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Minimally invasive McKeown's vs open oesophagectomy for cancer: A meta-analysis

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ABSTRACT

Background: The effectiveness of minimally invasive oesophagectomy (MIO) compared to open oesophagectomy (OO) remains controversial. Various techniques for performing MIO are currently used, but the evidence for them is lacking. The objective of this meta-analysis was to compare the safety, efficacy and oncological outcomes of McKeown's minimally invasive oesophagectomy (McKeown's-MIO) to OO.
Methods: PubMed, Embase and Cochrane Library databases were searched up to December 2016 for relevant articles comparing McKeown's-MIO to OO. As no randomised control trials (RCTs) currently exist, only cohort and case control studies were included. Fixed or random-effects models were used to calculate summary odds ratios (ORs) or relative risks (RRs) for binary outcomes, and hazard ratios (HRs) for time-to-event outcomes. Heterogeneity among studies were evaluated using I^2 statistics.
Results: Four studies, which consisted a total of 573 patients, were included in the meta-analysis. In comparison to patients undergoing OO, those who were treated with McKeown's-MIO had a reduced incidence of pneumonia and total respiratory complications, however, there were no statistically significant differences for other measures of safety such as RLN palsy and anastomotic leak. In terms of efficacy data, MIO had significantly less blood loss and a shorter duration of hospital stay but a longer operating time. Lymph node retrieval trended towards favouring McKeown's-MIO, but was not statistically significant. There was insufficient data to report on other oncological outcomes.
Conclusions: McKeown's-MIO is a safe and effective procedure that has comparable outcomes to OO. However, RCTs with large sample sizes are needed to confirm these results.

Introduction

Oesophageal cancer is the sixth most common cause of cancer-related deaths worldwide [1], and its incidence is on the rise in developed countries [2]. Surgery is an integral part of the multimodality treatment of oesophageal cancer. Traditionally, surgical resection has been done via 'open' surgical procedures such as transthoracic and transhiatal oesophagectomies. A major drawback of these procedures are the high rates of morbidity and mortality [3,4]. Even in experienced centres, complication rates of 70–80% and hospital mortalities between 4 and 7% are reported [5].

Minimal Invasive Oesophagectomy (MIO) has emerged as an alternative to open surgery claiming to reduce surgical trauma, operative complications and recovery time. Since the first MIOs were reported over 20 years ago [6,7], various thoracosopic and laparoscopic approaches for oesophagectomy have been described in the literature. Recent systematic reviews and meta-analyses have shown that MIO may reduce in-hospital mortality [8] and post-operative complications [9], with promising oncological outcomes [10]. However, these results are difficult to interpret due to the inconsistency in what has been defined as minimally invasive surgery [11]. Almost all reviews have included hybrid procedures, in which one stage of the procedure is minimally invasive and another stage is open, under the category of minimally invasive surgery. In the completely minimally invasive approach, both the

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abdominal and thoracic stages of the procedure are minimally invasive (i.e., a combination of thoracoscopy and laparoscopy). At present, no systematic review has compared an established complete MIO technique to OO.

Luketich et al. [12] have described in detail the complete minimally invasive form of the open procedure as originally described by McKeown [13] (McKeown's-MIO); consisting of a laparoscopic and thoracoscopic resection combined with a cervical anastomosis. It is also referred to as the 3-hole approach.

The purpose of the present study was to compare the safety, efficacy and oncological outcomes of McKeown's-MIO to OO. Here, we aim to answer two clinically important questions: (i) whether McKeown's-MIO improves safety and efficacy of surgery, and (ii) whether McKeown's-MIO has superior oncological outcomes compared to open surgery. To answer these questions, we conducted a meta-analysis according to PRISMA principles, hoping to provide a better evidence base for the choice of surgical method.

Material and methods

This study complies with the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [14]. A review protocol was written but not registered.

Literature search strategy

An electronic literature search was undertaken using PubMed, Embase and Cochrane Library databases up to December 2016. For completion, the “grey literature” such as conference proceedings, reports and other peer-reviewed research were searched as well.

We restricted the search to articles in English and studies relating to humans. The search terms used were: *oesophagectomy*, *oesophageal resection*, *esophagogastrectomy*, *carcinoma*, *malignancy*, *neoplasm*, *laparoscopy*, *thoracoscopy*, *McKeown* and *minimally invasive*. Logical combinations of these and related terms were used to maximise sensitivity. Where applicable, the above terms were used in “[MESH]” (PubMed and Cochrane Library), otherwise they were combined with the Boolean operators “AND/OR” and asterisks. References cited in retrieved articles were screened manually. Duplicates were identified and removed using EndNote (Thomson Reuters, Philadelphia, USA).

Inclusion and exclusion criteria

Given the paucity of papers relating to the study question, we were unable to limit our search to randomised controlled trials (RCTs). Therefore, all comparative studies of MIO and open oesophagectomy were made eligible for inclusion.

Inclusion Criteria:

(i) Published in English.
(ii) A minimum of 30 patients included in the study.
(iii) Randomised controls or non-randomised controls with parallel control studies.
(iv) Patients with oesophageal cancer treated surgically with at least twenty patients treated with McKeown's-MIO.

Exclusion Criteria:

(i) Outcomes of interest not reported or unable to calculate outcomes from published results.
(ii) If a distinct group of patients were not mentioned or outcomes of interest were not compared.
(iii) Greater than 10% of patients in a group treated for pathology other than adenocarcinoma or squamous cell carcinoma of the oesophagus.
(iv) Hybrid or hand assisted minimal invasive approaches with a laparotomy >5 cm or any thoracotomy or any hand assisted in the minimally invasive group.
(v) If publications belong to systematic reviews or meta-analyses.

