European Journal of Surgical Oncology 51 (2025) 110529

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Approaches for esophagectomy for esophageal cancer: a Network Meta-Analysis

Artur Rebelo [a,*], Elisabeth Wadewitz [a], Yoshiaki Sunami [a], Juliane Friedrichs [a], Maurizio Grilli [b], Johannes A. Vey [c], Johannes Klose [a], Onur Bayram [a], Marie Merling [c], Jörg Kleeff [a,1], Ulrich Ronellenfitsch [a,1]

[a] Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Halle (Saale), Germany
[b] Library of the Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
[c] Institute of Medical Biometry, University of Heidelberg, Heidelberg, Germany

A B S T R A C T

Introduction: Esophageal cancer remains a leading cause of cancer-related mortality worldwide. Esophagectomy is the cornerstone of curative treatment, but the optimal surgical approach remains debated. Newer techniques such as hybrid esophagectomy, minimally invasive esophagectomy (MIE), and robot-assisted minimally invasive esophagectomy (RAMIE) have been developed to improve perioperative outcomes while maintaining oncologic efficacy. We aim to compare the effects of open, hybrid, minimally invasive, and robot-assisted approaches to esophagectomy on survival and perioperative outcomes in patients with esophageal cancer.

Methods: A systematic review and network meta-analysis (NMA) were conducted, including 10 reports from 6 randomized controlled trials identified via PubMed, Cochrane Library, Embase, CINAHL, ClinicalTrials.gov, and ICTRP. Comparative analyses between open esophagectomy (OE), hybrid laparoscopy-thoracotomy (HYB LapS-ThoT), MIE, and RAMIE were performed using random-effects NMA models. Hazard ratios (HR), odds ratios (OR), and mean differences (MD) were calculated for outcomes.

Results: There were no significant differences in overall survival among OE, HYB LapS-ThoT, MIE, and RAMIE. Pulmonary complications were significantly lower with MIE (OR 0.47, 95 % CI 0.33–0.69, $p < 0.0001$) and RAMIE (OR 0.39, 95 % CI 0.27–0.57, $p < 0.0001$) compared to OE. RAMIE yielded a higher lymph node harvest (MD 1.56, 95 % CI 0.58–2.54, $p = 0.002$) and lower reoperation rates (OR 0.65, 95 % CI 0.45–0.93, $p = 0.020$) than OE. HYB LapS-ThoT was associated with increased anastomotic leakage compared to OE (OR 1.66, 95 % CI 1.02–2.69, $p = 0.041$).

Conclusion: MIE and RAMIE significantly reduce pulmonary complications without compromising survival. Hybrid approaches appear to increase the risk of anastomotic leakage. These findings support minimally invasive techniques, especially RAMIE; however, more evidence and further studies are needed to allow for a clearer and more definitive conclusion.

1. Background

Esophageal cancer, with an estimated 604,000 new cases and over 544,000 deaths in 2020, ranks as the seventh most commonly diagnosed cancer and the sixth leading cause of cancer-related deaths globally [1]. The 5-year relative survival rates for esophageal cancer are approximately 49 % for localized disease, 28 % for regional disease, 5 % for distant disease, and 22 % overall [2]. This cancer encompasses two epidemiologically and pathologically distinct types: squamous cell carcinoma and adenocarcinoma, which differ in etiology, tumor location, medical and radiation therapies, prognosis, risk factors, and incidence trends [3-5].

Esophagectomy remains the primary treatment with curative intent for esophageal cancer. It is recommended for all physically fit patients with esophageal cancer either upfront or following preoperative chemotherapy or chemoradiotherapy [6]. For squamous cell carcinoma and type I and II adenocarcinoma (AEG), an abdominothoracic approach is generally favored over a transhiatal approach [6]. Several surgical access techniques are available, with robotic techniques increasingly incorporated into clinical practice [7].

Despite the availability of various access routes—completely open, hybrid procedures (e.g., abdominally minimally invasive and thoracically open or vice versa), and completely minimally invasive, including robotic access—no clear consensus has emerged on the optimal surgical

* Corresponding author. Medical Faculty of the Martin Luther University Halle-Wittenberg and University Hospital Halle (Saale) Department of Abdominal, Vascular and Endocrine Surgery Ernst-Grube-Str. 40, 06120, Halle (Saale), Germany.
E-mail address: artur.rebelo@uk-halle.de (A. Rebelo).
[1] shared senior authorship.

https://doi.org/10.1016/j.ejso.2025.110529
Received 14 August 2025; Received in revised form 6 October 2025; Accepted 20 October 2025
Available online 21 October 2025

approach. Previous randomized controlled trials (RCTs) comparing different techniques have failed to establish a definitive advantage for any single approach [8–15]. Moreover, existing meta-analyses have either compared only two access routes or incorporated non-randomized studies and transhiatal resections, complicating the interpretation of results [7].

In this meta-analysis, we aim to provide a comprehensive evaluation of esophagectomy approaches by differentiating between surgical access methods with respect to efficacy and safety. Transhiatal resections will be excluded due to their distinct indications.

2. Methods

The work is reported according to the PRISMA guideline (Supplementary Online Content 1). It was registered in the PROSPERO Database [16] and the protocol was published a priori [17].

2.1. Inclusion criteria and literature search

We included randomized controlled trials (RCTs). Participants needed to have non-metastatic, resectable esophageal cancer and undergo abdominothoracic esophagectomy (Ivor-Lewis's procedure). There were no restrictions regarding blinding, follow-up duration, study size, or language of publication. We searched the following databases from inception to January 2024 using a predefined search strategy: PubMed, Cochrane Library, Embase, CINAHL, ClinicalTrials.gov, and ICTRP (Supplementary Online Content 1). Reference lists of included studies were also screened for additional relevant references.

