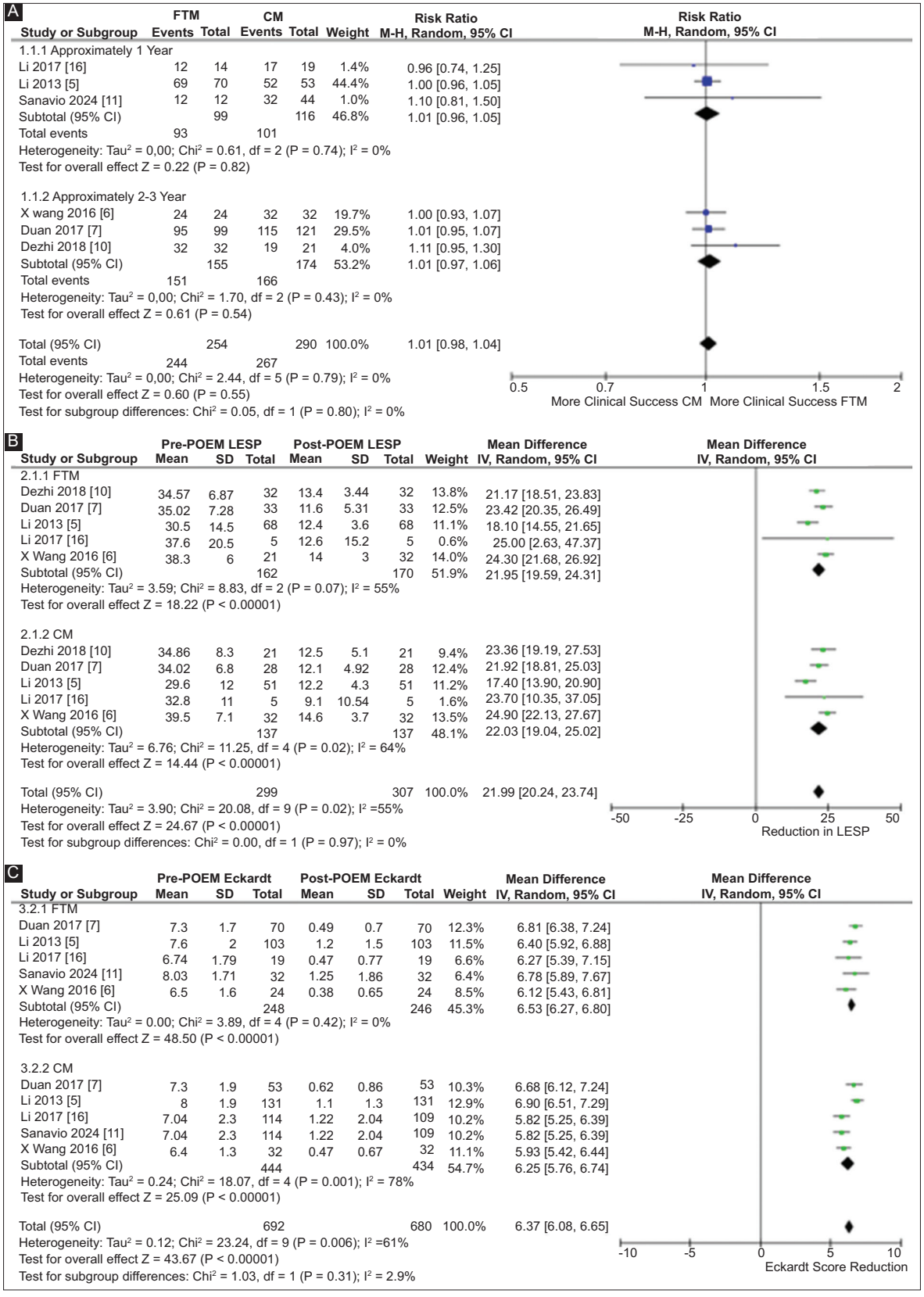

Figure 2 (A) FTM vs. CM for Clinical Success of POEM with 1 year and 3 years duration subgroups. (B) Pre vs. Post-Lower Esophageal Pressures in POEM by FTM and CM subgroups. (C) Pre vs. Post-Lower Eckardt Scores in POEM by FTM and CM subgroups

CM, circular myotomy; FTM, full-thickness myotomy; POEM, peroral endoscopic myotomy; SD, standard deviation; CI, confidence interval; M-H, Mantel-Haenszel; LESP, lower esophageal pressure

