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

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Abstract

BACKGROUND

Previous meta-analyses, with many limitations, described the beneficial nature of minimal invasivity.

AIM

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

METHODS

We conducted a systematic search of the MEDLINE, Embase, and CENTRAL databases to identify randomized controlled trials according to the following PICO (population, intervention, control, outcome): 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 effect model. We presented the geometry of the network, results with probabilistic statements, estimated of interventions' effects along with their 95%

credible interval (CrI), and the surface under the cumulative ranking curve for ranking the interventions.

RESULTS

We included 11 studies in our analysis. We found a significant difference considering postoperative pulmonary infection, which favored the minimally invasive intervention compared to transthoracic surgery (risk ratio 0.49; 95%CI: 0.23,0.99). Operation time was significantly shorter for transhiatal approach compared to transthoracic surgery (mean difference -85 minutes; 95%CI: -150, -29), hybrid intervention (mean difference -98 minutes; 95%CI: -190, -9.4), minimally invasive technique (mean difference -130 minutes; 95%CI: -210,-50), and robot-assisted esophagectomy (mean difference -150 minutes; 95%CI: -240, -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

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Core Tip: The implication of minimal invasive laparoscopic techniques is suggested concerning the treatment of esophageal cancer, due to the lower amount of postoperative pulmonarycomplication.

INTRODUCTION

The malignant neoplasm of the esophagus is the eighth most common type of cancer worldwide (1), with an incidence rate of 5.2 per 100,000 in the case of squamous cell cancer (SCC) and 0.7 per 100,000 considering 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 of 20% (3).

Surgical therapy occupies an essential place in the treatment of esophageal malignancy. However, it cannot be applied commonly due to the late diagnosis, as symptoms usually occur when the cancer is already unresectable (4). Traditionally, surgery meant open surgical interventions, including transhiatal and transthoracic techniques. A meta-analysis comparing these two open surgical modalities did not found 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 the hybrid surgical intervention, a combination of open and non-open technique is available (11).

Previous meta-analyses aimed to compare 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).

NMA is a relatively novel methodology, which allows the direct and indirect comparison of multiple interventions, thus providing more than traditional meta-analyses. Indirect comparison 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 work is to provide objective evidence considering the surgical treatment of resectable esophageal cancer by comparing each treatment modalities in the form of a network meta-analysis and possibly rank the different approaches.

MATERIALS AND METHODS

The meta-analysis was made following the PRISMA-NMA guideline (22).

Protocol

The protocol of this network meta-analysis was registered in advance in PROSPERO under the number CRD42020160978. Analysis 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 by using an updated risk assessment tool.

Search strategy and inclusion criteria

We conducted a systematic search of the MEDLINE (via PubMed), Embase, 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 a network meta-analysis (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 were included.

Selection and data extraction

After the removal of duplications, two independent reviewers (L.Sz., M.E) executed the selection first by title, second by abstract, last by full-text following prediscussed aspects. Data extraction was done by the same two independent reviewers (L.Sz., M.E) onto a pre-established Excel worksheet (Office 365, Microsoft, Redmond, WA, USA). 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, blood loss, length of hospitalization, length of surgical procedure, and demographic data including age, male-female ratio, SCC/AC ratio. Disagreements regarding both selection and data extraction were resolved by consensus. If consensus could not be reached a third reviewer (R.Zs.D) resolved the disagreement

Statistical analysis

A Bayesian method was used to perform pairwise meta-analyses and network meta-analyses. All the analyses were carried out under a random effect 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 interventions effects along with their corresponding 95 % CIs, as well as forest plotsFor 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 on individual study-level, according to the Revised Cochrane risk-of-bias tool for randomized trials (23).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the certainty of evidence into four levels: high, moderate, low, very low. The certainty of the evidence was classified into four levels: high, moderate, low, or very low. Two independent reviewers (L.Sz., M.E.) decided the overall quality of the evidence (24).

Disagreements were resolved by consensus. If consensus could not be reached a third reviewer (R.Zs.D) resolved the disagreement

RESULTS

Selection process

The database search yielded 3335 records, from which 2002 articles were left after removing duplications. Twenty-one full-text articles were screened for eligibility. Finally, we could include 11 randomized controlled trials (25-35), including 1525 patients in quantitative synthesis. (Figure 1) Baseline characteristics of the enrolled studies are presented in Table 1.

Outcomes

A significant difference was found considering pulmonary infection, which favored the minimally invasive intervention compared to transthoracic surgery (RR: 0.49, CI: 0.23 to 0.99) (Figure 2). Operation time was significantly shorter for transhiatal approach compared to transthoracic surgery (mean difference: -86 minutes, CI: -150 to -29 minutes), hybrid intervention (mean difference -99 minutes, CI: -190 to -9.4 minutes), minimally invasive technique (mean difference -130 minutes, CI: -210 to -53 minutes), and robot-assisted esophagectomy (mean difference -150 minutes, CI: -250 to -52 minutes) (Figure 3). We did not find significant difference regarding survival (Suppl. Figure 1-5), total adverse events (Suppl. Figure 6), cardiac adverse events (Suppl. Figure 7), anastomotic leakage (Suppl. Figure 8), atrial fibrillation (Suppl. Figure 9), wound infection (Suppl. Figure 10), total pulmonary adverse events (Suppl. Figure 11), vocal chord paralysis (Suppl. Figure 12), length of hospital stay (Suppl. Figure 13), and blood loss (Suppl. Figure 14).

The ranking and the detailed results of the comparisons of the intervenventions are presented in the supplementary files (Suppl. Figure 1-14).

Risk of bias assessment and grade of evidence

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

The results of the certainty of evidence (GRADE) is presented in Supplementary Table 1.

DISCUSSION

Our network meta-analysis confirmed the superiority of the minimally invasive esophagectomy over transthoracic open surgery, regarding one of the main complications during these procedures, which is 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 is visible demonstrated by the SUCRA curves, preferring non-open tehcniques, which is also supported by the individual studies.

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 MIE considering the quality of life (QoL), which our work failed to analyze, as there were not enough randomized controlled trials reporting on QoL. Furthermore, Guo *et al* (13) also described the advantages of minimally invasive techniques regarding total complications-rate, intraoperative blood loss, wound infection, and also 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 also favored MIE in a meta-analysis conducted by Nagpal *et al* (15). The work of Yibulayin *et al* (18) also supported the superiority of MIE in terms of in-hospital mortality and postoperative morbidity. On the contrary, Dantoc *et al* (12) focused on the oncological outcomes in their meta-analysis, where significant differences could not be proven. Sgourakis *et al* (17) found open surgery 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. In all the above comprehensive studies, 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 of new robotic platforms, the

benefit of less adverse events, 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 become the gold standard interventions considering esophageal cancer since the conduction of the TIME study, Results of this randomized controlled trial provide evidence to use minimally invasive surgery for patients with resectable esophageal cancer aiming at improving postoperative outcomes (especialy pulmonary complication) and quality of life with comparable oncologic results. (25)

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

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

We emphasize the application of minimally invasive esophagectomy 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 minimal invasivity considering pulmonary infection. To further assess any other potential differences between the techniques, randomized controlled trials and systematic analysis of these trials are needed.

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