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ABOUT COVER

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META-ANALYSIS

Network meta-analysis of randomized controlled trials on esophagectomies in esophageal cancer: The superiority of minimally invasive surgery

Lajos Szakó, Dávid Németh, Nelli Farkas, Szabolcs Kiss, Réka Zsuzsa Dömötör, Marie Anne Engh, Péter Hegyi, Balint Eross, András Papp

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Abstract

BACKGROUND

Previous meta-analyses, with many limitations, have described the beneficial nature of minimal invasive procedures.

AIM

To compare all modalities of esophagectomies to each other from the results of randomized controlled trials (RCTs) in a network meta-analysis (NMA).

METHODS

We conducted a systematic search of the MEDLINE, EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and CENTRAL databases to identify RCTs according to the following population, intervention, control, outcome (commonly known as PICO): P: Patients with resectable esophageal cancer; I/C: Transthoracic, transhiatal, minimally invasive (thoracolaparoscopic), hybrid, and robot-assisted esophagectomy; O: Survival, total adverse events, adverse events in subgroups, length of hospital stay, and blood loss. We used the Bayesian approach and the random effects model. We presented the geometry of the network, results with probabilistic statements, estimated intervention effects and their 95% confidence interval (CI), and the surface under the cumulative ranking curve to rank the interventions.

RESULTS

We included 11 studies in our analysis. We found a significant difference in postoperative pulmonary infection, which favored the minimally invasive intervention compared to transthoracic surgery (risk ratio 0.49; 95%CI: 0.23 to 0.99). The operation time was significantly shorter for the transhiatal approach compared to transthoracic surgery (mean difference -85 min; 95%CI: -150 to -29), hybrid intervention (mean difference -98 min; 95%CI: -190 to -9.4), minimally invasive technique (mean difference -130 min; 95%CI: -210 to -50), and robot-assisted esophagectomy (mean difference -150 min; 95%CI: -240 to -53). Other comparisons did not yield significant differences.

CONCLUSION

Based on our results, the implication of minimally invasive esophagectomy should be favored.

Key Words: Surgery; Esophageal cancer; Esophagectomy; Network meta-analysis; Minimally invasive; Laparoscopy

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Core Tip: Minimally invasive laparoscopic techniques should be the preferred approach for the treatment of esophageal cancer, due to the lower incidence of postoperative pulmonary complications.

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INTRODUCTION

Esophageal cancer is the eighth most common type of cancer worldwide[1], with an incidence of 5.2 per 100000 for squamous cell cancer (SCC) and 0.7 per 100000 for adenocarcinoma (AC)[2]. While the prognosis varies between the two histological diagnoses, both AC and SCC are associated with poor clinical outcomes, with a 5-year survival rate of 20%[3].

Surgical therapy plays an essential role in the treatment of esophageal cancer. However, it cannot be routinely used due to the late diagnosis, as symptoms usually occur when the cancer is already unresectable[4]. Traditionally, open surgical interventions are performed, including transhiatal and transthoracic techniques. A meta-analysis comparing these two open surgical modalities did not find a significant difference in 5-year survival[5]. While both techniques are successful in terms of removing the neoplasm, open esophagectomies are associated with significant limitations, most importantly, postoperative morbidity[6,7].

A transition to non-open surgical techniques has been the trend in almost every field of surgery in recent years[8]. A wide variety of non-open techniques are available, including minimally invasive surgery (thoracolaparoscopic) surgery or even robot-assisted esophagectomy[9,10]. In the form of hybrid surgical intervention, a combination of open and non-open technique is available[11].

Previous meta-analyses have compared the different types of surgical techniques, with variable success and significant limitations[12-19]. To date, convincing evidence is missing regarding the optimal surgical approach of resectable esophageal cancer, as it is presented in a recent guideline[20].

Network meta-analysis (NMA) is a relatively novel methodology, which allows the direct and indirect comparison of multiple interventions, thus providing more information than traditional meta-analyses. Indirect comparisons can be made in the case of missing trials comparing two interventions if those are compared with a third intervention[21]. Several meta-analyses were carried out focusing on esophageal cancer surgery, but none of those addressed the problem of the wide variety of surgical techniques.