2.2. Types of interventions

To be included in this network meta-analysis (NMA), trials had to compare at least two of the following interventions:

1 OE (Completely open abdominothoracic esophagectomy);
2 HYB LapS-ThoT (Hybrid abdominothoracic esophagectomy (laparoscopy and thoracotomy));
3 HYB LapT-ThoS (Hybrid abdominothoracic esophagectomy (laparotomy and thoracoscopy));
4 MIE (Completely minimally-invasive abdominothoracic esophagectomy (laparoscopy and thoracoscopy));
5 HYB RLapS-ThoT (Hybrid abdominothoracic esophagectomy (robotic laparoscopy and thoracotomy));
6 HYB LapT-RThoS (Hybrid abdominothoracic esophagectomy (laparotomy and robotic thoracoscopy));
7 RAMIE (Completely robot-assisted abdominothoracic esophagectomy (robotic laparoscopy and robotic thoracoscopy)).

Since a combination of minimally invasive and robot-assisted techniques is not practiced, seven nodes, one for each intervention, were defined.

2.3. Literature screening and data collection

Two reviewers independently screened titles, abstracts, and, if deemed potentially eligible, full texts of identified studies for inclusion. Disagreements were resolved through consultation with a third reviewer. Aggregate data (AD) were extracted from all included studies by two researchers independently. Where necessary, graphical data (e.g., from Kaplan-Meier plots) were digitized and entered into the data extraction table.

2.4. Risk of bias

Two researchers independently evaluated the risk of bias for each included study, following the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and utilizing version 2 of the Cochrane 'Risk of Bias' tool [18]. Discrepancies in assessments were resolved by discussion or by consulting a third reviewer.

2.5. Outcomes

AD were retrieved for study populations, trial characteristics, interventions, and the following outcomes: Overall survival (OS) (defined as time from surgery until death), postoperative mortality (defined as death within 90 days after surgery; if 90-day mortality was not defined, 30-day or in-hospital mortality was analyzed instead), postoperative morbidity (defined as any complication that would be classified as Clavien-Dindo grade III-V), disease-free survival (DFS, defined as time from surgery until recurrence or death from any cause), achievement of microscopically tumor-free resection margins (R0 resectability), the total number of lymph nodes resected during surgery, length of hospital and postoperative intensive care unit (ICU) stay, quality of life (QoL), postoperative pulmonary complications, anastomotic leakage, reoperation.

2.6. Statistical methods

Meta-analyses were conducted only when the studies were sufficiently similar in terms of outcome definitions, treatments, and participant characteristics. The standardized mean difference (SMD) with its 95 % confidence interval (CI) was used as the effect measure for continuous outcomes. The odds ratio (OR) with 95 % CI was calculated for binary outcomes. The hazard ratio (HR) with 95 % CI was calculated for time-to-event (TTE) outcomes. When the HR was not available, it was derived, if provided, from other summary data or Kaplan-Meier (KM) plots using validated methods described by Parmar et al. [19] and Tierney et al. [20]. For more details, see Supplementary Online Content 1.

Frequentist NMA using random-effects models, as proposed by Ruecker et al. [21], were applied to pool the effect measures of the interventions considering heterogeneity between studies. Heterogeneity between studies was assessed using the between-study variance τ^2 and the I^2 statistic. Consistency, representing the statistical confirmation of transitivity, was assessed by comparing direct and indirect evidence [22]. Results were presented using forest plots, where OE was used as reference treatment.

All analyses were performed using R version 4.4.1 [23].

3. Results

3.1. Study selection and study details

The literature search yielded 1,939 records (Fig. 1). After screening, 42 reports were assessed for eligibility, and 10 reports from 6 trials were included in the meta-analysis. We excluded one trial as it was not clearly stated in the publication if randomization was performed [24]. Three trials included patients with both squamous cell carcinoma (SCC) and adenocarcinoma of the esophagus and gastroesophageal junction (AEG). In the other trials, only participants with AEG were included. The included studies reported outcomes for four of the seven predefined surgical techniques: OE, HYB LapS-ThoT, MIE, and RAMIE.

Study characteristics are presented in Table 1.

3.2. Risk of bias

Seven reports were categorized with an overall "low" risk of bias [25–31]. Two reports were classified with "some concerns" [32,33], whereas one report was categorized with an overall "high risk of bias" [34]. (Supplementary Online Content 1).

The summary forest plots for the single outcomes are shown in Figs. 2–5.

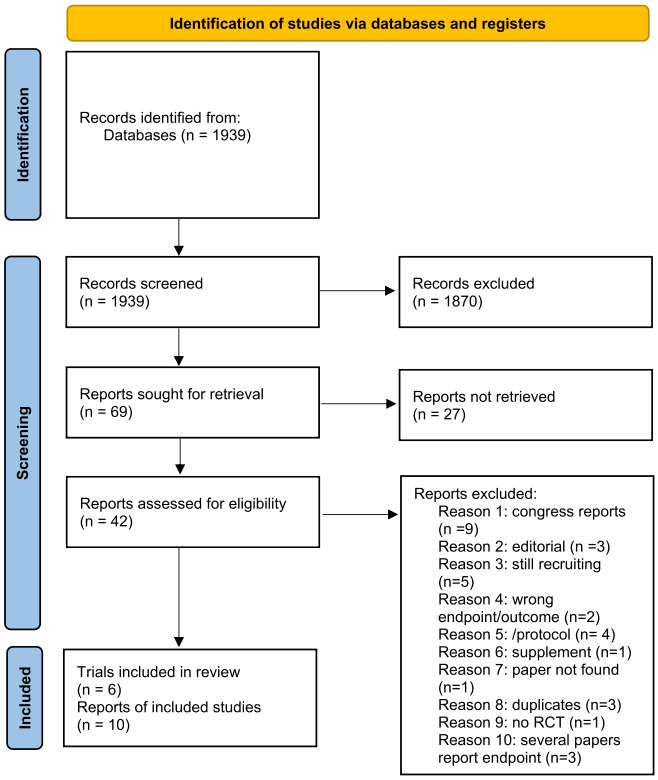

Fig. 1. PRISMA flow chart.