Data extraction

Two authors (RS and RH) independently selected studies based on the inclusion and exclusion criteria. Where necessary, disagreements on inclusion/exclusion were resolved by a third author (SG). Data was extracted into a preformed excel file (Microsoft Corporation, Redmond, Washington, USA). Data collected included first author, publication year, study interval, country, study design, number of patients in each group, and various postoperative outcome measures (outlined below).

Quality assessment of retrieved articles

The methodological index for non-randomised studies (MINORS) was used to assess the quality of selected studies [15]. MINORS is an instrument specifically designed for evaluating the quality of non-randomised surgical studies. The scores may range from 0 (low quality) to 24 (high quality). Each study was assessed and scored against the MINORS items by two independent investigators (RS and RH). Disagreements on study quality were resolved by discussion among the authors.

Outcome measures

This study had three main outcomes of interest: safety, efficacy and oncological outcomes. The endpoints used to measure safety were post-operative complications, including pneumonia, total respiratory complications, 30-day mortality, recurrent laryngeal nerve (RLN) palsy, anastomotic leak and chyle leak. Total respiratory complications was defined variably among the studies and included outcomes such as atelectasis, acute respiratory distress syndrome, pneumonia, pneumothorax and pulmonary embolism. Efficacy of surgery was assessed by blood loss, operating time and length of hospital stay. The endpoints for assessing oncological outcome were adequacy of resection (R0 resection rates), lymph node retrieval and overall survival.

Data analysis

Odds ratios (OR) were used to summarise dichotomous data, and mean difference (MD) were used for continuous data. If means and standard deviations were not reported, they were calculated from the data available using methods described by Hozo et al. [16]. For the meta-analysis of overall survival (time-to-event) data, hazard rations (HRs) and 95% confidence intervals (CIs) were extracted or estimated using methods reported by Parmar et al. [17].

Between-study heterogeneity was assessed using I^2 statistics. When the heterogeneity test was statistically significant, $p<0.10$ and $I^2>50\%$ [18], a random effects model was used, otherwise, a fixed effects model was used. The random-effects model assumes that there is variation in treatment effects between studies and estimates a more conservative overall treatment effect with wider confidence intervals. Potential publication bias was evaluated using funnel plots; asymmetry within the plot implies that the results

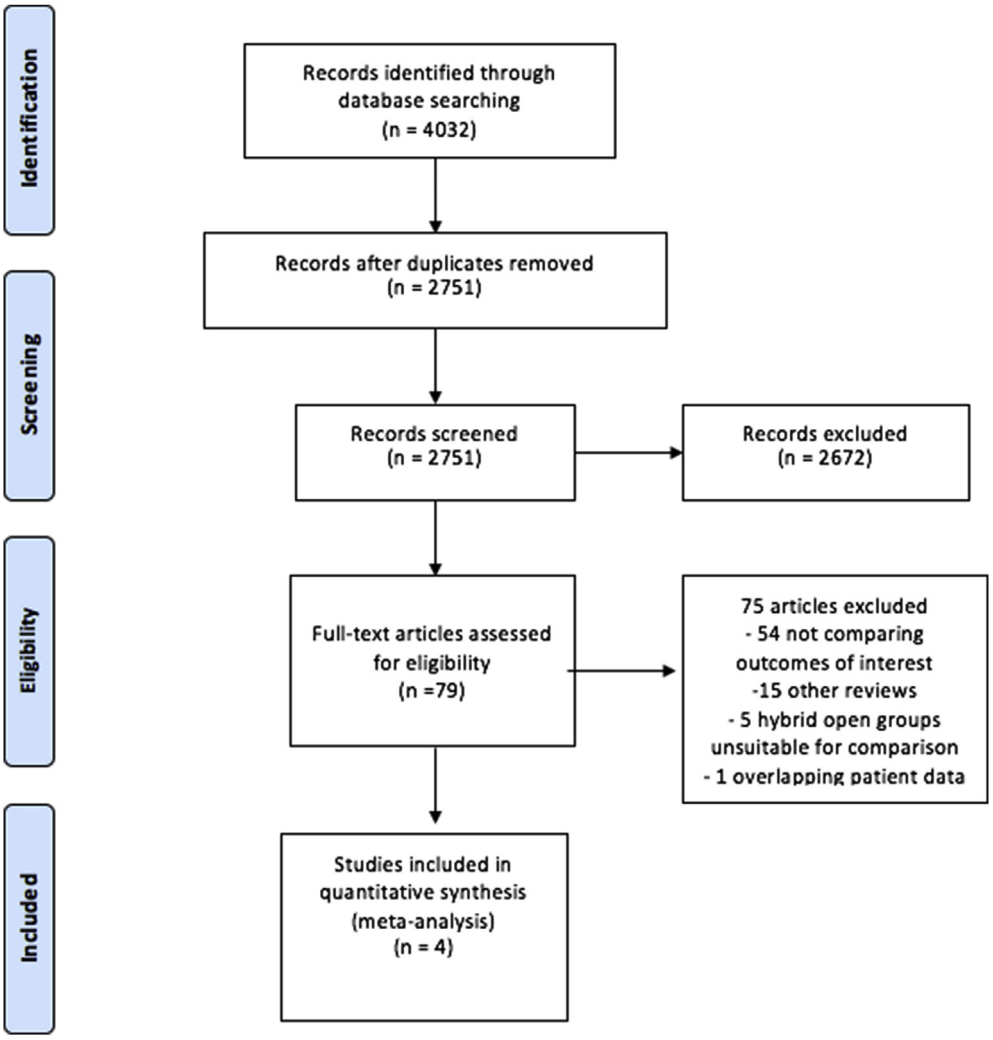

Fig. 1. PRIMSA flow diagram of literature search.