The purpose of our study was to provide objective evidence considering the surgical treatment of resectable esophageal cancer by comparing each treatment modality in the form of an NMA and possibly rank the different approaches.

MATERIALS AND METHODS

The NMA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-NMA guideline[22].

Protocol

The NMA protocol was registered in advance in PROSPERO under the number CRD42020160978. Analyses of the mortality and quality of life could not be carried out due to the low number of reporting articles. The risk of bias was assessed using an updated risk assessment tool.

Search strategy and inclusion criteria

We conducted a systematic search of the MEDLINE (*via* PubMed), EMBASE, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Cochrane Central Register of Controlled Trials (CENTRAL) from initiation until 2019 November to identify studies, comparing at least two types of esophagectomies from transthoracic, transhiatal, hybrid, laparoscopic or robot-assisted approach treating esophageal cancer without the restriction of histological subtype and an NMA was performed. The following search key was used: (((esophagus OR oesophagus OR esophageal OR oesophageal) AND (tumor OR tumour OR malign* OR cancer OR adenocarcinoma OR carcinoma)) AND (esophagectomy OR oesophagectomy OR Ivor-Lewis OR „Ivor Lewis" OR hybrid OR laparoscop* OR „minimal invasive")) AND random*. We also reviewed the reference lists of eligible articles for further studies. Only randomized controlled trials (RCTs) were included.

Selection and data extraction

After the removal of duplications, two independent reviewers (Szakó L, Engh MA) executed the selection first by title, second by abstract, last by full text following pre-discussed aspects. Data extraction was done by the same two independent reviewers (Szakó L, Engh MA) onto a pre-established Excel worksheet (Office 365, Microsoft, Redmond, WA, United States). Extracted data consisted of the year of publication, name of the first author, study design, country, applied surgical modalities, mortality, overall survival rate (referred as survival), adverse events (AEs), blood loss, length of hospitalization, length of surgical procedure, and demographic data including age, male-female ratio, and SCC/AC ratio. Disagreements regarding both selection and data extraction were resolved by consensus. If consensus could not be reached, a third reviewer (Dömötör RZ) resolved the disagree-ment.

Statistical analysis

The Bayesian method was used to perform pairwise meta-analyses and NMAs. All analyses were carried out using a random effects model. To ensure the interpretability of the NMA results (pooled of direct and indirect data), we presented the geometry of the network, the results with probabilistic statements, and estimates of intervention effects along with their corresponding 95% confidence intervals (CIs), as well as forest plots for ranking the interventions, we chose to use the surface under the cumulative ranking (SUCRA) curve, which provides a numerical summary of the rank distribution of each treatment.

Risk of bias assessment and quality of evidence

The risk of bias assessment was performed at the individual study level, according to the Revised Cochrane risk-of-bias tool for RCTs[23].

The Grading of Recommendations Assessment, Development, and Evaluation system was used to assess the certainty of evidence into four levels: high, moderate, low, and very low. The certainty of the evidence was classified into four levels: high, moderate, low, and very low. Two independent reviewers (Szakó L, Engh MA) decided the overall quality of the evidence[24]. Disagreements were resolved by consensus. If consensus could not be reached, a third reviewer (Dömötör RZ) resolved the