3.3. Associations of treatments with outcomes

3.4. Overall survival

The NMA of OS included four studies with four pairwise comparisons across four treatments: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 1) [25,27,29,32].

The analysis found no statistically significant difference in OS among the treatments. The pooled HR for HYB LapS-ThoT compared to OE was 1.46 (95 % CI: 0.98–2.18, p = 0.064). For MIE compared to OE, the HR was 1.13 (95 % CI: 0.69–1.85, p = 0.619). For RAMIE compared to OE, the HR was 0.99 (95 % CI: 0.61–1.62, p = 0.968).

Heterogeneity across studies was estimated as $\tau^2 = 0$ and $I^2 = 0$ % (95 % CI could not be estimated).

3.5. Disease-free survival

The NMA of DFS included four studies with four pairwise comparisons across four treatment modalities: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 2) [25,27,29,32].

Definitions of DFS varied slightly between studies. MIOMIE and ROBOT defined DFS as the time from surgery to recurrence of disease, while TIME and MIRO included additional endpoints, such as secondary cancer (MIRO only) and death from any cause (both).

For HYB LapS-ThoT compared to OE, the HR was 1.32 (95 % CI: 0.91–1.93, p = 0.144). For MIE versus OE, the HR was 1.12 (95 % CI: 0.71–1.78, p = 0.618), while RAMIE versus OE yielded a HR of 1.02 (95 % CI: 0.59–1.77, p = 0.943).

Heterogeneity across studies was estimated as $\tau^2 = 0$ and $I^2 = 0$ % (95 % CI could not be estimated).

Table 1
Study characteristics.

Trial Name	Study	Year	Time of recruiting	Follow-up period	Intervention
MIOMIE	Paireder et al.	2018	May 2010 to December 2012	3.5 years	OE and HYB LapS-ThoT
TIME	Biere et al.	2012	June 2009 to March 2011	1 year	OE and MIE
	Straatman et al.	2017	June 2009 to March 2011	1 year	
	Biere et al.	2017	June 2009 to March 2011	1 year	
ROBOT	de Groot et al.	2020	January 2012 to August 2016	5 years	OE and RAMIE
	van der Sluis et al.	2019	January 2012 to August 2016	5 years	
MIRO	Mariette et al. (nejm)	2019	October 2009 to April 2012	3 years	OE and HYB LapS-ThoT
	Mariette et al. (annals of surgery)	2019	October 2009 to April 2012	3 years	
–	Ma et al.	2018	September 2014 to 10/ 2015	1 year	OE and MIE
RAMIE	Yang et al.	2022	August 2017 to December 2019	–	MIE and RAMIE

3.6. Postoperative mortality

The NMA of postoperative mortality included six studies with six pairwise comparisons across four treatments: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 4) [25,28,29,31,32,34].

For OE versus HYB LapS-ThoT, the MIOMIE study reported a 7.7 % mortality rate for OE and 0 % for HYB LapS-ThoT, while the MIRO study reported 5.8 % for OE and 3.9 % for HYB LapS-ThoT. For OE versus MIE, the TIME study reported 0 % mortality for OE and 1.7 % for MIE, and the Ma et al. study reported 2.1 % for OE and 0 % for MIE. For OE versus RAMIE, the ROBOT study reported 1.8 % mortality for OE and 9.3 % for RAMIE. In the RAMIE study by Yang et al., comparing MIE to RAMIE, both groups reported a mortality rate of 0.6 %.

The OR for HYB LapS-ThoT versus OE was 0.65 (95 % CI: 0.28–1.51, p = 0.316). For MIE versus OE, the OR was 1.86 (95 % CI: 0.11–31.02, p = 0.665). For RAMIE versus OE, the OR was 4.06 (95 % CI: 0.45–36.94, p = 0.213).

Heterogeneity across studies was estimated as $\tau^2 = 0$ and $I^2 = 0$ % (95 % CI: 0–84.7 %).

3.7. Postoperative morbidity

The NMA of postoperative morbidity included three studies with three pairwise comparisons across four treatment modalities: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 2) [31,32,34].

The MIOMIE study reported morbidity rates of 38.5 % for OE and 46.2 % for HYB LapS-ThoT. The Ma et al. study showed morbidity rates of 8.2 % for OE and 10.6 % for MIE. The RAMIE study by Yang et al. reported morbidity rates of 10.2 % for MIE and 12.2 % for RAMIE.

The OR for HYB LapS-ThoT versus OE was 1.37 (95 % CI: 0.40–4.76, p = 0.619). For MIE versus OE, the OR was 1.32 (95 % CI: 0.65–2.68, p = 0.435), and for RAMIE versus OE, the OR was 1.62 (95 % CI: 0.77–3.39, p = 0.202).

Heterogeneity across studies could not be quantified.

