Effect of en bloc esophagectomy and meso-esophagectomy on esophageal cancer patients: a systematic review and meta-analysis

Feng Su (✉ 16301050033@fudan.edu.cn)  
Zhongshan Hospital Fudan University  
https://orcid.org/0000-0001-7469-5499

Heng Jiao  
Zhongshan Hospital Fudan University

Jun Yin  
Zhongshan Hospital Fudan University

Yong Fang  
Zhongshan Hospital Fudan University

Lijie Tan  
Zhongshan Hospital Fudan University

Yaxing Shen  
Zhongshan Hospital Fudan University

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Abstract

**Background**: Esophagectomy offers the chance of cure for esophageal cancer; however, the optimal circumferential extent of surgery remains uncertain. Yet, the practice of en bloc esophagectomy (EBE) and meso-esophagectomy (TME) reached inconsistent results, which led to the proposal of this study was to evaluate the surgical and oncological effect of EBE and TME on the esophageal cancer patients.

**Methods**: Five databases were searched through March 1st, 2022, and the references of eligible studies were further searched in the databases and assessed. Randomized controlled trials (RCTs) comparing the efficacy of EBE or TME were included. The outcomes were recorded in the forms of mean difference (MD), risk ratio (RR), odds ratio (OR) and hazard ratio (HR) with its corresponding 95% confidence intervals (CI).

**Results**: Overall, a total of 14 RCTs involving 3106 subjects were included. Compared with standard resection, a higher blood loss (MD=56.29, (14.80, 97.77), \(P=0.008\)) and better long-term outcomes for early cancer patients (OS: HR=0.31, (0.10, 0.96), \(p =0.04\); DFS: HR=0.71, (0.41, 1.21), \(P=0.21\)) and advanced staged esophageal cancer patients (OS: HR=0.47, (0.33, 0.66), \(p <0.001\); DFS: HR=0.62, (0.38, 0.99), \(P=0.05\)) were observed in the EBE surgery group, while TME showed less blood loss (MD=-74.03, (-96.69, -51.38), \(p <0.001\)), shorter operation time (MD=-32.37, (-65.12, 0.37), \(p =0.05\)) and better overall survival (HR=0.74, (0.55, 0.98), \(P=0.04\)).

**Conclusion**: EBE is highly technically demanding and associated with comparable surgical trauma and better long-term outcomes. And TME is accompanied with better long-term prognosis without improving operative bleeding and operation time. Further prospective studies are required to verify the efficacy of EBE and TME.

Background

Despite the progress in the multiple treatment modalities, esophageal cancer is one of the most prevalent and deadly carcinomas worldwide[1, 2]. Surgical resection remains the mainstage of the radical treatment, especially for localized esophageal cancer[3]. However, the radical resection of esophagus could be traumatic, while the non-extended resection is considered likely to lead to non-radical surgery in advanced stage carcinoma theoretically, and thus the optimal circumferential extent of surgical resection has not been determined yet.

Different modalities of esophagectomy have been developed in order to reach the optimal circumferential extent of surgery according to precise medicine[4, 5]. En bloc esophagectomy (EBE) was originally proposed by Logan as an extended esophageal surgery[6]. For middle and lower esophageal cancer, besides the esophagus, EBE refers to the resection of pericardium anteriorly, pleural surfaces laterally, thoracic duct and all other lymphoid tissue on the ventral side of the spine posteriorly[7]. Notably, Cuesta et al. described an anatomic fascia between descending aorta and carina called meso-esophagus, similar to mesorectum, and thus the total meso-esophagectomy (TME) has become a new exploration of surgical methods[8, 9]. During the TME, vascular and lymphatic fatty tissue and nerves around the esophagus were removed as a single anatomical unit ending at the level of the azygos vein superiorly, the mesoesophagus with tracheoesophageal sulcus and recurrent laryngeal nerve (RLN) lymph nodes (LN) was dissected along the spine to thoracic outlet. Theoretically, such extensive resections could be accompanied by high postoperative morbidity as well as superior long term oncologic outcomes[10]. As reported by several studies, the application of minimal invasive esophagectomy (MIE) after neoadjuvant therapy could be a safe and feasible modality for esophageal cancer, and the integration of EBE and TME with such advanced technique could probably shed a light on the surgical treatment of the esophageal cancer[11].
Therefore, based on the results of randomized controlled trials, we conducted the present systematic review and meta-analysis comparing the surgical outcomes of EBE and TME, as well as the long-term prognosis of two surgeries.

**Method**

**Searching strategy**

The conducted searching strategy including several electronic databases including PubMed, Cochrane Library, Web of Science and Embase databases, and the index date was up to March 1st, 2022. The search key words include “esophageal cancer”, “en bloc esophagectomy” and “meso-esophagectomy”. The references of the screened and selected studies were also manually searched in the databases and assessed. The details of the search strategy are listed in the supplementary material. The citation search of the eligible studies and reviews were also manually performed for potential related articles.