Table 1
Characteristics of included studies.

Study Reference	Study Interval	Country	Study Design	Confounding factor(s)	Study Quality (MINORS)	Number of Patients		Gender (M:F)		Age		% Adeno	TNM			
						Open	MIO	Open	MIO	Open	MIO		Open		MIO	
													0 + I + II	III + IV	0 + I + II	III + IV
Gao 2011	2008–2010	China	Prospective	None	19	78	96	70:8	89:7	59.04 ± 6.36	58.46 ± 7.28	5.2%	40	38	54	42
Meng 2014	2011–2013	China	Retrospective	None	18	89	94	63:26	65:29	61.1 ± 6.7	59.7 ± 9.3	4.4%	50	39	56	38
Nafteux 2011	2005–2010	Belgium	Retrospective	None	19	101	65	83:18	52:13	66 (29–82)	63 (41–82)	NR	NR	NR	NR	NR
Safraneck 2010	2000–2009	UK	Prospective	None	19	46	41	38:8	25:16	60 (44–77)	64 (41–74)	NR	29	17	31	44

UK, United Kingdom; USA, United States of America; NR, not reported; Adeno, Adenocarcinoma; TNM, tumour nodes metastasis. Age is reported as the mean ± standard deviation (SD) or median (range).

were subject to bias.

Forest plots were generated to illustrate pooled ORs and corresponding 95% CIs. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Review Manager Software, Version 5.3.5 (The Cochrane Collaboration, Oxford, UK).

Results

Selected studies and methodological quality

A PRIMSA flow diagram depicting the steps of our literature search is shown in Fig. 1. The initial search identified 4032 records. Of these, 1281 were identified as duplicates and removed. Titles and abstracts of the remaining 2751 papers were screened and 2672 were excluded for not meeting the selection criteria. The full texts for the remaining 79 articles were obtained and carefully examined. A further 75 articles were excluded as: (i) 15 belonged to other reviews or systematic analyses, (ii) 54 did not compare the outcomes of interest, (iii) 5 had both 3-stage and 2-stage procedures included in the open group, and (iv) 2 had an overlapping group of patients [19,20]. Where papers appeared to have overlapping patients, we chose the one that presented a wider body of data. In total, 4 articles were included in this meta-analysis, which consisted a total of 573 patients, with 296 (51.7%) patients undergoing McKeown's-MIO and 277 (48.3%) patients undergoing OO. Detailed characteristics of selected studies are shown in Table 1.

The quality scores of the selected studies ranged from 18 to 19 (Table 1). None of the included studies were randomised controlled trials. No studies performed an unbiased assessment of study outcomes.

Safety outcomes

In this study, McKeown's-MIO resulted in a significant reduction in pneumonia and total respiratory complications compared to OO. Data for pneumonia was available for two studies. As shown in Fig. 2A, the pooled OR of 0.46 ($p = 0.03$; 95% CI = 0.23–0.93) indicated a significant reduction in pneumonia among patients who underwent MI-McKeown's. Four studies included data on total respiratory complications, and the pooled OR of 0.50 ($p = 0.001$; 95% CI = 0.33–0.76) showed a significant result favouring McKeown's-MIO (Fig. 2B), with no heterogeneity among the included studies (Fig. 5A).

In terms of other parameters of surgical safety, McKeown's-MIO and OO had comparable outcomes. Three studies reported a total complication rate, and there was no difference seen between the two groups (OR:0.68; $p = 0.31$; 95% CI = 0.33–1.42) (Fig. 2C). There was no heterogeneity among these studies (Fig. 5B). Two studies, consisting of a total of 340 patients, reported 30-day mortality. Analysis of these as shown in Fig. 2D showed no difference (OR:0.86; $p = 0.83$; 95% CI = 0.23–3.24).

There was also no difference between McKeown's-MIO and OO in terms of RLN injury (OR:0.76; $p = 0.57$; 95% CI = 0.29–1.97), cardiovascular complications (OR:0.78; $p = 0.48$; 95% CI = 0.49–1.41), anastomotic leak (OR:0.69, $p = 0.68$; 95% CI = 0.40–1.54) or chyle leak (OR:0.39; $p = 0.08$; 95% CI = 0.13–1.13) (Fig. 2E, F, 2G and 2H, respectively).

Efficacy outcomes

McKeown's-MIO had a significantly longer operating time compared to OO (MD:41.24 min; $p = 0.008$, 95% CI = 10.64–71.84) (Fig. 3A). However, McKeown's-MIO was superior in terms of blood loss (MD:-138.18 mL; $p = 0.00001$; 95% CI = −220.60, −55.77) (Fig. 3B) and duration of postoperative hospital stay (MD:-3.04 days; $p = 0.02$; 95% CI = −5.68, −0.41) (Fig. 3C). Given the heterogeneity among studies, the random effects model was used for all efficacy outcomes. Funnel plots for operative time, blood loss and postoperative hospital stay are shown in Fig. 5C, D and 5E.