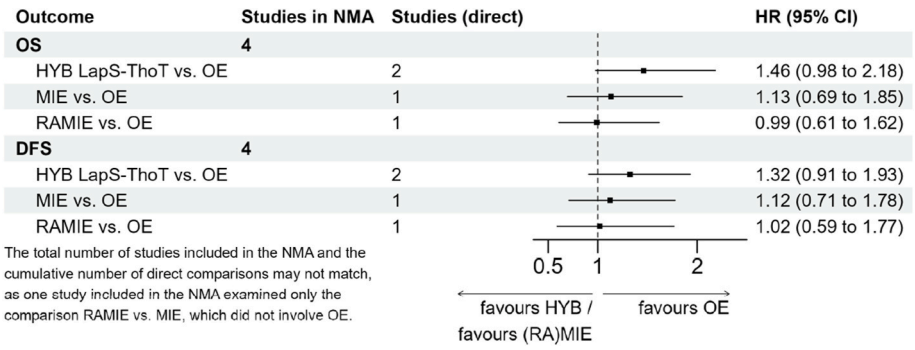

Fig. 2. Forest plot presenting the pooled hazard ratios (HR) with is 95 % confidence intervals (CI) of overall survival (OS) and disease-free survival (DFS). The number of studies included in the network-meta analysis (NMA), as well as the number of studies with direct comparison between the included interventions are provided, respectively.

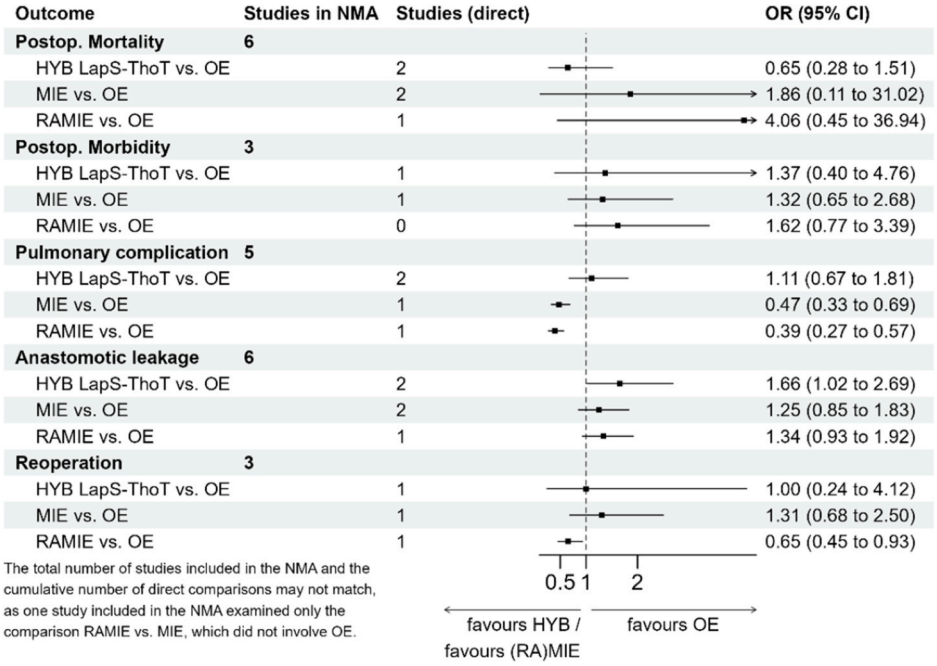

Fig. 3. Forest plot presenting the pooled odds ratios (OR) with their 95 % confidence intervals (CI) for dichotomous outcomes. The number of studies included in the network meta-analysis (NMA), as well as the number of studies providing direct comparisons between the included interventions, are indicated respectively.

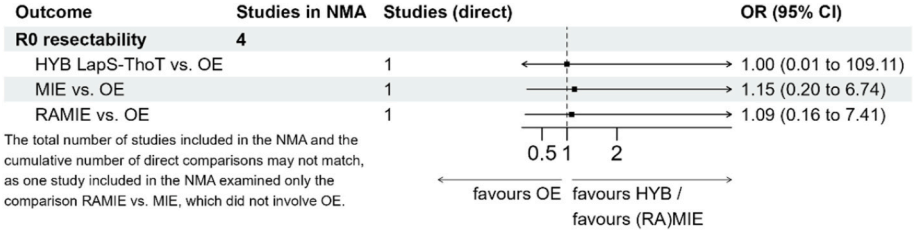

Fig. 4. Forest plot presenting the pooled odds ratios (OR) with their 95 % confidence intervals (CI) for R0 resection rates. The number of studies included in the network meta-analysis (NMA), as well as the number of studies with direct comparisons between the included interventions, are indicated respectively.

3.8. Pulmonary complications

The NMA of pulmonary complications included five studies with five pairwise comparisons across four treatments: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 2) [28,29,31,32,34].

The MIOMIE study reported equal rates of pulmonary complications (23.1 %) for both OE and HYB LapS-ThoT. The ROBOT [28] study showed significantly fewer pulmonary complications for RAMIE (31.5 %) compared to OE (58.2 %). In the MIRO [29] study, pulmonary complication rates were similar between OE (10.6 %) and HYB LapS-ThoT (11.7 %). The Ma et al. [34] study reported fewer pulmonary complications for MIE (23.4 %) compared to OE (35.1 %). The RAMIE [31] study showed similar pulmonary complication rates between MIE (14.7 %) and RAMIE (13.8 %).