Table 1 Baseline characteristics of the included studies

Ref.	Year	Country	Design	Compared interventions	Number of patients	Male/female ratio	Age in yr, mean	Squamous cell cancer/adenocarcinoma ratio	Inclusion criteria
Straatman *et al*[25]	2012	Netherlands, Spain, Italy	Multicenter	MI-TT	59-56	43/16-46/17	62.3–61.8	24/35-19/36	cT1-3, N0-1, M0
van der Sluis *et al* [26]	2019	Netherlands	Single center	RA-TT	54-55	46/8-42/13	64-65	13/41-12/43	T1-4a, N0-3, M0
Mariette *et al*[27]	2019	France	Multi center	H-TT	103-104	88/15-175/32	59-61 (median)	46/57-84/123	T1-3, N0-1, M0
Guo *et al* [28]	2013	China	Single center	MI-TT	111-110	68/43-72/38	57.3-60.8	No information	T1-3, N0-1, M0
Ma *et al* [29]	2018	China	Single center	MI-TT	47-97	36/11-83/14	61-59.3	43/0-91/2	Resectable cancer
Jacobi *et al* [30]	1997	Germany	Single center	TH-TT	16-16	No information	54-55	13/3-13/3	Resectable cancer
Goldminc *et al*[31]	1993	Australia	Single center	TH-TT	32-35	31/1-33/2	57.4-57.4	32/0-35/0	Resectable squamous cell cancer
Chu *et al* [32]	1997	China	Single center	TH-TT	20-19	18/2-17/2	60.7-63.9	No information	Lower third resectable cancer
Hulscher *et al*[33]	2002	Netherlands	Multicenter	TH-TT	106-114	92/14-97/17	69-64	0/106-0/114	Resectable adenocarcinoma
Yang *et al* [35]	2016	China	Single center	MI-TT	120-120	82/38-87/33	62.5 -67.8	75/45-72/48	T1-3, N0-1, M0
Paireder *et al*[34]	2018	Austria	Single center	H-TT	14-12	10/4-10/2	64.5-62.5 (median)	4/10-1/11	Siewert I-II, resectable squamous cell cancer

Number of patients, male/female ratio, age, and ratio of squamous cell cancer and adenocarcinoma are presented according to the compared interventional arms. H: Hybrid esophagectomy; MIE: Minimally invasive esophagectomy; RA: Robot assisted esophagectomy; TH: Transhiatal esophagectomy; TT: Transthoracic esophagectomy.

disagreement.

RESULTS

Selection process

The database search yielded 3335 records, of which 2002 articles were left after removing duplicates. Twenty-one full-text articles were screened for eligibility. Finally, we included 11 RCTs (25-35), including 1525 patients, in the quantitative synthesis (Figure 1). Baseline characteristics of the enrolled studies are presented in Table 1[25-35].

Outcomes

A significant difference was found for pulmonary infection, which favored the minimally invasive intervention compared to transthoracic surgery (relative risk [RR]: 0.49, 95%CI: 0.23-0.99) (Figure 2). Operation time was significantly shorter for the transhiatal approach compared to transthoracic surgery (mean difference: -86 min, 95%CI: -150 to -29 min), hybrid intervention (mean difference -99 min, 95%CI: -190 to -9.4 min), minimally invasive technique (mean difference -130 min, 95%CI: -210 to -53 min), and robot-assisted esophagectomy (mean difference -150 min, 95%CI: -250 to -52 min) (Figure 3). We did not find significant differences regarding survival (Supplementary Figures 1-5), total AEs (Supplementary Figure 6), cardiac AEs (Supplementary Figure 7), anastomotic leakage (Supplementary Figure 8), atrial fibrillation (Supplementary Figure 9), wound infection (Supplementary Figure 10), total pulmonary AEs (Supplementary Figure 11), vocal chord paralysis (Supplementary Figure 12), length of hospital stay (Supplementary Figure 13), and blood loss (Supplementary Figure 14). The ranking and detailed results of the comparisons of the interventions are presented in the supplementary files (Supplementary Figures 1-14).

Table 2 The results of the risk of bias assessment by each domain

Ref.	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Straatman *et al* [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
van der Sluis *et al* [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mariette *et al*[27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Guo *et al*[28]	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
Ma *et al*[29]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	High risk
Jacobi *et al*[30]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	High risk
Goldminc *et al* [31]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Chu *et al*[32]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	High risk
Hulscher *et al*[33]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Yang *et al*[35]	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	High risk
Paireder *et al*[34]	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk

Risk of bias is indicated according to each domain of the Revised Cochrane risk-of-bias tool for randomized trials[23]. By the assessment of overall risk of bias, low risk of bias was given in the case of low risk of bias by every domain; if one or two domains were assessed as unclear risk of bias, unclear overall risk of bias was given, and if at least three domains were accompanied with unclear risk of bias, the overall risk of bias was assessed as high risk of bias.