Oncological outcomes

There was insufficient data published in the papers to calculate long term survival. Four studies reported the number of lymph nodes retrieved, and analysis showed no statistically significant difference between the groups (MD: −1.65; $p = 0.06$; 95% CI = −3.37-0.07) (Fig. 4A). R0 resection rates were reported in two of the studies, Nafteux et al. reported 100% R0 resection rates in both groups, whilst Safranek et al. reported 24/46 (52.17%) in the open group compared to 25/41 (60.98%) in the McKeown's-MIO group.

Discussion

Surgery is a key component in the multimodality treatment of oesophageal cancer. The use of MIO is increasing in popularity, however, there remains a lack of evidence for the choice of minimally invasive technique. To our knowledge, this is the first meta-analysis comparing an established completely minimally invasive

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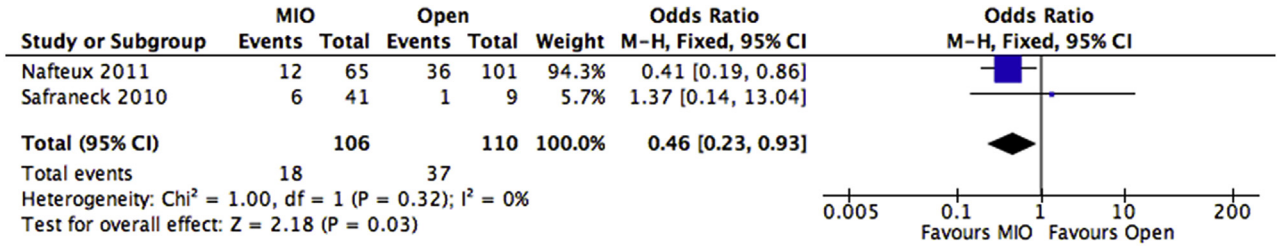

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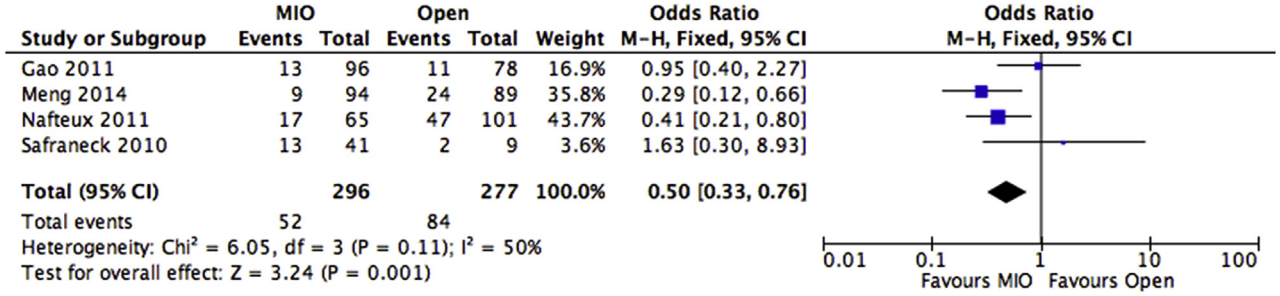

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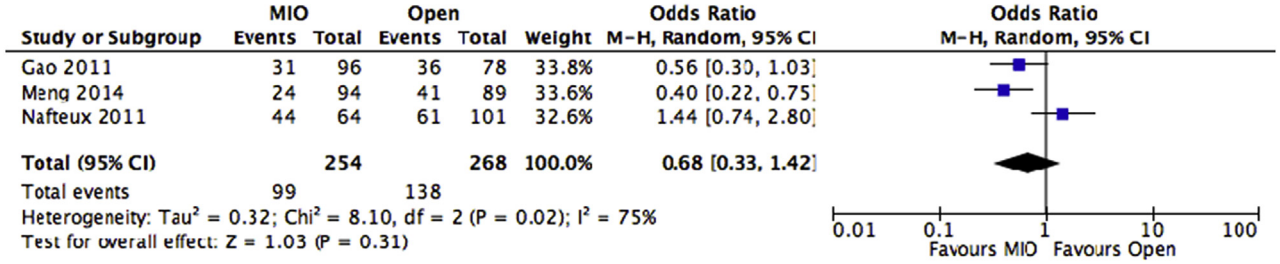

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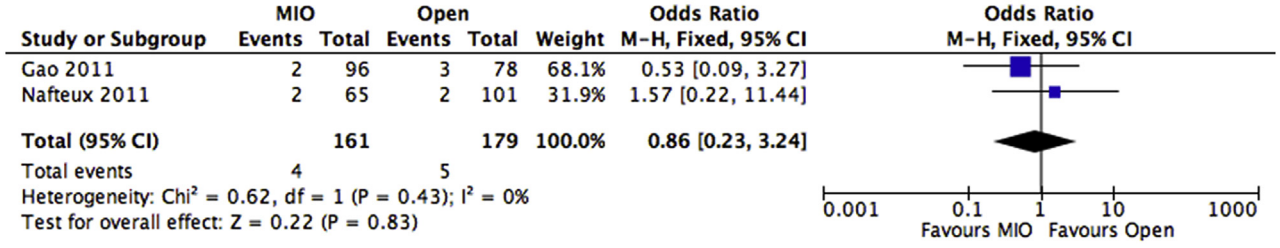

Fig. 2. McKeown's-MIO vs OO for safety outcomes (CI confidence interval, M–H Mantel–Haenszel): **A** pneumonia, **B** total respiratory complications, **C** total complications, **D** 30-day mortality, **E** RLN palsy, **F** cardiovascular complications, **G** anastomotic leak, **H** chyle leak.