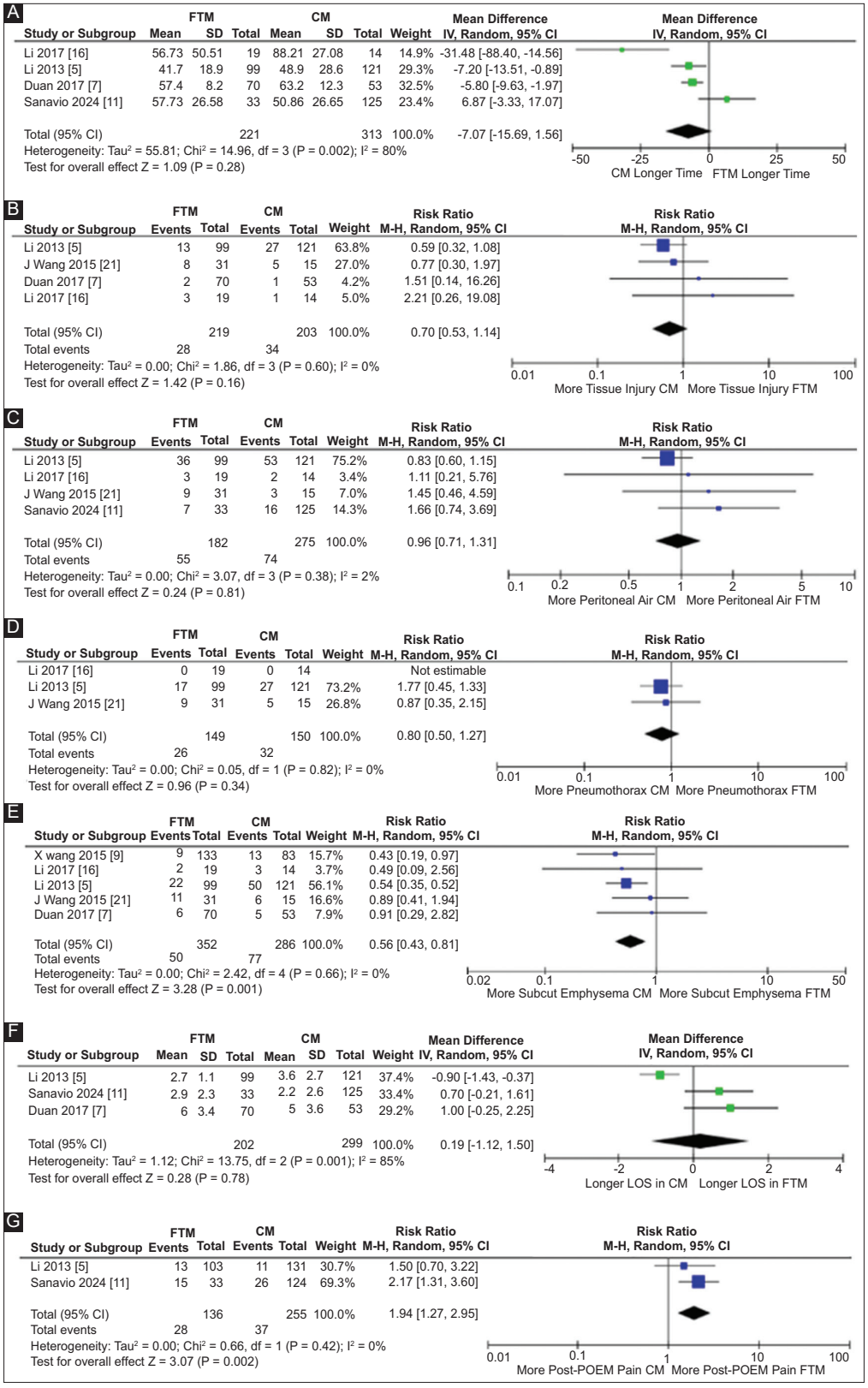

Figure 3 (A) FTM vs. CM for POEM procedure time, (B) FTM vs.CM for tissue injury rate, (C) FTM vs.CM for pneumoperitoneum rate, (D) FTM vs.CM for pneumothorax rate, (E) FTM vs.CM for subcutaneous emphysema rate, (F) FTM vs.CM for length of hospital stay, (G) FTM vs.CM for post-POEM pain

CM, circular myotomy; FTM, full-thickness myotomy; POEM, peroral endoscopic myotomy; SD, standard deviation; CI, confidence interval; M-H, Mantel-Haenszel; LOS, length of hospital stay