**Study selections**

The literatures were identified by two reviewers independently according to the inclusion and exclusion criteria. Inclusion criteria is as follows: (1) available randomized controlled trials (RCTs), (2) patients pathologically diagnosed with esophageal cancer were included in the RCTs, (3) en bloc esophagectomy or meso-esophagectomy was performed only in one arm in the RCTs and was compared with other surgeries. The exclusion criteria are listed: (1) single arm studies; (2) non clinical studies.

**Data extraction**

Two authors reviewed the studies independently and extracted the continuous and discontinuous data from the study. Besides, details of the study including first author, publication year, research centers, methodology (study design, randomization, and allocation), sample size, demographic characteristics, treatment modality as well as short-term and long-term outcomes. The sample size, mean and standard deviation (SD) were collected for continuous variables such as age, operation time, blood loss and the number of LN harvest. If the SD was not available in the literature, then the SDs would be calculated according to the guideline of the Cochrane handbook, while sample size and number of events were collected for discontinuous data such as sex distribution and R0 resection[12]. As for overall survival (OS) and disease-free survival (DFS), rate at every time point was estimated from Kaplan-Meier curve with Engauge Digitizer (version 11.1). Besides, sample size and cases at risk at several time points were documented.

**Evaluation of quality**

The quality of the selected studies was evaluated by two reviewers with Cochrane risk of bias tool for RCTs. The tool contains seven key items that is: (1) randomization, (2) allocation concealment, (3) participants blinding, (4) outcome assessments blinding, (5) incomplete outcome data, (6) bias in reporting, and (7) other bias. Each study in each item were rated as three levels “low bias risk”, “unclear bias risk” and “high bias risk” according to the reviewers.

**Statistical analysis**

Before comparison, the units of the outcomes were converted into standard international unit. The software Review Manager 5.4 was used to calculate every outcome for the meta-analysis. For short term outcomes, the risk ratio (RR) was used for the assessment of discontinuous data and the mean difference (MD) for continuous data. The log-
rank and the log-rank Variance (V) were derived from Kaplan-Meier curve data and follow up data[13]. The survival benefits were recorded with hazard ratio (HR) calculated from O-E and V. The 95% confidence interval (CI) was used to estimate the population parameter. The \( p < 0.05 \) is considered statistically significant, while \( 0.05 \leq p < 0.10 \) is considered borderline significant. The short-term and long-term results would be shown in the forest plot and a funnel plot containing not less than 10 studies would be used to avoid the potential publication bias with Begg's rank correlation test and Egger-test in STATA (version 16.0).

\( I^2 \) and Chi squared were derived from the result to evaluate the heterogeneity between the studies. The \( p \) value was interpreted as follows: in the short-term outcomes analysis, if \( I^2 \leq 50\% \) is got or could be adjusted by excluded several heterogeneous studies, then we considered the heterogeneity between studies is not important and the fixed-effects model with Mantel-Haenszel method was used in the secondary analysis. If \( I^2 > 50\% \), there is moderate or greater heterogeneity, and the random-effects model with the Der-Simonian and Laird method was used for further analysis. The degree of heterogeneity is judged in terms of \( p \) value: \( 0.01 < p \leq 0.05 \) is moderate heterogeneity and \( p \leq 0.01 \) for substantial heterogeneity. High heterogeneity may greatly harm the level of evidence grade, except that all of studies show a consistent direction in the forest plot.

### Results

#### Search result

The searching strategy yielded 1719 literatures in total, and 538 duplicated records were removed with Endnote X9. In the rest of screened 1181 results, 1129 were excluded for the reasons including topic irrelevant, review articles, and commentary article. After evaluating the full text, 38 further exclusions were made according to the inclusion and exclusion criteria. Finally, 14 studies met the inclusion criteria and were included in the meta-analysis (Flow Diagram showed in Fig. 1).

#### Study characteristics

The publication centers of included studies, which are published between 1993 and 2021, are in Europe (n = 5), North America (n = 4) and Asia (n = 5). Five of included studies were published in the recent five years, while 2 were published before 2000. In 10 studies of EBE, patients in control groups received transhiatal esophagectomy (THE) in 8 studies and received standard resection in two groups, while the non-total meso esophagectomy was performed in the control groups of 4 TME studies. In 10 studies[14–23], 1105 patients received EBE were contained in the studied group with 892 patients in the control groups. In the rest of 4 studies[24–27], 566 cases of meso esophagectomy were performed compared with 553 cases of standard esophagectomy. A brief summary of the included studies was shown in the Table. 1.

#### Bias Assessment

According to the Cochrane Library Handbook, the performance biases, detection biases or other biases were not observed in the study. The main possible biases focus on the selection bias and attrition bias. More than half of literatures didn't describe the precise method in the random sequence generation, and the allocation method is unable to evaluate in five literatures. Three reports in attrition bias and one report in reporting bias showed an unclear risk. The detailed biases of the included studies are shown in the Table.2, and the comprehensive risk of bias that affect the result could be fairly low.