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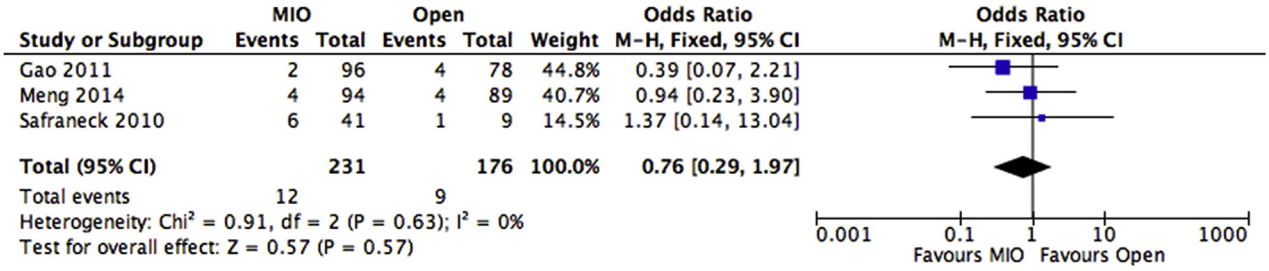

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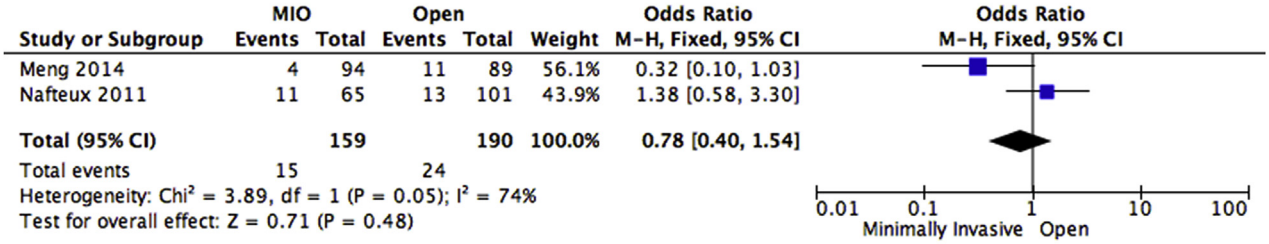

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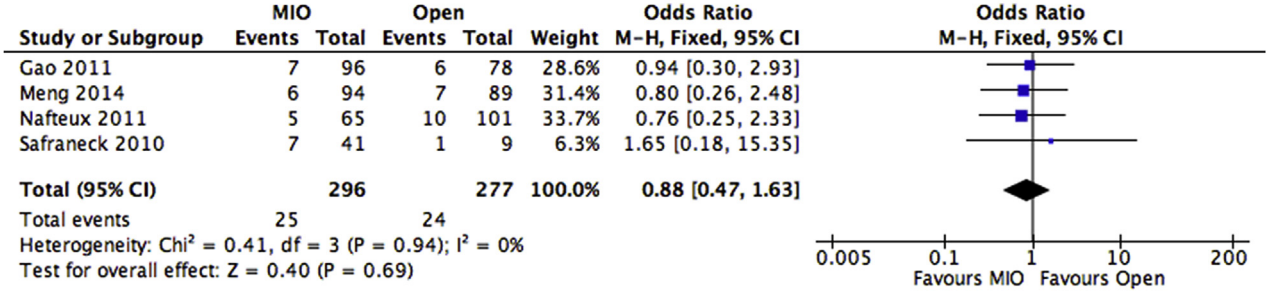

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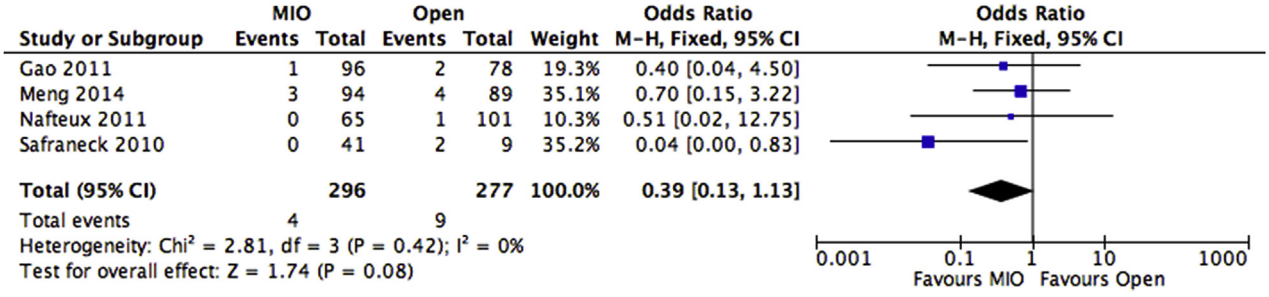