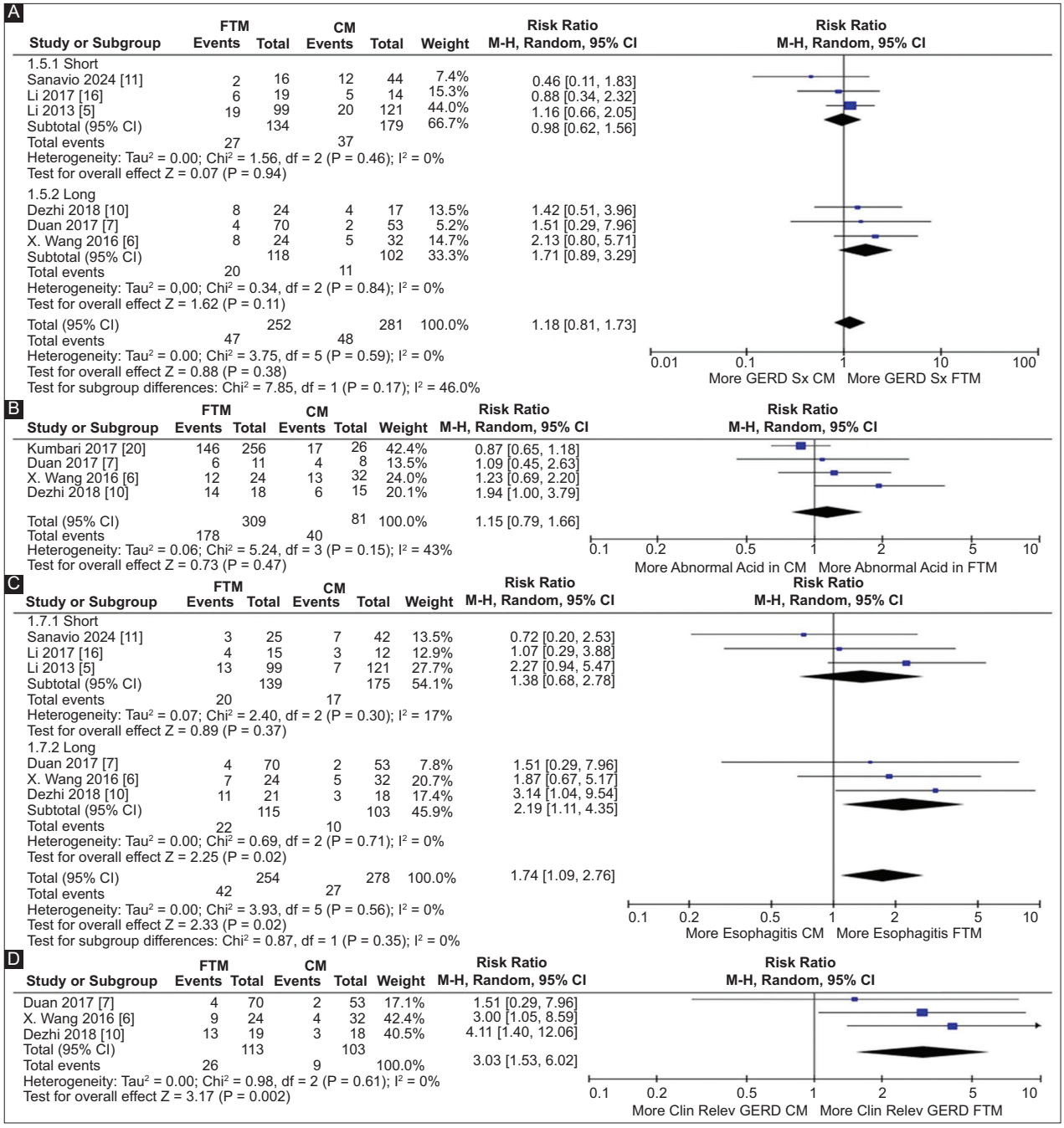

Figure 4 (A) FTM vs.CM for GERD symptoms, (B) FTM vs.CM for abnormal acid exposure, (C) FTM vs.CM for esophagitis on EGD (D) FTM vs.CM for clinically relevant GERD

CM, circular myotomy; FTM, full-thickness myotomy; POEM, peroral endoscopic myotomy; GERD, gastroesophageal reflux disease; CI, confidence interval; M-H, Mantel-Haenszel; EGD, esophagogastroduodenoscopy

statistically insignificant trends toward increased tissue injury, pneumoperitoneum and pneumothorax.

