

BMJ Open Right versus left thoracic approach oesophagectomy for oesophageal cancer: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Oesophageal cancer is one of the most common malignant tumours and has been identified as one of the leading causes of cancer death worldwide. Surgery is considered to be the optimal treatment for patients with resectable oesophageal cancer. Oesophagectomy for oesophageal cancer can significantly extend the survival period of patients and provide a potential opportunity for a cure. However, there is still controversy regarding which thoracic approach (right or left) during oesophagectomy for oesophageal cancer can lead to better surgical outcomes globally. This systematic review and meta-analysis will be performed to determine which thoracic approach during oesophagectomy will achieve longer patient survival and will be more beneficial for patients.

Methods and analysis We will search PubMed, Web of Science, Embase, Cancerlit, the Cochrane Central Register of Controlled Trials and Google Scholar databases for relevant clinical trials published in any language before 1 October 2019. Randomised controlled trials (RCTs), quasi-RCTs, propensity score-matched comparative studies and prospective cohort studies of interest, published or unpublished, that meet the inclusion criteria will be included. Subgroup analysis of the type of operation, tumour pathological stage and ethnicity will be performed.

PROSPERO registration number CRD42019124133.

Ethics and dissemination Because this study will be based on published or unpublished records and studies, there is no need for ethics approval. The results of the study will be published in a peer-reviewed journal.

BACKGROUND

Oesophageal cancer is one of the most common malignant tumours in the world and its incidence rate ranks seventh among all malignant tumours.¹ Oesophageal cancer has been identified as one of the leading causes of cancer death because of the high degree of malignancy and low survival rate of patients.^{2–4} Surgery is regarded as the best option for patients with resectable oesophageal cancer. Oesophagectomy for patients with oesophageal cancer can significantly

Strengths and limitations of this study

- As far as we know, this study will be the first meta-analysis to compare the efficacy of the right and left thoracic approaches of video-assisted thoracoscopic oesophagectomy for patients diagnosed with resectable oesophageal cancer.
- This study will provide high-quality and reliable evidence for clinicians' decision-making by comparing published or completed but unpublished trial data.
- Due to the nature of the disease and intervention methods, randomised controlled trials may be inadequate, and we will carefully consider inclusion in high-quality, non-randomised controlled trials, but this may result in high heterogeneity and affect the reliability of the results.

extend the survival period and provide a potential opportunity for a cure.^{5–7}

In the last dozen years, video-assisted thoracoscopic oesophagectomy has developed rapidly, and a variety of available technical approaches have been formed.^{8,9} Many trials have reported that video-assisted thoracoscopic oesophagectomy can bring more benefits to patients than traditional open thoracic oesophagectomy.^{10–13} However, which thoracic approach side for oesophagectomy is more beneficial for patients with oesophageal cancer, as well as the extent of lymphadenectomy, remains controversial.¹⁴

The advantages of a left thoracic approach oesophagectomy include simple incision and adequate exposure of the hiatus, but inadequate upper mediastinal lymph node resection remains. In contrast, right thoracic approach oesophagectomy was designed to improve survival by providing more extensive radial lymphadenectomy.^{15–17} However, the survival effects of this procedure have not yet been determined.¹⁸ This study will compare the efficacy and safety of the two

different surgical methods to determine which is more likely to benefit patients with oesophageal cancer and to provide a basis for clinicians to develop optimal treatment strategies for patients.

OBJECTIVE

We will conduct a systematic review and meta-analysis to estimate the efficacy and safety of the right versus left thoracic approaches during oesophagectomy for patients with oesophageal cancer.

METHODS

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.¹⁶ The results of this systematic review and meta-analysis will be published with reference to the PRISMA guidelines.¹⁹

Patient and public involvement

This study will be based on published or unpublished studies, and records and will not involve patients or the public directly.

Eligibility criteria

Types of studies

Randomised controlled trials (RCTs), quasi-RCTs, propensity score-matched comparative studies and prospective cohort studies of interest, published or unpublished, will be included. These should be completed, and the efficacy and safety of the right versus left thoracic approach during oesophagectomy for patients with oesophageal cancer will be compared.

Types of participants

The participants will be patients diagnosed with resectable, pathologically confirmed oesophageal cancer who were treated with video-assisted thoracoscopic oesophagectomy, and there will be no restrictions on sex, ethnicity, economic status or education.

Types of interventions

All types of right versus left thoracic approaches of video-assisted thoracoscopic oesophagectomy for patients diagnosed with resectable oesophageal cancer will be studied.

Types of outcome measures

Primary outcomes

The primary outcome will be the overall survival of patients with resectable oesophageal cancer after surgery.

Secondary outcomes

We will evaluate the 5-year survival, recurrence-free survival and median survival rates as well as the quality of life and complication rate of patients with resectable oesophageal cancer after surgery.

Information sources

Two reviewers (CTC and SZM) will search PubMed, Web of Science, Cancerlit, Embase, Cochrane Central Register of Controlled Trials and Google Scholar databases for relevant trials published before 1 October 2019, without any language restrictions.