The OR for HYB LapS-ThoT versus OE was 1.11 (95 % CI: 0.67–1.81, $p = 0.692$). For MIE versus OE, the OR was 0.48 (95 % CI: 0.33–0.69, p

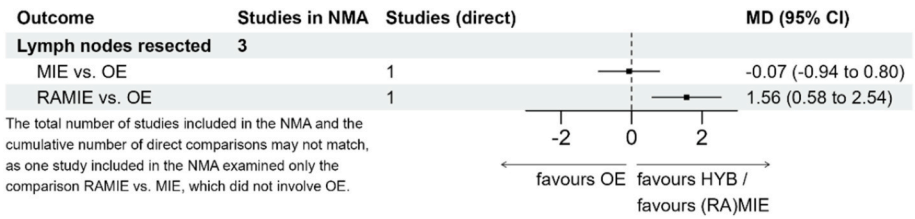

Fig. 5. Forest plot presenting the pooled mean differences (MD) with their 95 % confidence intervals (CI) for the number of lymph nodes resected. The number of studies included in the network meta-analysis (NMA), as well as the number of studies with direct comparisons between the included interventions, are indicated respectively.

< 0.0001). RAMIE versus OE yielded an OR of 0.39 (95 % CI: 0.27–0.57, $p < 0.0001$).

Heterogeneity across studies was moderate, with $\tau^2 = 0.0308$ and $I^2 = 44.3$ % (95 % CI: 0–83.4).

3.9. Anastomotic leakage

The NMA of anastomotic leakage included six studies with six pairwise comparisons across four surgical techniques: OE, HYB LapS-ThoT, MIE, and RAMIE [26,28,29,31,33,34].

In the MIOMIE study, leakage rates were 15.4 % for OE and 23.1 % for HYB LapS-ThoT. The TIME trial reported rates of 7.1 % for OE and 11.9 % for MIE. In the ROBOT study, leakage rates were 20.0 % for OE and 24.1 % for RAMIE. The MIRO trial showed rates of 6.7 % for OE and 10.7 % for HYB LapS-ThoT. The Ma et al. study reported leakage rates of 6.2 % for OE and 6.4 % for MIE. Finally, the RAMIE study by Yang et al. showed leakage rates of 11.3 % for MIE and 12.2 % for RAMIE.

The OR for HYB LapS-ThoT versus OE was 1.66 (95 % CI: 1.02–2.69, $p = 0.041$), indicating a statistically significant increase in leakage rates with HYB LapS-ThoT. For MIE versus OE, the OR was 1.25 (95 % CI: 0.85–1.83, $p = 0.257$), and for RAMIE versus OE, the OR was 1.34 (95 % CI: 0.93–1.92, $p = 0.113$), with neither showing significant differences compared to OE.

Heterogeneity across studies was estimated as $\tau^2 = 0$ and $I^2 = 0$ % (95 % CI: 0–84.7 %).

3.10. Reoperation

The NMA of reoperation rates included three studies with three pairwise comparisons across four surgical techniques: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 3) [30,32,36].

In the MIOMIE study, reoperation rates were identical at 30.8 % for both OE and HYB LapS-ThoT. The TIME trial reported rates of 10.7 % for OE and 13.6 % for MIE. In the ROBOT study, OE had a reoperation rate of 32.7 %, compared to 24.1 % for RAMIE.

The OR for HYB LapS-ThoT versus OE was 1.00 (95 % CI: 0.24–4.12, $p = 1.000$). For MIE versus OE, the OR was 1.31 (95 % CI: 0.68–2.50, $p = 0.419$), also showing no significant difference. RAMIE versus OE yielded an OR of 0.65 (95 % CI: 0.45–0.93, $p = 0.020$), indicating a statistically significant reduction in reoperation rates for RAMIE.

Heterogeneity across studies could not be quantified.

3.11. Achievement of tumor-free resection margins (R0 resection)

The NMA of R0 resection included four studies with four pairwise comparisons across four treatments: OE, HYB LapS-ThoT, MIE, and RAMIE (Fig. 4) [26,28,31,33]. The studies reported high rates of R0 resection across all treatment groups.

In the MIOMIE study, both OE and HYB LapS-ThoT achieved an R0 resection rate of 92.3 %. The TIME study reported R0 rates of 83.9 % for OE and 91.5 % for MIE. In the ROBOT study, OE achieved a rate of 96.4 % compared to 92.6 % for RAMIE. Finally, in the RAMIE study by Yang et al., MIE and RAMIE achieved R0 rates of 92.1 % and 95.0 %, respectively.

Compared to OE, the OR was 1.00 (95 % CI: 0.01–109.11, $p = 1.000$) for HYB LapS-ThoT, 1.15 (95 % CI: 0.20–6.74, $p = 0.878$) for MIE, and 1.09 (95 % CI: 0.16–7.41, $p = 0.927$) for RAMIE.

Heterogeneity was estimated as $\tau^2 = 1.04$ and $I^2 = 79.9$ % (95 % CI: 13.4–95.3 %).

3.12. Number of resected lymph nodes

The NMA of the number of resected lymph nodes included three studies with three pairwise comparisons across three treatments: OE, MIE, and RAMIE (Fig. 5). [26,28,31]

In the TIME study, both OE and MIE achieved a mean of 20.33 resected lymph nodes, with SDs of 3.94 and 3.62, respectively. In the ROBOT study, OE resulted in a mean of 24.33 resected lymph nodes, compared to 25.67 for RAMIE, with SDs of 4.60 and 5.25, respectively. In the RAMIE study by Yang et al., MIE achieved a mean of 22.33 resected lymph nodes compared to 24.00 for RAMIE, with SDs of 5.35 and 5.69.