Review of existing knowledge

A published meta-analysis [22] compared FTM to CM, though only in terms of post-POEM GERD measures. It found no difference in GERD symptoms and abnormal acid exposure, with a statistically insignificant trend towards esophagitis on EGD. In addition to assessing additional outcomes, our meta-analysis differs in 2 respects. First, we used RRs to assess the effect size of post-POEM GERD outcomes; this is more appropriate than risk difference, as the latter assumes a similar baseline risk [18]. Second, our analysis adds data from 2 more recent studies [10,11] and a new outcome: clinically relevant GERD. These differences

lead to our initial analysis resulting in significantly greater values for esophagitis risk and clinically relevant GERD with FTM.

In terms of POEM complications, an included study [9] revealed that CM was associated with more gas-related complications. Another [23] revealed that FTM was associated with a statistically insignificant greater incidence of mucosal injury. Our SRMA revealed a statistically insignificant higher frequency of most post-POEM complications associated with CM, with only subcutaneous emphysema being significantly greater in CM. No other SRMA has compared the effect of myotomy depth on POEM complications, procedure time, length of stay, and clinical efficacy.

Our SRMA shows similar clinical success rates for FTM and CM. However, a major limitation was that the retrospective design of 7 of 8 studies led to suboptimal control (CM) groups, because of the selection bias introduced by FTM being performed at the endoscopist's discretion in more severe cases of achalasia. Examples of this across studies included the FTM group having higher pre-POEM Eckardt scores [10,11], FTM being performed because CM was ineffective [6,10], a narrower LES [21], or the more severe [24] sigmoid achalasia variant being present twice as often [5,6]. This demonstrates that FTM was as efficacious as CM even when more severe cases were in the FTM group. Therefore, endoscopists should consider using the FTM technique in patients with more severe achalasia, including higher Eckardt scores, prior failed myotomies and achalasia variants. Our primary outcome of clinical efficacy may be underpowered without prospective calculation of sample sizes, so further studies are needed, ideally including CM in cases of more severe achalasia.

Our SRMA showed no difference in procedural times between FTM and CM, despite the notion that CM is more time-intensive because of the careful dissection to preserve the outer longitudinal layer [3]. This outcome has high heterogeneity, attributable to the finding of a single study [17] that CM took up to 30 min longer, compared to a few minutes longer in the other studies. This may have been due to this study's unique CM technique [17], called "partial full thickness" myotomy where CM was performed throughout the entire myotomy length, with additional FTM performed from 2 cm above the esophagogastric junction (EGJ) all the way through to the gastric fundus.

This customized dissection, maintaining 2 depths, together with its novelty, may have been the reason CM took longer here. Additionally, in the most recent multicenter study [11] FTM took longer than the CM, despite the straightforward nature of the cut. It is notable that here the FTM and CM cohorts were divided between medical centers, with the CM center performing a significantly higher volume. It is possible that the endoscopists at the CM center were more experienced with the procedure. Even if procedural experience was a confounder in the multicenter study [11], it would add to evidence that CM procedure time can be reduced with experience. Pooling the remaining outcomes in a sensitivity analysis reveals that there is no significant difference in procedural time between the myotomies.

In terms of complications, there were weak trends towards more gas-related complications [9] in CM overall, with statistical significance found only for the incidence of subcutaneous emphysema. This contradicts the notion that preservation of the outer longitudinal muscle provides a preventive barrier. Our findings could possibly be due to the longer time spent on dissection of the inner circular muscle CM with electrocautery [3], allowing more time for air to leak into the mediastinum and peritoneum [7]. This observation comes with a major caveat, however, which is that the study reporting the highest gas-related complications associated with CM [5] in our analysis used room-air insufflation for POEM, which has been documented to increase air-complications [25]. This introduced heterogeneity into the meta-analysis, possibly magnifying the effect CM had on gas-related complications in this study relative to other studies. Additionally, subcutaneous emphysema and other gas-related complications in the context of POEM are mostly self-limited [26], which provides reassurance that many are not clinically consequential; however, in 1 included study [5] a CM patient had a bilateral pneumothorax requiring intervention, so further study is needed. Regarding other procedural complications, not all studies reported similar outcomes: therefore, mucosal perforation, bleeding and injury were combined and classified as tissue injury, with a trend towards a positive association with CM. Additionally, complications such as pneumonia and pleural effusion were not reported consistently across studies, probably because of their low incidence, so our meta-analysis lacks data on major complications resulting from FTM vs. CM. Overall, CM may not reduce procedural time and may increase complications; it should thus not necessarily be performed to minimize either in, for example, a frail elderly patient.