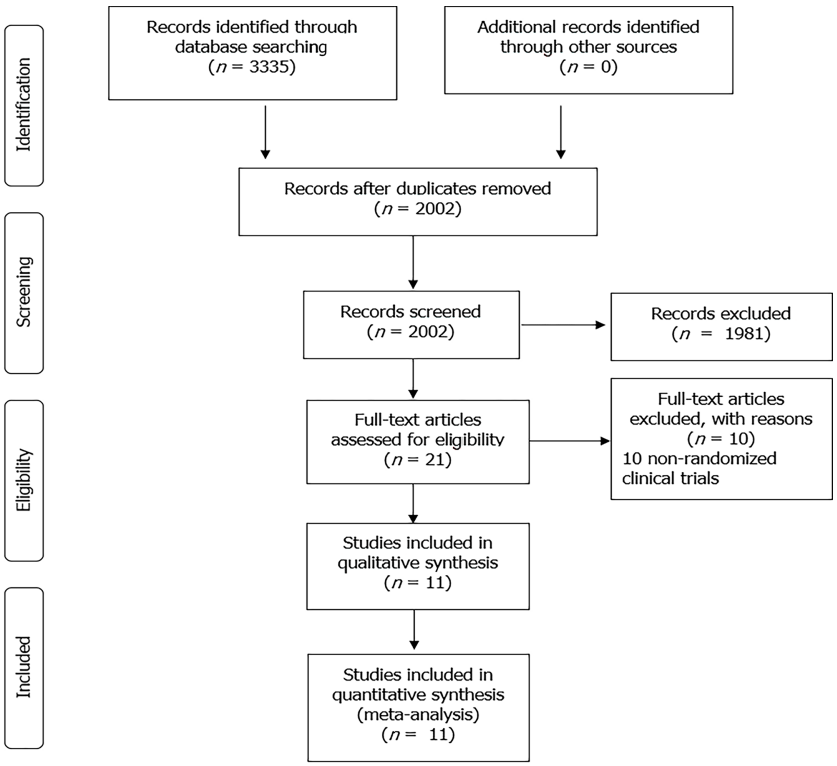

Figure 1 Results of the selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Available from: https://prisma-statement.org//prismastatement/flowdiagram.aspx.

Risk of bias assessment and grade of evidence

Results of the risk of bias assessment for the outcome of survival were assessed following the Cochrane Risk of Bias Assessment Tool 2. Details are shown in Table 2.