#### Demographical characteristics
The demographical characteristics of gender and age was collected. 8 EBE studies and 4 TME studies have statistics on the gender distribution[14, 15, 17–22, 24–27], and the gender distribution did not differ in the experimental group or control group (OR = 0.91, (0.73, 1.12), p = 0.34) but shows a heterogeneity from subgroup differences and within-group differences. No significant difference was found in the subgroup analysis (Figure. 3A). As for age, the results of 7 EBE studies and 3 TME studies were concluded[14, 15, 18–22, 24, 26, 27]. Although a substantial heterogeneity exists, we observed that there were more younger participants in the experimental group (MD=-4.27, (-4.92, -3.63), p < 0.001) (Figure. 3B). And this difference mainly comes from the EBE subgroup (MD=-5.21, (-5.90, -4.52), p < 0.001), but the TME subgroup showed an opposite result (MD = 1.93, (0.15, 3.70), p = 0.03).

**Operation outcomes**

The operation outcomes mainly include operation time, blood loss during the surgery, the number of LN dissected and R0 resection rate.

**Operation time**: The operation time involves 7 studies and 2027 patients (Figure. 4A)[14, 18, 19, 24–27]. For the heterogeneity is obvious between the studies ($I^2 = 99\%$, $p < 0.001$), we used the random effect model in the comparison. A different effect on the operation time were observed in the two subgroups: borderline longer operation time for EBE (MD = 101.44, (-1.66, 204.55), p = 0.05), and shorter operation time for TME (MD=-32.37, (-65.12, 0.37), p = 0.05). Although the heterogeneity is substantial in both subgroups ($I^2 = 98\%$, $p < 0.001$ for EBE; $I^2 = 98\%$, $p < 0.001$ for TME), studies in EBE subgroup unanimously indicated a longer operation time for EBE.

**Intraoperative blood loss**

The $I^2$ is higher than 50% between 6 studies included researched ($I^2 = 94\%$, $p < 0.001$), as a result, we used the random effect model in the analysis of blood loss during the surgery (Figure. 4B)[18, 19, 24–27]. A diametrically opposed effect of EBE and TME on the blood loss was presented, so the superposition of the two surgeries was not considered together. There is a significantly greater blood loss in EBE compared with the control group (MD = 56.29, (14.80, 97.77), $p = 0.008$, $I^2 = 0\%$, $p = 0.44$). On the other hand, a same trend of less blood loss was obtained in the 5 researches on TME (MD=-74.03, (-96.69, -51.38), $p < 0.001$), regardless of the heterogeneity ($I^2 = 94\%$, $p < 0.001$).

**LN dissected**

The comparation of LN acquired incorporates 12 literatures and 2765 patients; 8 literatures and 1759 patients is from EBE studies; and 4 literatures with 1006 patients from TME studies (Figure. 4C)[14–19, 21, 22, 24–27]. The experimental acquired more LN than compared group (MD = 11.63, (6.11, 17.15), $p < 0.001$) in the random effect model for the substantial heterogeneity ($I^2 = 97\%$, $p < 0.001$). All the studies showed a unanimous effect in the experimental group. Although the difference in TME subgroup is not significant, both subgroups has substantial within-group heterogeneity ($I^2 = 88\%$, $p < 0.001$ for EBE; $I^2 = 99\%$, $p < 0.001$ for TME) and has a greater number of LN dissection (MD = 14.39, (9.79, 19.00), $p < 0.001$ for EBE group; MD = 6.80, (-2.76, 16.35), $p = 0.16$ for TME group).

**R0 resection rate**

In TME subgroup, only Lin and associates described that non R0 resection was one of the exclusion criteria[25], other studies have not mention the R0 resection rate, so we only compared the R0 rate of EBE with control group. The heterogeneity is not significant between six included studies with 1701 patients ($I^2 = 0\%$, $P = 0.62$), so the fixed
effect model was used for the analysis (Figure. 4D)[14, 16, 18, 19, 21, 23]. The EBE surgery has a higher R0 resection rate (RR = 1.06, (1.02, 1.11), p = 0.002).

**Postoperative outcomes**

The postoperative outcomes calculated includes pulmonary complications, recurrent laryngeal nerve (RLN) injury, anastomotic complications, and postoperative mortality.

**Pulmonary complications**

Pulmonary complications mainly refer to postoperative pneumonia, respiratory failure, pulmonary embolism, atelectasis pleural effusion requiring drainage. 6 studies about EBE and 4 studies about TME were reviewed in this analysis (Figure. 5A)[14, 16, 18, 19, 21, 23–27]. Regard to high heterogeneity ($I^2 = 60\%, p = 0.008$), there was no significant difference in the pulmonary complications postoperatively in the random effect model (RR = 1.13, (0.89, 1.43), $p = 0.27$). And no significant difference in the incidence of pulmonary complications was got in the subgroup analysis (RR = 1.22, (0.85, 1.75), $p = 0.27$ and $I^2 = 71\%, p = 0.004$ for EBE subgroup; RR = 0.97, (0.79, 1.18), $p = 0.75$ and $I^2 = 0\%, p = 0.75$ for TME subgroup).