In terms of LOS, the earliest study [5] was an outlier that, when removed, eliminated statistical heterogeneity. This might be due to a lack of familiarity with post-POEM monitoring, as POEM was introduced only 2 years prior to the study and the room-air insufflation mentioned above may have led to more complications, resulting in longer post-POEM monitoring. Additionally, the age of the CM group in this study [5] was statistically higher than that of the FTM group, driving up the LOS in the CM group. When this was taken into account by excluding the study in a sensitivity analysis, LOS was longer in FTM. The greater LOS in FTM may be attributable to post-POEM pain, as our analysis revealed a twofold risk of pain with FTM. This is consistent with the most recent included study [11], where FTM was associated with significantly higher levels of post-POEM pain, requiring significantly higher opiate analgesics. Overall, FTM is associated with a greater LOS, but this should be weighed against the potential benefit of FTM's greater efficacy in cases of advanced achalasia.

CM has been proposed as an option to reduce post-POEM GERD [6]. Our initial results suggest that FTM was associated with significantly greater incidences of esophagitis

and clinically relevant GERD. However, assessment of the methodologies highlighted 4 caveats that led our sensitivity analysis to challenge the notion of performing FTM to avoid significant post-POEM GERD. First, in 41 cases from included studies where Los Angeles (LA) esophagitis grade was reported [5-7,11], severity was mild/moderate and relieved with a short course of PPI, raising the question of whether choosing CM to mitigate post-POEM GERD provides any meaningful clinical benefit. Second, PPI prescription practices varied across studies. The most recent study [11] had a 93% post-POEM PPI prescription rate for up to 56 weeks [11], in contrast to others where PPI was only used to treat esophagitis [6,7] or preemptive post-POEM PPI use was limited to 8 weeks [5,10,16]. With this practice, CM had a higher rate of esophagitis. Therefore, when the sensitivity analysis excluded studies that did not report preemptive post-POEM PPI use, our pooled results indicate no significant difference in esophagitis between FTM and CM. Third, as reflected in Table 2, prior POEM treatments were not consistently reported and could be an important confounder. For example, there was a slightly higher rate of prior Heller myotomy in the FTM group in 1 study [7], while all patients who underwent FTM had undergone prior CM (POEM) in 2 studies [6,10], which may have contributed to the higher post-POEM incidence of GERD in the FTM group. Fourth, a large single-center study [27] found that 26% of patients with post-POEM esophagitis had an endoscopic pattern more consistent with ischemia, possibly related to the POEM tunnel scarring that is more prevalent with FTM [3,5,27]. This calls into question whether the esophagitis noted in our included studies was truly related to GERD.

Altogether, the above considerations suggest that CM should not be performed to avoid or reduce post-POEM GERD, as even if an association with FTM exists, it is likely to be overestimated and manageable with PPI therapy. It was notable, however, that, compared to CM, FTM was associated with more GERD symptoms and esophagitis in the long-term (3 year) subgroup than the short-term (1 year) subgroup. This suggests patients with FTM should be monitored for signs of GERD several years post-POEM, which should remain in the differential when assessing esophageal symptoms.

In conclusion, critical appraisal of our findings supports the use of FTM in POEM, as it was used in more severe achalasia yet maintained a similar clinical efficacy to CM. Additionally, while it is associated with a longer LOS and a higher incidence of post-POEM GERD, the latter may be mitigated with PPI use. FTM also reduced periprocedural complications relative to CM. Prospective studies assessing the influence of myotomy depth on short- and long-term outcomes of POEM efficacy, safety and GERD are indicated. These should be higher powered to capture rarer but severe POEM complications, prescribe PPIs consistently, and stratify esophagitis by LA grade.

Summary Box

What is already known:

- Peroral endoscopic myotomy (POEM) is an effective minimally invasive treatment for esophageal achalasia developed in 2010
- Two major myotomy depth options in POEM exist for dissecting the lower esophageal sphincter (LES): these are circular myotomy (CM), where the thick inner circular muscle layer is cut, preserving the thin outer longitudinal muscle layer of the LES; and full-thickness myotomy (FTM), in which the outer layer is also cut in addition to the inner layer
- FTM has been reported to be associated with a higher incidence of post-POEM gastroesophageal reflux disease (GERD)

What the new findings are:

- FTM and CM were associated with similar clinical efficacy at 1 and 3 years, although FTM may be more efficacious in severe cases of achalasia, with no difference in procedure time between them
- FTM was associated with a higher incidence of post-POEM GERD, especially over longer time durations, but the association with esophagitis disappeared when studies with consistent PPI use are taken into account
- CM was associated with a trend towards more peri-POEM complications, with a significant difference found only for subcutaneous emphysema
- FTM was associated with a longer hospital stay, possibly related to more post-procedural pain