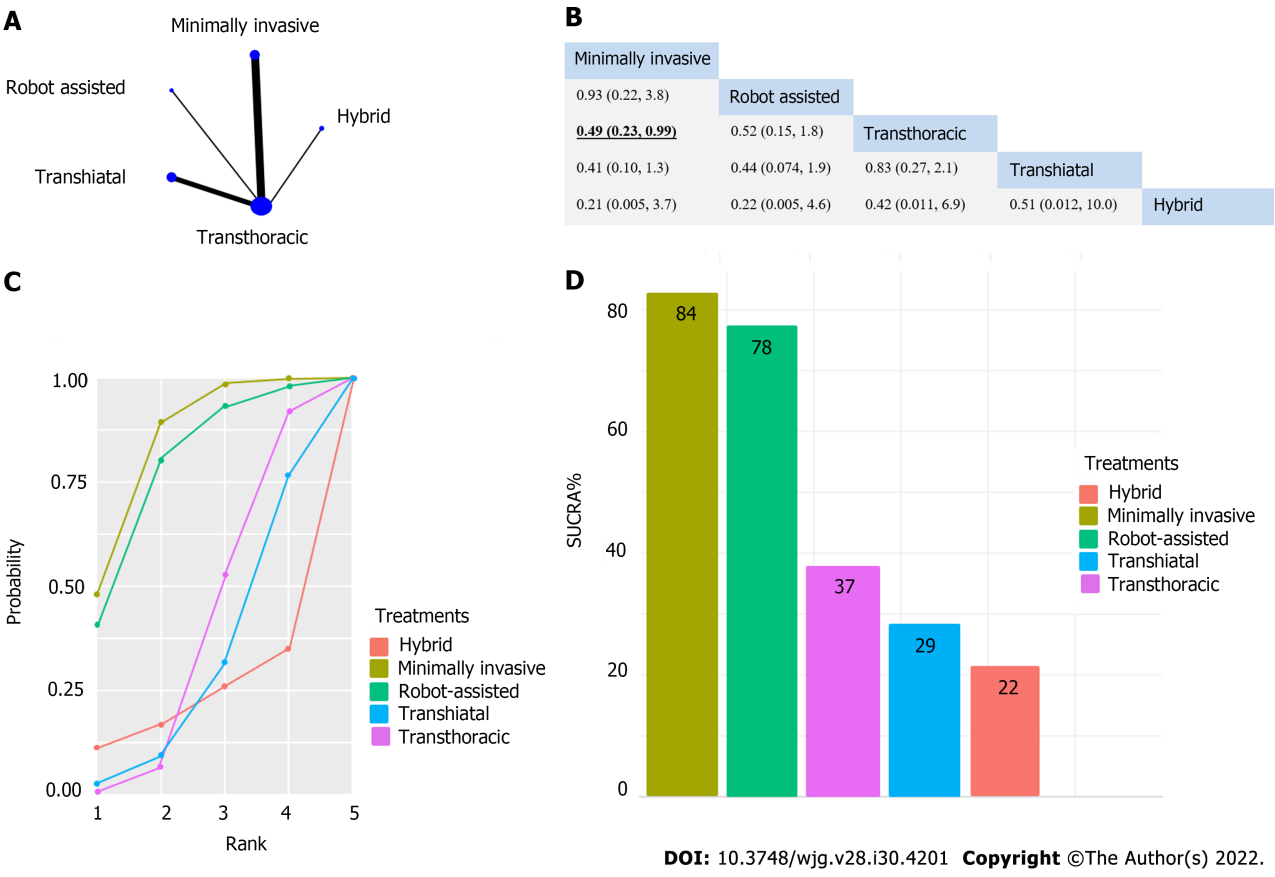

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Figure 2 A significant difference was found considering pulmonary infection, which favored the minimally invasive intervention compared to transthoracic surgery. A: The network of eligible studies for pulmonary infection (the width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants [sample size]); B: League table of the analysis for pulmonary infection. Comparisons should be read from left to right. The values are presented in risk ratios, with corresponding credible interval. Significant result is in TextTitle and underlined; C: Cumulative probability of treatment rank; D: Treatment rank in SUCRA% histogram.

The results of the certainty of evidence are presented in Supplementary Table 1.

DISCUSSION

Our NMA confirmed the superiority of the minimally invasive esophagectomy over transthoracic open surgery regarding one of the main complications during these procedures, namely pulmonary infection. On the other hand, non-open surgical techniques require significantly more time to perform compared to open techniques. While statistically significant results were only achieved in the case of pulmonary infection, a clear tendency was demonstrated by the SUCRA curves, showing a preference for non-open techniques, which is also supported by the individual studies.

The results of previous meta-analyses and systematic reviews are not congruent regarding the comparison of minimally invasive and open surgical techniques. Kauppila *et al*[14] described the superiority of minimally invasive esophagectomy (MIE) regarding quality of life (QoL), which our work failed to analyze, as there were not enough RCTs reporting on QoL. Guo *et al*[13] also described the advantages of minimally invasive techniques regarding total complication rate, intraoperative blood loss, wound infection, and pulmonary infection, supporting our findings. MIE was also favorable in the analysis of Wang *et al*[19] considering blood loss. Besides blood loss and hospital stay, fewer respiratory complications were also shown by MIE in a meta-analysis conducted by Nagpal *et al*[15]. The work of Yibulayin *et al*[18] also supports the superiority of MIE in terms of in-hospital mortality and postoperative morbidity. By contrast, Dantoc *et al*[12] focused on oncological outcomes in their meta-analysis, where significant differences could not be proven. Sgourakis *et al*[17] showed that open surgery was more beneficial in terms of anastomotic stricture, while morbidity favored MIE. Oor *et al*[16] also described the benefit of open surgery in the case of hiatal hernia. The above comprehensive studies show that the inclusion of non-randomized studies carries a notable limitation.