**Recurrent laryngeal nerve injury**

Symptoms described as vocal cord paralysis, RLN palsy and hoarse voice were also involved in the analysis. The included studies were the same as pulmonary complication and related to 2707 patients (Figure. 5B)[14, 16, 18, 19, 21, 23–27]. We observed a heterogeneous result with no difference in the incidence of RLN injury in the random model (RR = 1.08, (0.52, 2.22), $p = 0.84$; $I^2 = 67\%, p = 0.001$). Both EBE (RR = 0.76, (0.27, 2.13), $p = 0.60$) and TME (RR = 1.77, (0.56, 5.60), $p = 0.33$) are not associated with higher risk of postoperative RLN injury.

**Anastomotic complications**

The postoperative anastomotic complications are mainly anastomotic leakage. Similarly, 6 RCTs of EBE and 4 RCTs of TME were included (Figure. 5C)[14, 16, 18, 19, 21, 23–27]. Considering the heterogeneity between and within groups is minor ($I^2 = 0\%, p = 0.87$ for total; $I^2 = 0\%, p = 0.85$ for EBE subgroup; $I^2 = 0\%, p = 0.46$ for TME subgroup), the fixed effect model was used. No significant difference was observed in the incidence anastomotic complications (RR = 0.79, (0.60, 1.05), $p = 0.10$), and a similar result was obtained in the subgroup analysis (RR = 0.86, (0.58, 1.27), $p = 0.45$ for EBE subgroup; RR = 0.73, (0.50, 1.08), $p = 0.12$ for TME subgroup).

**Postoperative mortality**

8 studies and 2339 participants were included in the comparation of postoperative mortality (Figure. 5D)[14, 16, 18, 19, 21, 23, 25, 26]. For no significant heterogeneity was observed in the comparation or subgroup analysis ($I^2 = 0\%, p = 0.96$ for global analysis; $I^2 = 0\%, p = 0.93$ for EBE; $I^2 = 0\%, p = 0.46$ for TME), the fixed effect model was used. We have no evidence to make the conclusion that the postoperative mortality is different between experimental group and control group in global analysis or subgroup analysis (RR = 1.15, (0.71, 1.84), $p = 0.57$ for global analysis; RR = 1.17, (0.72, 1.91), $p = 0.52$ for EBE subgroup; RR = 0.77, (0.10, 6.10), $p = 0.81$ for TME subgroup).

**Long term outcomes**
The main indicators for long term outcomes are OS and DFS. Besides, the patients in EBE studies were further grouped into early stage and advanced stage by TNM stage and lymph node status according to postoperative pathology. The pathological stage in the study by J A Hagen et al. was different from others, and it was considered as two studies in the advanced subgroup analysis, with J A Hagen-1 for intermediate stage and J A Hagen-2 for late stage[20].

**Overall survival**

7 studies provided the OS information of 1364 patients (Figure. 6A)[14, 15, 20–22, 24, 25]. The heterogeneity is considerable between studies ($I^2 = 58\%, \ p = 0.03$) and the OS is better in the extended surgical group than in the standard group (HR = 0.79, (0.66, 0.94), $p = 0.008$). In the subgroup analysis, EBE group showed a moderate heterogeneity ($I^2 = 62\%, \ p = 0.03$) and borderline significantly better OS (HR = 0.82, (0.65, 1.03), $p = 0.08$). And the TME group produce a similar heterogeneity ($I^2 = 69\%, \ p = 0.07$) and significantly better OS (HR = 0.74, (0.55, 0.98), $p = 0.04$).

**Disease-free survival**

6 literatures offered the DFS data of 1799 patients (Figure. 6B)[14, 17, 18, 21, 25, 26]. The result showed a better DFS in the experimental group (HR = 0.82, (0.70, 0.95), $p = 0.008$) with subtle heterogeneity ($I^2 = 24\%, \ p = 0.25$). In the EBE subgroup, the DFS is also better than that in control group (HR = 0.83, (0.70, 0.98), $p = 0.03$) with little heterogeneity ($I^2 = 11\%, \ p = 0.34$), on the other hand, there was no strong positive result in the TME subgroup (HR = 0.79, (0.59, 1.06), $P = 0.11$; $I^2 = 68\%, \ p = 0.08$).

**Long term outcomes for early stage**

The long-term outcomes of EBE were further analyzed. The analysis of OS included 2 studies and 36 subjects (Figure. 7A)[15, 20], and produced a result that the survival of EBE is longer than regular surgery (HR = 0.31, (0.10, 0.96), $p = 0.04$; $I^2 = 0\%, \ p = 0.36$). As for DFS, the data of 351 patients from 3 RCTs were extracted (Figure. 7B)[14, 17, 18], and no DFS benefits was observed in the EBE group or the control group (HR = 0.71, (0.41, 1.21), $p = 0.21$; $I^2 = 0\%, \ p = 0.99$).