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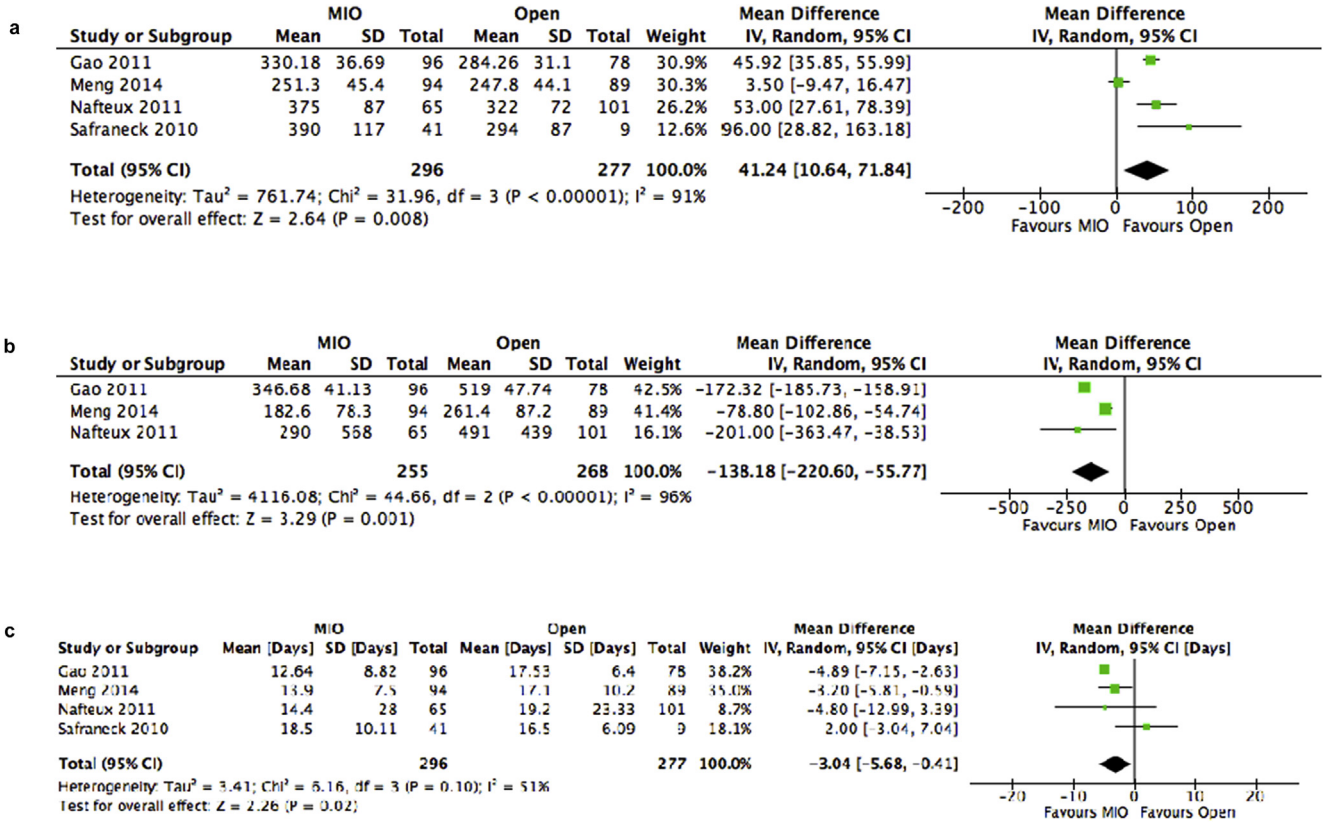

Fig. 3. McKeown's-MIO vs OO for efficacy outcomes: **A** operating time, **B** blood loss, **C** length of hospital stay.

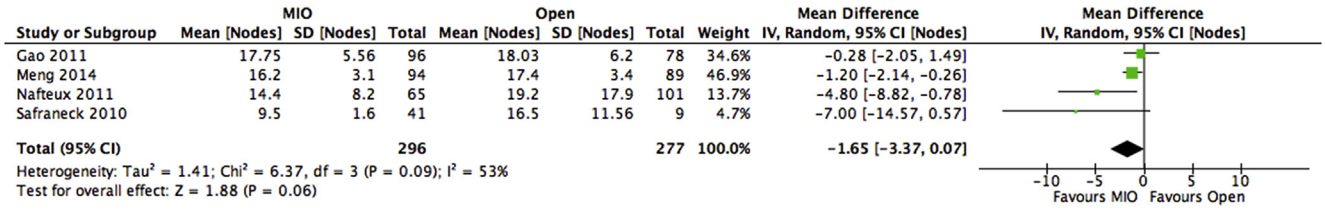

Fig. 4. McKeown's-MIO vs OO for efficacy outcomes: **A** lymph nodes retrieved.

technique to open surgery; excluding studies that considered hybrid or hand assisted procedures under the category of MIO. However, we did not exclude studies that used incisions <5 cm for specimen removal or extracorporeal gastric conduit formation.

Our meta-analysis assessed the safety, efficacy and oncological outcomes of McKeown's-MIO compared to OO in 573 patients from 4 studies. We found that in comparison to OO, McKeown's-MIO has superior postoperative outcomes in terms of post-operative pneumonia, total respiratory complications, operative blood loss and duration of post-operative hospital stay. Within the limits of our analysis for oncological outcomes, we were able to show that there was no difference in lymph node harvest rate.

Pulmonary complications are the most common cause of post-operative morbidity in patients undergoing oesophagectomy. They are particularly significant as they have been shown to correlate with in-hospital mortality [21]. In our analysis, we found that patients undergoing McKeown's-MIO had significantly lower odds of developing pneumonia and total respiratory complications compared to patients in the OO group. This may be attributable to the avoidance of the thoracotomy in the MIO and has also been reported in studies comparing hybrid procedures [22].