Although the results of our analysis are only supportive in terms of pulmonary complication, the future perspectives are promising regarding minimally invasive esophagectomy, as the limelight shifts towards robot-assisted surgical techniques. The technique is time consuming, but with the development

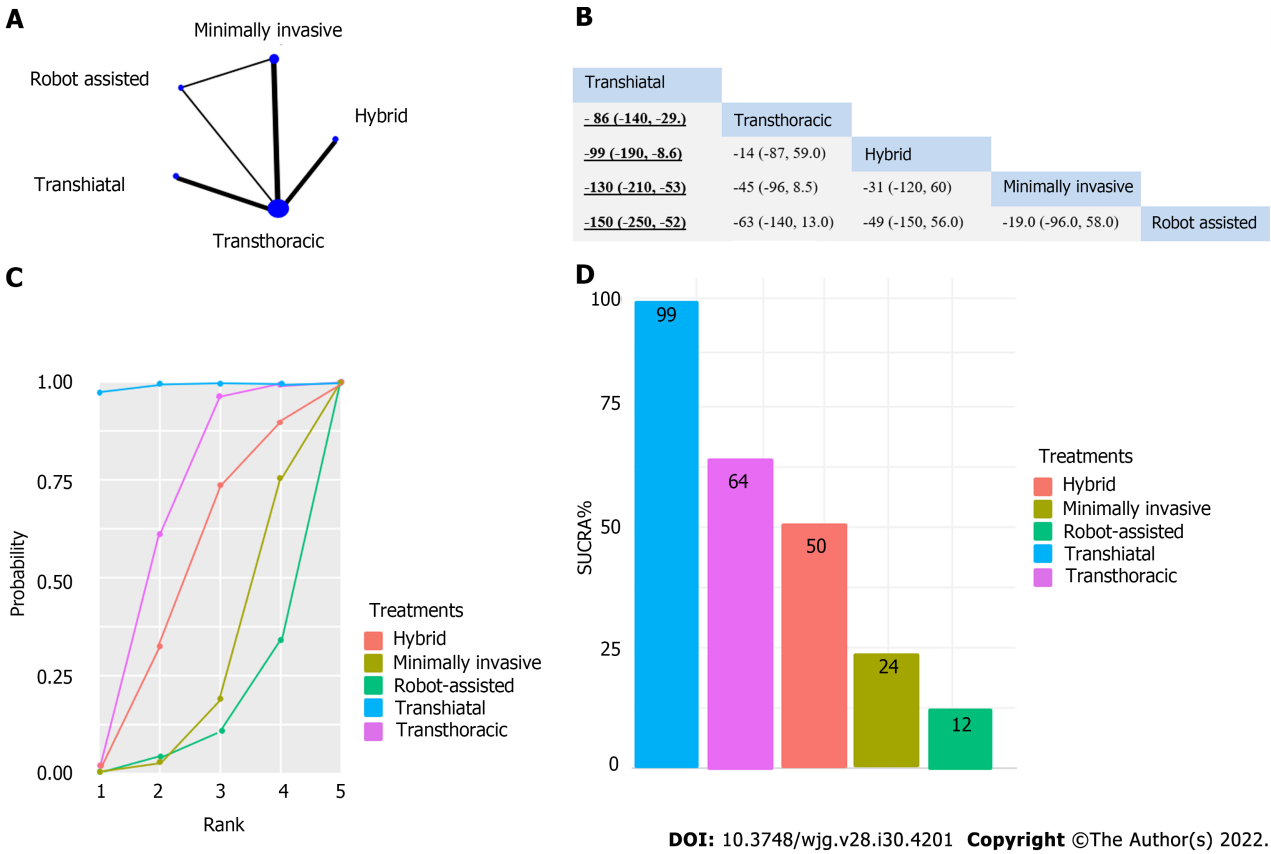

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Figure 3 Operation time was significantly shorter for transhiatal approach compared to transthoracic surgery, hybrid intervention, minimally invasive technique, and robot-assisted esophagectomy. A: The network of eligible studies for operation time [the width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size)]; B: League table of the analysis for operation time. Comparisons should be read from left to right. The values are presented in weighted mean difference (minutes), with corresponding credible interval. Significant results are in TextTitle and underlined; C: Cumulative probability of interventions rank; D: Intervention ranking in surface under the cumulative ranking (SUCRA)% histogram.

of new robotic platforms, the benefit of less AEs and more precise procedure will overcome this limitation[36]. The steep learning curve will be possibly managed by allowing the intervention to be carried out only in larger centers, as it has been seen in northern countries[37]. Despite the missing cumulative evidence, minimal invasive techniques have become the gold standard interventions for esophageal cancer since the TIME study. The results of this RCT provide evidence for using minimally invasive surgery for patients with resectable esophageal cancer aimed toward improving postoperative outcomes (especially pulmonary complication) and QoL with comparable oncologic results[25].