For MIE versus OE, the MD was −0.07 (95 % CI: 0.94 to 0.80, $p = 0.872$). For RAMIE versus OE, the MD was 1.56 (95 % CI: 0.58 to 2.54, $p = 0.002$).

Heterogeneity across studies was estimated as $\tau^2 = 0$ and $I^2 = 0$ % (95 % CI could not be estimated).

Analysis of local- and distant-recurrence-free survival (LRFS and DRFS) was not feasible, and therefore no results could be reported for these outcomes. Results concerning Length of Hospital Stay, ICU Stay and Quality of life are provided in Supplementary Online Content 1.

3.13. Summary of Findings

Summary of Findings tables were created for OS, DFS, postoperative mortality, postoperative morbidity, R0-resection, pulmonary complication, anastomotic leakage and reoperation. They are provided in Supplementary Online Content 1.

4. Discussion

This NMA compared OE, HYB, LapS-ThoT, MIE, and RAMIE across multiple outcomes in patients undergoing esophagectomy for esophageal cancer. The studies were considered comparable in terms of study populations, interventions, and overall methodological quality. While the risk of bias was low in most studies, statistical heterogeneity could not be reliably estimated for the majority of endpoints, limiting the ability to draw conclusive statements in this regard.The NMA showed that RAMIE and MIE were associated with comparable OS and DFS to OE. RAMIE achieved a significantly higher lymph node yield than OE, although the absolute difference in the number of resected lymph nodes was small. R0 resection rates were high across all modalities suggesting similar efficacy in achieving tumor-free margins. Postoperative morbidity and mortality did not differ between surgical approaches. However, RAMIE and MIE were associated with fewer pulmonary complications compared to OE, while HYB LapS-ThoT exhibited a higher

rate of anastomotic leakage. RAMIE also demonstrated significantly lower reoperation rates than OE, reinforcing its potential for improved surgical safety. QoL outcomes suggested early postoperative benefits for RAMIE and MIE over OE, particularly in global health and physical function domains. Additionally, RAMIE and MIE were associated with shorter ICU and hospital stays compared to OE. However, no NMA was performed for QoL, ICU and hospital stay, and the findings are based on individual studies with limited comparability due to inconsistent reporting. These results suggest a safety benefit for MIE and RAMIE with comparable survival outcomes. While MIE is acknowledged in contemporary guidelines, the role of RAMIE still remains debated as of now. The ongoing ROBOT-2 trial is designed to carry out this important comparison in patients with esophageal adenocarcinoma [35].

Neoadjuvant treatment and prehabilitation potentially affect outcomes after esophagectomy. In our analysis, we were unable to perform subgroup analyses regarding neoadjuvant therapies or prehabilitation, because those data were not reported from the single trials. Beyond prehabilitation, enhanced postoperative recovery (EPR) after surgery plays an important role in achieving optimal safety and functional outcomes after esophagectomy. Key components include preoperative nutritional support, optimized pain management, early mobilization, and early oral feeding. Many EPR programs hinge on minimally-invasive approaches given the reduced postoperative pain and need for analgesics, whose use in turn is associated with adverse effects such as ileus, nausea, and fatigue. From the RCTs included in the meta-analysis, no detailed information on applied EPR measures was available. However, the lower postoperative pain levels shown in the MIE and RAMIE arms of the trials underscore the important role of minimally-invasive surgery in EPR. Conversely, the full effect of MIE and RAMIE on postoperative safety and functional outcomes can most likely only be attained if a dedicated EPR program is in place. Adherence to EPR varies. A survey of Canadian thoracic surgeons revealed high compliance with preoperative and postoperative EPR recommendations, but lower adherence to intraoperative guidelines. This underscores the need for ongoing education and institutional support to ensure consistent application of EPR principles across all phases of surgical care [36].

In our NMA, RAMIE achieved a significantly higher lymph node yield than OE, reflecting its potential for enhanced oncological precision due to better visualization of anatomic structures and higher accuracy in surgical dissection. Lymph node yield is commonly regarded an oncological surrogate parameter. Nonetheless, there is an ongoing debate about the recommended extent of lymph node dissection in esophagectomy, weighing oncological radicality against increased morbidity associated with more extensive dissection [37]. The German S3 guidelines for the diagnosis and treatment of esophageal carcinoma emphasize the importance of thorough lymphadenectomy. These guidelines recommend the resection of an adequate number of LNs to ensure accurate staging and to potentially improve survival outcomes [38]. The extent of lymphadenectomy should be tailored based on tumor location and histological subtype. Our results support the notion that MIE and RAMIE can increase lymph node yield for a given planned extent of lymphadenectomy without jeopardizing safety. However, the absolute difference in lymph node yield between MIE and RAMIE and OE is rather small and thus its immediate clinical implications remain unclear.

Meta-analyses in general and NMAs in particular inherently face certain limitations. The integration of data from randomized controlled trials (RCTs) with diverse inclusion criteria, treatment approaches, and study designs unavoidably introduces heterogeneity. Although this study adhered to stringent eligibility criteria, differences across the included trials likely contributed to clinical variability. Overall, only six studies were included, with an even smaller number contributing data to many of the single objectives, as not all outcomes were reported across all studies. Some NMAs could not be conducted due to a lack of data, for example for the outcomes local recurrence-free survival and distant recurrence-free survival. Additionally, for several outcomes, data reporting was inconsistent or incomplete across trials. For example, the QoL analysis was hindered by the use of different assessment tools and varying follow-up intervals. Similarly, the analysis of ICU and hospital length of stay was limited by insufficient reporting of appropriate summary statistics.