**Long term outcomes for advanced stage**

Similarly, the long-term outcomes data of late-stage patients were collected. 3 three studies with 185 patients were analyzed (Figure. 7C), and we found that EBE surgery has a significant better survival than non EBE surgery (HR = 0.47, (0.33, 0.66), $p < 0.001$; $I^2 = 0\%, \ p = 0.65$). 410 subjects in two studies were further compared for the DFS with advanced disease (Figure. 7D)[14, 18], but a positive significant result was derived from the data (HR = 0.62, (0.38, 0.99), $P = 0.05$; $I^2 = 0\%, \ p = 0.57$).

**Evaluation of publication bias**

The evaluation of gender distribution and LN dissection includes most studies, so the funnel plots based on meta-analysis of these two indicators were performed (Figure. 8). The figures showed that there is a potential, and substantial publication bias resulted from delay or lack in the publication of non-statistically significant small RCTs. In addition, to find the possible bias in detail, the Begg's test and Egger's test were performed for the other outcomes.
where no more than 10 articles were included (Table. 2). There is no evidence suggesting the presence of publication bias in the most outcomes except for age, operation time, and LN dissection.

**Discussion**

Based on the result of 14 RCTs, we performed this systematic review to investigate the clinical outcomes of EBE and TME surgery. To our knowledge, this is the first meta-analysis evaluating the efficacy of the EBE and further the safety and feasibility of TME. In the study, we established a result that EBE was accompanied with more intraoperative blood loss, more lymph nodes removal, higher R0 resection rate as well as a better long-term OS and DFS in both early and advanced stage diseases, but there is no significant difference on the postoperative complication or incidence of mortality. As for TME, less intraoperative blood loss, shorter operation time, more lymph nodes acquired, and lower HR for OS and DFS were observed. The literatures did not compare the efficacy of EBE and TME directly, considering the control group as a reference, two surgeries were further compared. A conclusion that TME probably has shorter operation time, less intraoperative bleeding and a bit less in the lymph nodes acquirement when comparing with EBE while the postoperative outcomes of two surgeries could be comparable was derived. However, the results of the long-term prognosis are hard to compare through the articles included.

In this review, no survival benefits were observed, this may partially because that EBE group has more proportion of subjects with advanced stage[15, 17, 19, 21], and this imbalance of the disease staging between groups could harm the long-term efficacy in survival benefits. After dividing that the subgroup comparations were performed and a lower HR in both early and advanced stage was observed. We also noticed that not all patients in EBE group achieved R0 resection, which is different from what is assumed, which may partially result from the inclusion of patients with stage III and IV. And these R0 resection rate indicated the need for comprehensive treatment. Besides, no significant difference of the postoperative complications was observed, and whether it is result from the feasibility of EBE or unbalanced distribution of demographic characteristics between groups needs further investigation.

As for the TME surgery, the less blood loss and operation time, this may because the removal of esophagus and its mesangial structure as a single unit according the anatomical gap could possibly reduce the vessel injury, ameliorate operative condition, improve lymph nodes dissection and optimize the learning curve, and this entire unit excision is not associated with higher incidence of postoperative pulmonary complications, anastomotic complications, RLN injury or mortality[25, 26]. Notably, as a newly developed surgical technique, the practice of TME is not widely spread, as a result, the number of literatures investigating the TME is limited, which is possibly responsible for part of negative outcomes such as DFS.

Interestingly, in several literatures included in the meta-analysis, thoracoscopic or laparoscopic surgical approach was used in part of EBE surgery and all of TME surgery[19, 24–27]. As is known to all, MIE is a surgical approach with less trauma, enhanced recovery and improved quality of life with comparable oncological results[28–30]. Besides, MIE is optional even in advanced esophageal cancer[31, 32]. However, considering the blood loss and operation time of EBE, the combination with EBE could be highly technically demanding, which possibly limits its wide application. On the other hand, several studies have proved the feasibility of MIE combined with TME[24, 25, 27, 33], considering the effect of its learning curve, such combination has the potential to become one the mainstream procedures for esophagectomy in the future.

There are several limitations in our meta-analysis. Firstly, there are some potential biases in the study. The included studies are mostly retrospective, and the assessment found that publication biases could not completely avoided.
Besides, risks of some studies, especially in selection bias and attrition bias, are unclear. And four out of 14 studies included in the meta-analysis were "small size study", which could limit the extrapolation of its conclusions. Another limitation is that several outcomes are fairly heterogenous, probably resulting from that widespread of the research units around the world, likely to reduce the reproducibility of conclusions in particular population. Notably, we included two studies that are published in Chinese in the meta-analysis when searched the Web of Science database. Considering that China is one of areas with largest burden for esophageal cancer[2], articles in languages other than English, especially in Chinese was not rejected for further evaluation.