The length of hospital stay was significantly lower in McKeown's-MIO, however, there was significant heterogeneity among the studies reporting this outcome. Nevertheless, the majority of studies reported a shorter length of hospital stay for patients in the McKeown's-MIO group, demonstrating that it may provide a faster recovery. Similarly, we found reduced blood loss in McKeown's-MIO but with significant heterogeneity. Reduced blood loss is expected with minimally invasive operations, however, the heterogeneity can be explained by the fact that blood loss is highly dependent on operator and tumour characteristics.

Our results also show that McKeown's MIO has comparable oncological outcomes to OO as assessed by lymph node retrieval. The extent to which lymphadenectomy affects survival remains a controversial issue [23,24]. Nonetheless, we found no differences in LN yield. The R0 resection rate was only reported in two of the studies, with one study reporting a 100% R0 rates in both open and minimally invasive groups, and the other study reporting 52.17% in

the open group compared to 60.98% in the McKeown's-MIO group. Comparing short-term and long-term survival data was an initial goal of our study, however, the reporting of these outcomes is scarce in the literature and therefore we were unable to do any meaningful analysis.

In this study, we conducted a meta-analysis using cohort and case control studies in order to improve the validity of current clinical evidence for the use of MI-McKeown's-MIO compared to OO. However, our study has some limitations that must be taken into account when considering its results. Firstly, there were no RCTs included in our meta-analysis. The nine studies used in our meta-analysis consisted of six retrospective studies and three prospective studies and are susceptible to recall and selection bias. Currently, there has only been one RCT published comparing MIO to OO [25] but this was not included in this meta-analysis as it combined the data from MI-McKeown's with other minimally invasive techniques. Conducting RCTs on a surgical intervention is a significant challenge [26], and in the absence of RCTs, meta-analysis such as this is important to synthesise the available evidence and provide a guide to researchers conceiving RCTs in the future. We note that two protocols for multi-centre RCTs have been registered, and the data from these will be a welcome addition to the evidence available to assess the merits of MIO [27,28]. Further, it was not possible to match patient groups based on TNM staging, (neo)