Statistical heterogeneity appeared to be generally low across most outcomes. However, with only a few studies included in the network, the estimation of heterogeneity might be unstable and imprecise. Therefore, the lack of observed heterogeneity should not be interpreted as evidence of its absence. Given the estimation of a low but uncertain τ^2 and I^2, the corresponding confidence intervals of the outcomes may be too narrow, warranting cautious interpretation of the results.

Despite employing an extensive search strategy across multiple databases and including non-English publications, there remains a potential risk of overlooking relevant studies, particularly unpublished research.

These limitations reduced the possibility to detect meaningful differences between treatments and emphasized the need for further prospective studies in these areas.

The results of this network meta-analysis are specific to the interventions and outcomes examined. Variations in perioperative management, surgical expertise, and institutional practices may limit the transferability of these findings. In particular, the conclusions are applicable primarily to studies, centers, and patient populations that align with the defined criteria of this analysis. They should not be generalized to settings, institutions, or patient groups that differ substantially in these respects. Nevertheless, this study provides valuable insights into the comparative effectiveness and safety of surgical approaches for esophageal cancer. Ongoing trials and longer follow-up periods will be essential to further validate and expand upon these findings.

5. Conclusions

This NMA might offer that MIE and RAMIE offer comparable oncological outcomes to OE, with potential benefits in postoperative recovery, including reduced pulmonary complications and shorter hospital stays. While heterogeneity and data limitations necessitate cautious interpretation, these findings highlight the growing role of minimally-invasive surgical approaches in the management of esophageal cancer, underscoring the need for further prospective high-quality studies to validate these outcomes and optimize treatment strategies.

CRediT author statement

- **Artur Rebelo**: Conceptualization, Study design, Literature search, Data analysis, Bias analysis, Interpretation of results, Writing – Original Draft, Project administration.
- **Juliane Friedrichs**: Literature screening, Data collection.
- **Yoshiaki Sunami**: Bias analysis.
- **Elisabeth** Wadewitz: Bias analysis.
- **Maurizio** Grilli: Development and refinement of the search strategy.
- **Johannes A. Vey**: Statistical analysis. Draft Revision.
- **Marie Merling**: Statistical analysis. Draft Revision.
- **Johannes Klose:** Academic oversight. Draft Revision.
- **Onur Bayram:** Academic oversight. Draft Revision.
- **Ulrich** Ronellenfitsch: Supervision, Academic oversight.
- **Jörg** Kleeff: Supervision, Academic oversight.

Funding Disclosure

This work was not supported by the National Institutes of Health (NIH), the Wellcome Trust, the Howard Hughes Medical Institute (HHMI), or any other external funding agencies.