**Conclusion**

In this systematic review and meta-analysis, the results shows that EBE is accompanied with higher blood loss and longer operation time, and better long-term outcomes without increasing the incidence of postoperative complications. The operation time is shorter and bleeding is less in TME surgery, which could also improve the surgical and oncological efficacy. In conclusion, EBE is a safe and feasible extended esophagectomy and TME is a promising innovative esophageal surgery, which is associated with better surgical outcomes in clinical practice. Further well-designed prospective RCTs are required to verify the result of the meta-analysis.

Abbreviations used in this manuscript: EBE, en bloc esophagectomy; TME, total meso-esophagectomy; RCT, randomized controlled trials; RLN, recurrent laryngeal nerve; LN, lymph nodes; MIE, minimal invasive esophagectomy; SD, standard deviation; OS, overall survival; DFS, disease-free survival; MD, mean difference; RR, risk ratio; OR, odds ratio; HR, hazard ratio; CI, confidence intervals; O-E, expected events; V, log-rank Variance; THE, transhiatal esophagectomy

**Abbreviations**

EBE, en bloc esophagectomy; TME, total meso-esophagectomy; RCT, randomized controlled trials; RLN, recurrent laryngeal nerve; LN, lymph nodes; MIE, minimal invasive esophagectomy; SD, standard deviation; OS, overall survival; DFS, disease-free survival; MD, mean difference; RR, risk ratio; OR, odds ratio; HR, hazard ratio; CI, confidence intervals; O-E, expected events; V, log-rank Variance; THE, transhiatal esophagectomy

**Declarations**

*Ethics approval and consent to participate:* Not applicable

*Consent for publication:* Not applicable

*Availability of data and materials:* All data generated or analysed during this study are included in this published article and its supplementary information files.

*Competing interests:* The authors declare that they have no competing interests

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Authors' Contributions: FS and HJ searched the databases, extracted and analyzed the data. JY and FY screened and selected the qualified literatures. YXS and LJT designed and conceived the study. FS, YXS and HJ formulated the manuscript. All authors read and approved the final manuscript.

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**Tables**

Table.1 Basic characteristics of the studies included in the meta-analysis.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Histology (SCC/AC/Others)</th>
<th>Treatment strategy</th>
<th>Participants</th>
<th>Study design</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Brechtje A Grotenhuis et al. 2010[14]</td>
<td>Netherlands</td>
<td>46/ 86/- 12/ 78/-</td>
<td>Transthoracic EBE with extended lymphadenectomy THE surgery</td>
<td>132/ 90</td>
<td>RCT</td>
<td>Gender, age, operation time, LN acquired, R0 resection, postoperative complication, OS and DFS</td>
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<td>C Rizzetto et al. 2008[15]</td>
<td>USA</td>
<td>-/ 40/- -/ 18/-</td>
<td>neoadjuvant therapy followed by EBE neoadjuvant therapy followed by THE</td>
<td>40/ 18</td>
<td>RCT</td>
<td>Gender, age, LN acquired and OS</td>
</tr>
<tr>
<td>Claire L Donohoe et al. 2012[16]</td>
<td>Ireland</td>
<td>Unknown 8/ 24/-</td>
<td>Transthoracic EBE THE surgery</td>
<td>438/ 32</td>
<td>RCT</td>
<td>LN acquired, R0 resection, postoperative complication and OS</td>
</tr>
<tr>
<td>Emre F Yekebas et al. 2006[17]</td>
<td>Germany</td>
<td>79/ -/- 41/ -/-</td>
<td>Transthoracic EBE with two-field lymphadenectomy THE with en bloc lymphadenectomy</td>
<td>79/ 41</td>
<td>RCT</td>
<td>Gender, LN acquired and DFS</td>
</tr>
<tr>
<td>Erin M Corsini et al. 2021[18]</td>
<td>USA</td>
<td>-/ 133/- -/ 471/-</td>
<td>En bloc transthoracic Ivor Lewis esophagectomy Modified transthoracic Ivor Lewis esophagectomy</td>
<td>133/ 471</td>
<td>RCT</td>
<td>Gender, age, operation time, blood loss, LN acquired, R0 resection, postoperative complication and DFS</td>
</tr>
<tr>
<td>FU Jun-hui et al. 2012[27]</td>
<td>China</td>
<td>unreported</td>
<td>Thoracoscopic meso esophagectomy Thoracoscopic esophagectomy</td>
<td>45/ 61</td>
<td>RCT</td>
<td>Gender, age, operation time, blood loss, LN acquired and postoperative complications</td>
</tr>
<tr>
<td>FU Jun-hui et al. 2017[24]</td>
<td>China</td>
<td>122/ 10/- 121/ 9/-</td>
<td>Thoracoscopic meso esophagectomy Mckeown open esophagectomy</td>
<td>132/ 130</td>
<td>RCT</td>
<td>Gender, age, operation time, blood loss, LN acquired, postoperative complication and OS</td>
</tr>
<tr>
<td>H Fujiwara et al. 2016[19]</td>
<td>Japan</td>
<td>31/ 1/ 2 21/ 2/-</td>
<td>THE plus transthoracic en bloc mediastinal dissection</td>
<td>34/ 23</td>
<td>RCT</td>
<td>Gender, age, operation time, blood loss, LN acquired and postoperative complications</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>En bloc esophagogastrectomy</td>
<td>Transhiatal subtotal esophagectomy</td>
<td>Acquired, R0 resection and postoperative complication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------</td>
<td>------------------------------</td>
<td>-----------------------------------</td>
<td>------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J A Hagen et al. 1993[20]</td>
<td>USA</td>
<td>4/10/16</td>
<td>13/10/16</td>
<td>RCT Gender, age and OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan B F Hulscher et al. 2002[21]</td>
<td>Netherlands</td>
<td>-/114/-</td>
<td>-/106/-</td>
<td>RCT Gender, age, LN acquired, R0 resection, postoperative complication, OS and DFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jan Johansson et al. 2004[22]</td>
<td>Sweden</td>
<td>-/27/-</td>
<td>-/22/-</td>
<td>RCT Gender, age, LN acquired, R0 resection and OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jihong Lin et al. 2021[25]</td>
<td>China</td>
<td>249/-/-</td>
<td>249/-/-</td>
<td>RCT Gender, operation time, blood loss, postoperative complication, OS and DFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N K Altorki et al. 1997[23]</td>
<td>USA</td>
<td>38/90/-</td>
<td>en bloc esophageal resection</td>
<td>RCT R0 resection, postoperative complication and DFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuji Akiyama et al. 2018[26]</td>
<td>Japan</td>
<td>84/2/1</td>
<td>meso esophagectomy</td>
<td>RCT Gender, age, operation time, blood loss, LN acquired and postoperative complication</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>51/-2</td>
<td>non-meso esophagectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: EBE, en bloc esophagectomy; THE, transhiatal esophagectomy; RCT, randomized controlled trial; LN, lymph nodes; OS, overall survival; DFS, disease free survival.