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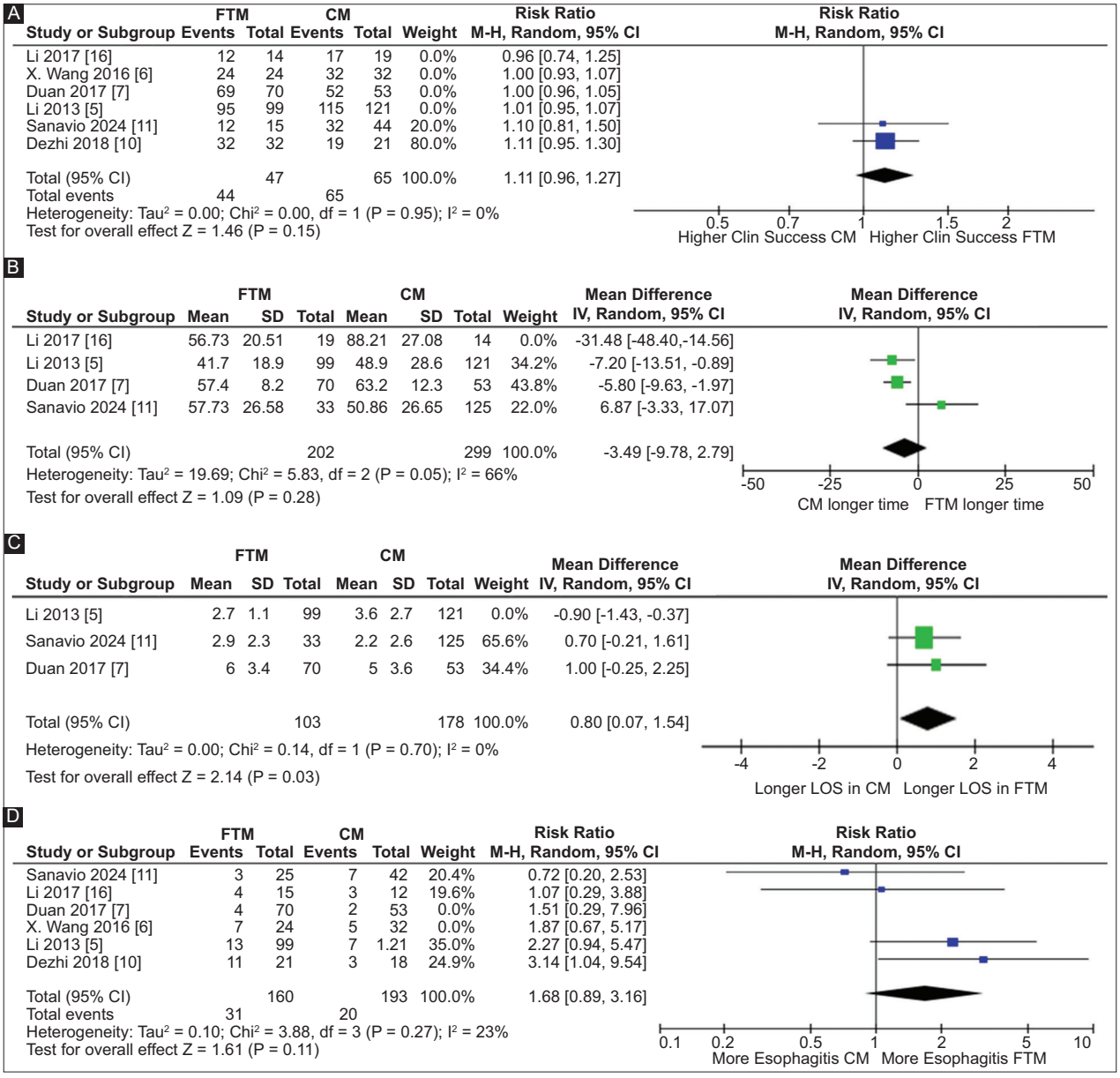
Supplementary material



Supplementary Figure 1 (A) Sensitivity analysis of clinical success in patients with Higher Eckardt in baseline FTM group. (B) Sensitivity analysis of procedure time excluding studies that generated high heterogeneity. (C) Sensitivity analysis of LOS excluding studies that generated high heterogeneity. (D) Sensitivity analysis of esophagitis on EGD excluding studies without PPI use after POEM

CM, circular myotomy; FTM, full-thickness myotomy; POEM, peroral endoscopic myotomy; LOS, length of hospital stay; EGD, esophagogastroduodenoscopy

Supplementary Table 1 Full Search Strategies (all searches devised January 29, 2024, and updated September 10, 2024)