Declaration of interest statement

On behalf of my co-authors, I declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work has been funded by the Medical Faculty of the Martin Luther University Halle-Wittenberg, Halle (Saale), Germany, Advanced Clinician Scientist Program. The funder had no direct influence on the design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.110529.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68 2018;6:394–424. [Accessed 12 September 2018].
[2] American Cancer Society. Survival rates for esophageal cancer [Internet]. Atlanta: American Cancer Society; 2024. https://www.cancer.org/cancer/types/esophagus-cancer/detection-diagnosis-staging/survival-rates.html. [Accessed 6 October 2025].
[3] Lagergren J, Smyth E, Cunningham D, et al. Oesophageal cancer. Lancet 2017;390(10110):2383–96.
[4] Smyth EC, Lagergren J, Fitzgerald RC, et al. Oesophageal cancer. Nat Rev Dis Primers 2017;3:17048.
[5] Torre LA, Siegel RL, Ward EM, et al. Global cancer incidence and mortality rates and Trends–An update. Cancer Epidemiol Biomarkers Prev 2016;25(1):16–27.
[6] NCCN. NCCN Guidelines: esophageal and esophagogastric junction cancers. 2023.
[7] Szakó L, Németh D, Farkas N, et al. Network meta-analysis of randomized controlled trials on esophagectomies in esophageal cancer: the superiority of minimally invasive surgery. World J Gastroenterol 2022;28(30):4201–10.
[8] Casas MA, Angeramo CA, Bras Harriott C, et al. Surgicaloutcomesaftertotallyminimallyinvasive Ivor Lewisesophagectomy: Asystematicreviewandmeta-analysis. Eur J Surg Oncol 2022;48(3):473–81.
[9] Wang B, Zuo Z, Chen H, et al. The comparison of thoracoscopic-laparoscopic esophagectomy and open esophagectomy: a meta-analysis. Indian J Cancer 2017;54(1):115–9.
[10] Guo W, Ma X, Yang S, et al. Combined thoracoscopic-laparoscopic esophagectomy versus open esophagectomy: a meta-analysis of outcomes. Surg Endosc 2016;30(9):3873–81.
[11] Bras HC, Angeramo CA, Casas MA, et al. Open versus hybrid versus totally minimally invasive Ivor Lewis esophagectomy: systematic review and meta-analysis. J Thorac Cardiovasc Surg 2022;164(6):e233–54.
[12] Magouliotis DE, Zotos P-A, Fergadi MP, et al. Meta-analysis of robot-assisted versus video-assisted McKeown esophagectomy for esophageal cancer. Updates in Surgery 2022;74(5):1501–10.
[13] Mederos MA, de Virgilio MJ, Shenoy R, et al. Comparison of clinical outcomes of robot-assisted, video-assisted, and open esophagectomy for esophageal cancer: a systematic review and meta-analysis. JAMA Netw Open 2021;4(11):e2129228.
[14] Wei Z-D, Zhang H-L, Yang Y-S, et al. Effectiveness of transthoracic hybrid minimally invasive esophagectomy: a meta-analysis. J Invest Surg 2021;34(9):963–73.
[15] Yibulayin W, Abulizi S, Lv H, et al. Minimally invasive oesophagectomy versus open esophagectomy for resectable esophageal cancer: a meta-analysis. World J Surg Oncol 2016;14(1):304.
[16] PROSPERO. PROSPERO - international prospective register of systematic reviews [Online] NIHR - National Institute for Health and Care Research . [Cited: 03 24, 2025, https://www.crd.york.ac.uk/prospero/.
[17] Rebelo A, Friedrichs J, Grilli M, Vey J, Klose J, Merling M, et al. Approaches for thoracoabdominal oesophagectomy for oesophageal cancer: a network meta-analysis - study protocol. BMJ Open 2025;15(3):e093561. March 13.
[18] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Br Med J 2019.
[19] *Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints.* Parmar MKB, Torri V, Stewart L. 24, S. 2815–34, s.l. Stat Med 1988;17(24).
[20] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. s.l. Trials 2007;16. Quelle
[21] Rücker G, et al. Network meta-analysis, electrical networks and graph theory. 3, s.l. Res Synth Methods 2012.
[22] Checking consistency in mixed treatment comparison meta-analysis, Dias S, Welton NJ, Caldwell DM, Ades AEsl. Stat Med 2010;9.
[23] Team RCore R. A language and environment for statisticalcomputing. Austria R Foundation for Statistical Computing; 2021 [Hrsg.] Vienna.
[24] Guo M, Xie B, Sun X, Hu M, Yang Q, Lei Y. A comparative study of the therapeutic effect in two protocols: video-assisted thoracic surgery combined with laparoscopy versus right open transthoracic esophagectomy for esophageal cancer management. Chin Ger J Clin Oncol 2013:68–71.
[25] Straatman J, Van Der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally invasive versus open esophageal resection: three-year Follow-up of the previously reported randomized controlled trial the TIME trial. . August. Ann Surg August 2017;266(2):232–6.
[26] Biere SS, Van Berge Henegouwen MI, Maas KW, Bonavina L, Rosman C, Garcia JR, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet 2012;379(9829):1887–92.
[27] De Groot EM, Van Der Horst S, Kingma BF, Goense L, Van Der Sluis PC, Ruurda JP, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open esophagectomy: long-term follow-up of a randomized clinical trial. Diseases of the Esopha. Dis Esophagus November 26, 2020;33(Supplement_2):doaa079.
[28] Van Der Sluis PC, Sylvia Van Der Horst, May AM, Schippers C, Brosens LAA, Joore HCA, et al. Robot-assisted minimally invasive thoracolaparoscopic esophagectomy versus open Transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial. Ann Surg April 2019;269(4):621–30.
[29] Mariette C, Markar SR, Dabakuyo-Yonli TS, Meunier B, Pezet D, Collet D, et al. Hybrid minimally invasive esophagectomy for esophageal cancer. N Engl J Med 2019;380(2):152–62. January 10.
[30] Mariette C, Markar S, Dabakuyo-Yonli TS, Meunier B, Pezet D, Collet D, et al. Health-related quality of life following hybrid minimally invasive versus open esophagectomy for patients with esophageal cancer, analysis of a multicenter, open-label, randomized phase III controlled trial: the MIRO trial. Ann Surg June 2020;271(6):1023–9.
[31] Yang Y, Li B, Yi J, Hua R, Chen H, Tan L, et al. Robot-assisted versus conventional minimally invasive esophagectomy for resectable esophageal squamous cell carcinoma: early results of a multicenter randomized controlled trial: the RAMIE trial. Ann Surg April 2022;275(4):646–53.
[32] Paireder M, Asari R, Kristo I, Rieder E, Zacherl J, Kabon B, et al. Morbidity in open versus minimally invasive hybrid esophagectomy (MIOMIE): long-term results of a randomized controlled clinical study. Eur Surg December 2018;50(6):249–55.
[33] Biere SS, Van Berge Henegouwen MI, Bonavina L, Rosman C, Roig Garcia J, Gisbertz SS, et al. Predictive factors for post-operative respiratory infections after esophagectomy for esophageal cancer: outcome of randomized trial. J Thorac Dis July 2017;9(S8):S861–7.
[34] Ma G, Cao H, Wei R, Qu X, Wang L, Zhu L, et al. Comparison of the short-term clinical outcome between open and minimally invasive esophagectomy by comprehensive complication index. J Cancer Res Therapeut 2018;14(4):789–94.
[35] Tagkalos E, van der Sluis PC, Berlth F, Poplawski A, Hadzijusufovic E, Lang H, et al. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus minimally invasive esophagectomy for resectable esophageal adenocarcinoma, a randomized controlled trial (ROBOT-2 trial). BMC Cancer 2021;21(1):1060. Sep. 26.
[36] Jogiat U, Sisson D, Sasewich H, Islam T, Low D, Darling G, et al. ERAS guidelines for esophagectomy: adherence patterns among Canadian thoracic surgeons. Updates Surg 2023;75(5):1203–10. Epub 2023 Mar 21.
[37] Peyser Cardoso R, Agarwal L, Cardoso SA, Agarwal A, Varshney V, Soni S, et al. Impact of intraoperative recurrent laryngeal nerve monitoring on minimally invasive esophagectomy outcomes for esophageal cancer: a meta-analysis of case-control studies. Dis Esophagus 2025;38(1):doae116. Jan 7.
[38] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus, Kurzversion 4.0. AWMF-Registernummer: 021-023OL 2023.