Table 2. Publication bias of pooled results in global analysis and subgroup analysis.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Publication bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global analysis</td>
</tr>
<tr>
<td></td>
<td>Included studies</td>
</tr>
<tr>
<td>Gender</td>
<td>12</td>
</tr>
<tr>
<td>Age</td>
<td>10</td>
</tr>
<tr>
<td>Operation time</td>
<td>7</td>
</tr>
<tr>
<td>Blood loss</td>
<td>6</td>
</tr>
<tr>
<td>LN dissection</td>
<td>12</td>
</tr>
<tr>
<td>R0 resection</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary complication</td>
<td>11</td>
</tr>
<tr>
<td>RLN injury</td>
<td>10</td>
</tr>
<tr>
<td>Anastomotic complications</td>
<td>10</td>
</tr>
<tr>
<td>Postoperative mortality</td>
<td>8</td>
</tr>
</tbody>
</table>

**Figures**
Figure 1
Legend not included with this version.
Figure 2

Legend not included with this version.
Table A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Experimental Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 EBE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brechtje A Grotenhuis 2010</td>
<td>100</td>
<td>132</td>
<td>79</td>
<td>80</td>
<td>13.4%</td>
<td>0.04 [0.01, 0.30]</td>
</tr>
<tr>
<td>C Rizzotto 2008</td>
<td>35</td>
<td>40</td>
<td>18</td>
<td>18</td>
<td>1.6%</td>
<td>0.80 [0.15, 5.60]</td>
</tr>
<tr>
<td>Erne F Yekebas 2006</td>
<td>63</td>
<td>79</td>
<td>27</td>
<td>41</td>
<td>4.1%</td>
<td>2.04 [0.88, 4.76]</td>
</tr>
<tr>
<td>Erin M Corsini 2021</td>
<td>120</td>
<td>133</td>
<td>424</td>
<td>471</td>
<td>10.3%</td>
<td>1.02 [0.54, 1.95]</td>
</tr>
<tr>
<td>H Fujiwara 2016</td>
<td>30</td>
<td>34</td>
<td>18</td>
<td>23</td>
<td>1.3%</td>
<td>3.29 [0.83, 12.91]</td>
</tr>
<tr>
<td>J A Hagen 1993</td>
<td>27</td>
<td>30</td>
<td>32</td>
<td>39</td>
<td>1.6%</td>
<td>1.97 [0.46, 8.26]</td>
</tr>
<tr>
<td>Jan B F Hulscher 2002</td>
<td>97</td>
<td>114</td>
<td>92</td>
<td>106</td>
<td>8.0%</td>
<td>0.87 [0.40, 1.86]</td>
</tr>
<tr>
<td>Jan Johansson 2004</td>
<td>26</td>
<td>27</td>
<td>18</td>
<td>22</td>
<td>0.4%</td>
<td>5.78 [0.60, 56.05]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>589</td>
<td>800</td>
<td>400</td>
<td>460</td>
<td>0.92 [0.66, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>498</td>
<td>704</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 19.83, df = 7 (P = 0.006); I² = 85%
Test for overall effect: Z = 0.50 (P = 0.62)