Considering the strengths of our analysis, by the inclusion of only RCTs, we managed to achieve a higher quality of evidence than previous works. Furthermore, a thorough methodology was applied. With the application of NMA, we were also able to make indirect comparisons. To date, this work is the most comprehensive review of the available RCTs.

One of the limiting factors of our study was the low number of cases and limited number of direct comparisons. Other limitations were the different enrollment criteria of the individual studies considering the histological subtype and stage of esophageal cancer. Furthermore, our analysis included many indirect comparisons, with weak direct comparisons. Additionally, we only included studies published until 2019.

We emphasize the application of MIE over open surgical techniques. Further analyses should focus on the outcomes of robot-assisted esophagectomies, and direct comparisons should be carried out between robot-assisted esophagectomy and thoracolaparoscopic intervention. Following recent trends, the centralization of upper gastrointestinal surgery is suggested, thus achieving the possibility of the implementation of such techniques without the limitation originating from the low number of cases and the learning curve of minimally invasive techniques.

CONCLUSION

While practice is already shifting towards the application of minimally invasive techniques, it should be

noted that clear evidence is still needed to form guidelines. As we aimed to fill this void, we were only able to prove the beneficial nature of these techniques regarding pulmonary infection. To further assess any other potential differences between the techniques, RCTs and systematic analysis of these trials are needed.

ARTICLE HIGHLIGHTS

Research background

The differences considering esophagectomies as the most applied curative methodology in the case of esophageal cancer are not clearly described. Minimally invasive techniques have become more popular in the belief of their superiority, although objective evidence is missing.

Research motivation

Recent guidelines are not yet clear considering the usage of minimally invasive esophagectomies. The authors wanted to provide the most objective evidence available, considering the differences between every subtype of minimally invasive and open esophagectomies.

Research objectives

The authors aimed to find every randomized controlled trial (RCT) providing comparative information about at least two types of esophagectomies, and pool the results using NMA.

Research methods

After establishing our clinical question using the population, intervention, control, outcome (commonly known as (PICO) framework a systemic search was carried out using three different databases. The results of the search were pooled, duplications were removed, suitable studies were selected, from which the data extraction was carried out onto a data sheet. With the help of biostatisticians, a network meta-analysis was performed. The quality of the included studies was assessed, as well as the grade of evidence.

Research results

Eleven articles were included in our analysis, according to which the minimally invasive surgical technique was superior compared to the transthoracic open approach in terms of pulmonary infection, while transthoracic surgery took less time to perform than any other surgical technique.

Research conclusions

The authors conclude that minimally invasive surgical techniques should be performed, whenever possible, for resectable esophageal cancer.

Research perspectives

The conduction of additional RCTs evaluating the same problem would be welcomed, while we hope that our work will help clinicians in the decision-making of the selection of the right surgical technique.

FOOTNOTES

Author contributions: Szakó L conceptualized the work, contributed to establishment of the search key, selection strategy, data extraction, interpretation of the results, and writing of the manuscript; Németh D and Farkas N performed the bio-statistical analyses, and contributed to the interpretation of the results and writing of the manuscript; Kiss S helped was involved in the conceptualization, coordination of the work, and writing the manuscript; Dömötör RZ conceptualized, wrote, and critically appraised the manuscript; Engh MA was involved in the conceptualization, data extraction, risk of bias assessment, writing of the manuscript, and language revision of the manuscript; Hegyi P contributed to the conceptualization, interpretation of the results, critical appraisal, and writing of the manuscript; Erőss BM conceptualized the work, interpreted the results, critically appraised and wrote the manuscript; Papp A provided supervision, and was involved in the conceptualization, interpretation of the results, critical appraisal, and writing of the manuscript.

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