Embase (Embase.com, Elsevier)

No.	Query	Results
#1	'peroral endoscopic myotomy'/syn OR 'per oral endoscopic myotom*' OR 'peroral endoscopic myotom*' OR poem OR poems OR (('esophagus myotomy'/syn OR peroral OR oral OR oesophag* OR esophag* OR pharyng* OR transpharyng*) AND ('natural orifice endoscopic surger*' OR 'natural orifice transluminal endoscopic surger*' OR 'natural orifice transluminal endoscopic surgery'/syn))	10108
#2	'esophagus achalasia'/syn OR achalasia* OR cardiospasm* OR 'cardio spasm*' OR megaesophag*	17426
#3	#1 AND #2	3352
#4	circular* OR circle*	263734
#5	'ft' OR 'ftm' OR 'full thick*'	121685
#6	#3 AND #4	216
#7	#3 AND #5	126
#8	#6 OR #7	301
#9	#8 NOT ([animals]/lim NOT [humans]/lim) NOT ('conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR 'tombstone'/it OR 'case report'/de OR 'meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'systematic review topic'/de)	219

MEDLINE (PubMed, National Center for Biotechnology Information, National Library of Medicine)

No.	Query	Results
1	(Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR POEM OR POEMs OR ((Peroral OR Oral OR oesophag* OR esophag* OR pharyng* OR transpharyng* OR "Pyloromyotomy"[Mesh]) AND (Natural-Orifice-Endoscopic-Surger* OR natural-orifice-transluminal-endoscopic-surger* OR "Natural Orifice Endoscopic Surgery"[Mesh])))	6,047
2	"Esophageal Achalasia"[Mesh] OR Achalasia* OR cardiospasm* OR cardio-spasm* OR Megaesophag*	10,488
3	#1 AND #2	1,471
4	"FT"[Text Word] OR "FTM"[Text Word] OR full-thick*[Text Word]	82,124
5	Cicular*[Text Word] OR circle*[Text Word]	33,942
6	#3 AND #4	37
7	#3 AND #5	1
8	#6 OR #7	38
9	#8 NOT ("animals"[mesh] NOT "humans"[mesh]) NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "guideline"[Publication Type] OR "introductory journal article"[Publication Type] OR "meta analysis"[Publication Type] OR "news"[Publication Type] OR "retracted publication"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Publication Type])	22

Cochrane Central Register of Controlled Trials (CochraneLibrary.com platform, Wiley, Issue 8 of 12, August 2024)

ID	Search	Hits
#1	(Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR POEM OR POEMs OR ((Peroral OR Oral OR oesophag* OR esophag* OR pharyng* OR transpharyng* OR [mh "Pyloromyotomy"]) AND (Natural-Orifice-Endoscopic-Surger* OR natural-orifice-transluminal-endoscopic-surger* OR [mh "Natural Orifice Endoscopic Surgery"])))	769
#2	[mh "Esophageal Achalasia"] OR Achalasia* OR cardiospasm* OR cardio-spasm* OR Megaesophag*	516
#3	#1 AND #2	204
#4	FT OR "FTM" OR full-thick*	5424
#5	Cicular* OR circle*	2336
#6	#3 AND #4	8
#7	#3 AND #5	1
#8	#6 OR #7	9
#9	#8 in Trials	9

Web of Science Core Collection (Web of Science Platform, Clarivate, Editions = Arts & Humanities Citation Index, Emerging Sources Citation Index [previous 5 years], Conference Proceedings Citation Index, Science Citation Index-EXPANDED, and Social Science Citation Index)

Cicular* OR circle* OR "FT" OR "FTM" OR full-thick* (Topic) AND (Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR POEM OR POEMs OR ((Peroral OR Oral OR oesophag* OR esophag* OR pharyng* OR transpharyng*) AND (Natural-Orifice-Endoscopic-Surger* OR natural-orifice-transluminal-endoscopic-surger*))) (Topic) AND Achalasia* OR cardiospasm* OR cardio-spasm* OR Megaesophag* (Topic) and Preprint Citation Index (Exclude – Database) and Review Article or Editorial Material or Case Report or Biography or Letter (Exclude – Document Types) and Web of Science Core Collection (Database)	48

KCI-Korean Journal Database (Web of Science Platform, Clarivate)