1.1.2 TME

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Experimental Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
<th>Odds Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu Junhui 2012</td>
<td>34</td>
<td>45</td>
<td>49</td>
<td>61</td>
<td>5.7%</td>
<td>0.76 [0.30, 1.91]</td>
</tr>
<tr>
<td>Fu Junhui 2017</td>
<td>105</td>
<td>132</td>
<td>98</td>
<td>130</td>
<td>11.4%</td>
<td>1.27 [0.71, 2.27]</td>
</tr>
<tr>
<td>Jihong Lin 2021</td>
<td>219</td>
<td>302</td>
<td>236</td>
<td>309</td>
<td>36.1%</td>
<td>0.82 [0.57, 1.17]</td>
</tr>
<tr>
<td>Yuji Akiyama 2018</td>
<td>70</td>
<td>87</td>
<td>45</td>
<td>53</td>
<td>6.2%</td>
<td>0.73 [0.29, 1.84]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>566</td>
<td>553</td>
<td>59.4%</td>
<td>0.89 [0.67, 1.17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>428</td>
<td>428</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.94, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)

Total (95% CI) 1155 1353 100.0% 0.90 [0.73, 1.12]

1.2.1 EBE

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>Experimental SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brechtje A Grotenhuis 2010</td>
<td>6.3</td>
<td>1.2</td>
<td>132</td>
<td>88</td>
<td>10.75</td>
<td>90</td>
<td>4.5%</td>
</tr>
<tr>
<td>C Rizzotto 2008</td>
<td>5.45</td>
<td>0.9</td>
<td>40</td>
<td>64</td>
<td>11.5</td>
<td>18</td>
<td>1.2%</td>
</tr>
<tr>
<td>Erin M Corsini 2021</td>
<td>6.21</td>
<td>1.29</td>
<td>133</td>
<td>82</td>
<td>9.7</td>
<td>471</td>
<td>7.4%</td>
</tr>
<tr>
<td>H Fujiwara 2016</td>
<td>6.7</td>
<td>7</td>
<td>34</td>
<td>71</td>
<td>10.5</td>
<td>23</td>
<td>1.7%</td>
</tr>
<tr>
<td>J A Hagen 1993</td>
<td>5.98</td>
<td>1.6</td>
<td>30</td>
<td>65.6</td>
<td>1.7</td>
<td>39</td>
<td>67.5%</td>
</tr>
<tr>
<td>Jan B F Hulscher 2002</td>
<td>6.4</td>
<td>10.75</td>
<td>114</td>
<td>69</td>
<td>14</td>
<td>109</td>
<td>3.8%</td>
</tr>
<tr>
<td>Jan Johansson 2004</td>
<td>5.7</td>
<td>16.5</td>
<td>27</td>
<td>71</td>
<td>7.5</td>
<td>22</td>
<td>0.9%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>510</td>
<td>769</td>
<td>86.9%</td>
<td>-5.21 [-5.96, -4.52]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>926</td>
<td>1132</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 32.01, df = 6 (P < 0.0001); I² = 81%
Test for overall effect: Z = 14.81 (P < 0.0001)

1.2.2 TME

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>Experimental SD</th>
<th>Total Mean</th>
<th>Total SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu Junhui 2012</td>
<td>6.04</td>
<td>7.6</td>
<td>45</td>
<td>58.6</td>
<td>5.3</td>
<td>61</td>
<td>6.2%</td>
</tr>
<tr>
<td>Fu Junhui 2017</td>
<td>5.94</td>
<td>8.3</td>
<td>34</td>
<td>60</td>
<td>8.4</td>
<td>23</td>
<td>2.1%</td>
</tr>
<tr>
<td>Yuji Akiyama 2018</td>
<td>6.69</td>
<td>8.7</td>
<td>87</td>
<td>83.7</td>
<td>8.5</td>
<td>53</td>
<td>4.8%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>166</td>
<td>137</td>
<td>13.1%</td>
<td>1.93 [0.15, 3.70]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>676</td>
<td>906</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.99, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)

Total (95% CI) 676 906 100.0% -4.27 [-4.92, -3.63]

Heterogeneity: Chi² = 87.90, df = 9 (P < 0.00001); I² = 90%
Test for overall effect: Z = 13.03 (P < 0.00001)
Test for subgroup differences: Chi² = 53.90, df = 1 (P < 0.00001); I² = 98.1%

Figure 3

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Figure 4

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Figure 5

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Figure 6

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Figure 7

Legend not included with this version.

Figure 8

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