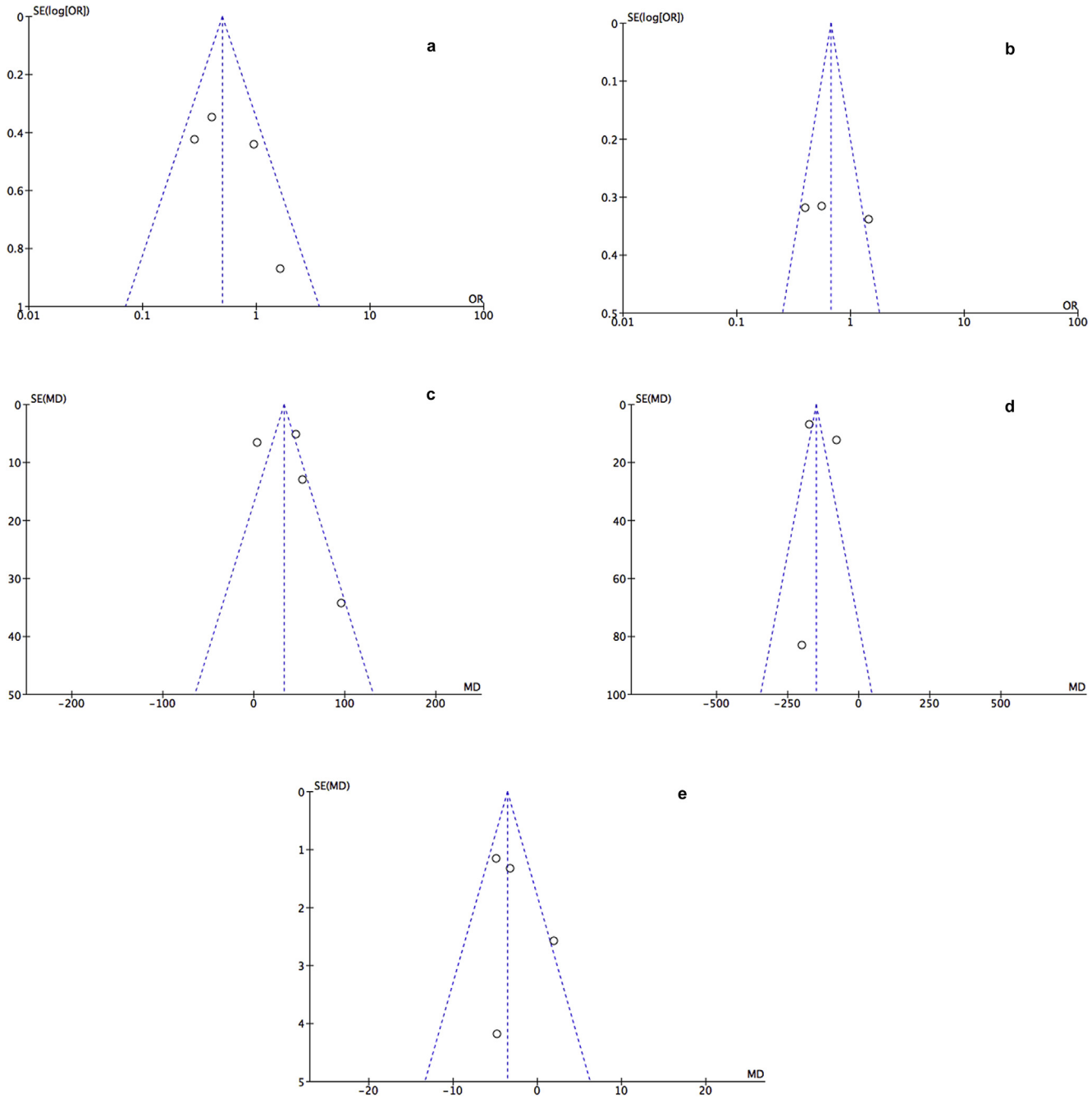

Fig. 5. Funnel plots for safety outcomes with 95% confidence limits: **A** total respiratory complications, **B** total complications, **C** operating time, **D** blood loss, **E** length of hospital stay.

adjuvant chemo/radiotherapy or comorbidities, all of which can affect the outcomes for patients undergoing oesophagectomy. Finally, the patients who received McKeown's-MIO are unlikely to have been a true representation of all patients requiring oesophagectomy. Patients selected to undergo McKeown's-MIO could potentially have had more limited disease, better overall health, and higher socioeconomic status.

Conclusions

In conclusion, this study found that McKeown's-MIO is a safe and effective procedure that has comparable oncological outcomes to OO. However, RCTs with large sample sizes are needed to confirm these results.

Disclosure statements

The authors declare no conflict of interests. No funding was received for this study.

Author contributions

Conceived and designed the search: SG and RS. Performed the search: RS, RH, Analysed the data: TN, RS. Wrote the paper: RS. Reviewed/Edited the manuscript: SG, EB, JF, TN.

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References

[1] Pennathur A, et al. Oesophageal carcinoma. Lancet 2013;381:400–12.
[2] Jemal A, et al. Global cancer statistics. CA A Cancer J Clin 2011;61:69–90.
[3] Atkins BZ, et al. Reducing hospital morbidity and mortality following esophagectomy. Ann Thorac Surg 2004;78:1170–6. discussion -6.
[4] Abunasra H, et al. Predictors of operative death after oesophagectomy for carcinoma. Br J Surg 2005;92:1029–33.
[5] Pierre AF, Luketich JD. Technique and role of minimally invasive esophagectomy for premalignant and malignant diseases of the esophagus. Surg Oncol Clin 2002;11:337–50 [x].
[6] DePaula AL, et al. Laparoscopic transhiatal esophagectomy with esophagogastroplasty. Surg Laparosc Endosc 1995;5:1–5.
[7] Collard JM, et al. En bloc and standard esophagectomies by thoracoscopy. Ann Thorac Surg 1993;56:675–9.
[8] Zhou C, et al. Superiority of minimally invasive oesophagectomy in reducing in-hospital mortality of patients with resectable oesophageal cancer: a meta-analysis. PloS One 2015;10:e0132889.
[9] Dantoc M, et al. Evidence to support the use of minimally invasive esophagectomy for esophageal cancer: a meta-analysis. Arch Surg 2012;147:768–76.
[10] Butler N, et al. Minimally invasive oesophagectomy: current status and future direction. Surg Endosc 2011;25:2071–83.
[11] Uttley L, et al. Minimally invasive esophagectomy versus open surgery: is there an advantage? Surg Endosc 2013;27:4401–2.
[12] Luketich JD, et al. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003;238:486–94. discussion 94-5.
[13] McKeown KC. Total three-stage oesophagectomy for cancer of the oesophagus. Br J Surg 1976;63:259–62.
[14] Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1–34.
[15] Slim K, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712–6.
[16] Hozo SP, et al. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
[17] Parmar MK, et al. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815–34.
[18] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[19] Singh RK, et al. Minimally invasive esophagectomy provides equivalent oncologic outcomes to open esophagectomy for locally advanced (stage II or III) esophageal carcinoma. Arch Surg 2011;146:711–4.
[20] Pham TH, et al. Comparison of perioperative outcomes after combined thoracoscopic-laparoscopic esophagectomy and open Ivor-Lewis esophagectomy. Am J Surg 2010;199:594–8.
[21] Kubo N, et al. The impact of combined thoracoscopic and laparoscopic surgery on pulmonary complications after radical esophagectomy in patients with resectable esophageal cancer. Anticancer Res 2014;34:2399–404.
[22] Nagpal K, et al. Is minimally invasive surgery beneficial in the management of esophageal cancer? A meta-analysis. Surg Endosc 2010;24:1621–9.
[23] Herrera LJ. Extent of lymphadenectomy in esophageal cancer: how many lymph nodes is enough? Ann Surg Oncol 2010;17:676–8.
[24] Peyre CG, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008;248:549–56.
[25] Biere SS, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 2012;379:1887–92.
[26] Cook JA. The challenges faced in the design, conduct and analysis of surgical randomised controlled trials. Trials 2009;10:9.
[27] Avery KN, et al. The feasibility of a randomized controlled trial of esophagectomy for esophageal cancer–the ROMIO (Randomized Oesophagectomy: minimally Invasive or Open) study: protocol for a randomized controlled trial. Trials 2014;15:200.
[28] Mu J, et al. Open three-stage transthoracic oesophagectomy versus minimally invasive thoraco-laparoscopic oesophagectomy for oesophageal cancer: protocol for a multicentre prospective, open and parallel, randomised controlled trial. BMJ Open 2015;5:e008328.