Cicular* OR circle* OR "FT" OR "FTM" OR full-thick* (Topic) AND (Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR POEM OR POEMs OR ((Peroral OR Oral OR oesophag* OR esophag* OR pharyng* OR transpharyng*) AND (Natural-Orifice-Endoscopic-Surger* OR natural-orifice-transluminal-endoscopic-surger*))) (Topic) AND Achalasia* OR cardiospasm* OR cardio-spasm* OR Megaesophag* (Topic) and Preprint Citation Index (Exclude – Database) and Review Article or Editorial Material or Case Report or Biography or Letter (Exclude – Document Types) and KCI-Korean Journal Database (Database)	3

Global Index Medicus (World Health Organization)

tw:((tw:(cicular* OR circle* OR "FT" OR "FTM" OR "full thickness")) AND (tw:(achalasia* OR cardiospasm* OR cardio-spasm* OR megaesophag*)) AND (tw:("peroral endoscopic myotomy" OR "per-oral endoscopic myotomy" OR poem OR poems OR ((peroral OR oral OR oesophag* OR esophag* OR pharyng* OR transpharyng*) AND ("natural orifice endoscopic surgery" OR "natural orifice transluminal endoscopic surgery")))))	11

Supplementary Table 2 Search results summary by date

ORIGINAL Search - January 29, 2024

Database	Results	Platform
Embase	193	Embase.com (Elsevier)
MEDLINE	20	PubMed (NCBI, National Libraries of Medicine)
Cochrane Central Register of Controlled Trials	7	Cochrane Library (Wiley)
Web of Science Core Collection	46	Web of Science (Clarivate)
KCI - Korean Journal Index	2	Web of Science (Clarivate)
Global Index Medicus	11	World Health Organization
Total	279	
With duplicates removed	227	

UPDATES - September 10, 2024

Database	Results	Platform
Embase	26	Embase.com (Elsevier)
MEDLINE	2	PubMed (NCBI, National Libraries of Medicine)
Cochrane Central Register of Controlled Trials	2	Cochrane Library (Wiley)
Web of Science Core Collection	2	Web of Science (Clarivate)
KCI - Korean Journal Index	0	Web of Science (Clarivate)
Global Index Medicus	0	World Health Organization
Total	32	
With duplicates removed	20	

Supplementary Table 3 Preferred reporting items for systematic reviews and meta-analysis (PRISMA Checklist)

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review	1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist	3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge	4
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses	4
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	5
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	5, Figure 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect	5-6
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	6
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results	6

(*Contd...*)

Supplementary Table 3 (*Contined*)

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression)	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	6, rationale for why not used
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	6
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	7
Study characteristics	17	Cite each included study and present its characteristics	7, Table 1/2
Risk of bias in studies	18	Present assessments of risk of bias for each included study	7/8, Supplementary Figure 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g., confidence/credible interval), ideally using structured tables or plots	7, Figure 2 and 4
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	7
	20c	Present results of all investigations of possible causes of heterogeneity among study results	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	7/8

Supplementary Table 3 (*Contined*)

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	N/A, see #14
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	7
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	8
	23b	Discuss any limitations of the evidence included in the review	9-11
	23c	Discuss any limitations of the review processes used	8-9
	23d	Discuss implications of the results for practice, policy, and future research	9-11

Supplementary Table 4 Quality assessment of FTM vs. CM studies

Study [ref.]	1	2	3	4	5	6	7	8	9	10	11	12	Total
Li 2013 [5]	2	2	2	2	1	2	2	0	2	1	2	2	21/24
Wang 2015 [21]	2	2	2	2	1	1	2	0	2	0	1	2	17/27
Wang 2016 [6]	2	1	1	2	1	2	1	0	2	1	2	2	18/24
Duan 2017 [7]	2	1	1	2	1	2	2	0	2	1	2	2	19/24
Kumbari 2017 [20]	2	1	1	2	1	2	0	0	2	1	2	2	17/24
Dezhi 2018 [10]	2	1	1	2	1	2	0	0	2	1	1	2	16/24
Savarino 2024 [11]	2	2	1	2	1	2	0	0	2	1	1	2	17/24

The MINORS (Methodological Index for Non-Randomized Studies) criteria are used the quality of non-randomized studies. Each criteria is scored from 0 to 2 (0=not reported, 1=reported but inadequate, 2=reported and adequate). The checklists ask following information: 1. A clearly stated aim. 2. Inclusion of consecutive patients. 3. Prospective collection of data. 4. Endpoint appropriate to the aim of the study. 5. Unbiased assessment of the study endpoint. 6. Follow-up period appropriate to the aim of the study. 7. Loss of follow up less than 5%. 8. Prospective calculation of the study size. 9. An adequate control group. 10. Contemporary group. 11. Baseline equivalent of group. 12. Adequate statistical analysis

CM, circular myotomy; FTM, full-thickness myotomy