Search strategy

The subject terms and keywords corresponding to Medical Subject Heading (MeSH) terms will be used to search for eligible trials in the databases as mentioned above with no language restrictions. Search strategies in PubMed are shown in [table 1](#).

Data collection and analysis

We will adopt the methods described in the Cochrane Handbook for Systematic Reviews of Interventions to pool the evidence.²⁰

Study selection

Two authors (CTC and SZM) will independently screen each title and abstract of all the papers searched, and the trials that do not meet the inclusion criteria described in this protocol will be excluded. The full text of all the possibly eligible trials will be screened independently and in duplicate by the two

Table 1 PubMed search strategies

Query	Search term
# 1	Oesophageal Neoplasm OR Neoplasm, Oesophageal OR Oesophagus Neoplasm OR Oesophagus Neoplasms OR Neoplasm, Oesophagus OR Neoplasms, Oesophagus OR Neoplasms, Oesophageal OR Cancer of Oesophagus OR Cancer of the Oesophagus OR Oesophagus Cancer OR Cancer, Oesophagus OR Cancers, Oesophagus OR Oesophagus Cancers OR Oesophageal Cancer OR Cancer, Oesophageal OR Cancers, Oesophageal OR Oesophageal Cancers
# 2	Surgeries, Video-Assisted Thoracic OR Surgery, Video-Assisted Thoracic OR Thoracic Surgeries, Video-Assisted OR Thoracic Surgery, Video Assisted OR Video-Assisted Thoracic Surgeries OR Video-Assisted Thoracoscopic Surgery OR Surgeries, Video-Assisted Thoracoscopic OR Surgery, Video-Assisted Thoracoscopic OR Thoracoscopic Surgeries, Video-Assisted OR Thoracoscopic Surgery, Video-Assisted OR Video Assisted Thoracoscopic Surgery OR Video-Assisted Thoracoscopic Surgeries OR Video-Assisted Thoracic Surgery OR Video Assisted Thoracic Surgery OR Surgery, Thoracic, Video-Assisted OR VATS OR VATSs
# 3	Right thoracic approach oesophagectomy OR Left thoracic approach oesophagectomy
# 4	Randomized controlled trial (Publication Type) OR Controlled clinical Trial (Publication Type) OR Randomized (tiab) OR Placebo (tiab) OR Drug Therapy (sh) OR Randomly (tiab) OR trial (tiab) OR Groups (tiab)) NOT (animals (mh) NOT humans (mh))
# 5	# 1 AND # 2 AND # 3 AND # 4

authors. Trials that are irrelevant or do not meet the inclusion criteria will be excluded. Trials that meet the inclusion criteria and excluded studies along with the reasons for their exclusion will be documented by the two authors (CTC and SZM). If there is a disagreement between the two authors, we will come to a resolution by discussing it with the third author (LJB). If necessary, we will consult the fourth author (KMQ) to resolve the disagreement. The selection process will be shown in a PRISMA flow chart in detail.

Data extraction and management

We will extract the following data from the included trials.

- ▶ Study characteristics: author, publication date, country, study design, randomization, periods of data collection, follow-up duration, withdrawals and overall duration of the study.
- ▶ Population characteristics: age, sex, pathology diagnosis, tumour stage, pathological tumour size, performance status, ethnicity, history of smoking and inclusion criteria.
- ▶ Interventions: type of operation, number of lymph nodes retrieved, extent of resection, duration of operation, bleeding and postoperative adjuvant therapy.
- ▶ Outcomes: overall survival, 5-year survival, recurrence-free survival, median survival, length of stay, length of ICU stay, quality of life, complications and adverse events.

We will use the predesigned table to record the data extracted from the included trials. If relevant data from the trials are lost or unclear, we will consult the author via email before determining whether the study is to be included.

Assessment of risk of bias

The Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias of each trial included. The two authors (CTC and SZM) will evaluate the risk of bias based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other biases.²¹ The risk of bias in each domain will be assessed as high, low or uncertain, and the results of the evaluation will be shown on the risk of bias graph. Effective Practice and Organisation of Care (EPOC) guidelines will be used to assess the risks of the non-randomised controlled trials included.²²

Data analysis

We will use Review Manager and Stata software to synthesise the data extracted. If the data extracted from the included studies are evaluated as highly homogeneous, we will use them to conduct a meta-analysis for the purpose of obtaining a clinically meaningful result. To carry out a standard meta-analysis, we will use the X^2 and I^2 statistical tests to evaluate statistical heterogeneity among the studies. If there is high heterogeneity ($p < 0.1$ or I^2 statistic $> 50\%$), then we will use the DerSimonian and Laird random effect

model to analyse the extracted data. Because high heterogeneity may be caused by different types of tumours and different stages of tumours diagnosed by pathology and different means of adjuvant therapy may be used after the operation, we will perform a subgroup analysis of the types of tumours (oesophageal squamous cell carcinoma and oesophageal adenocarcinoma), the pathological stages of the tumours and the means of adjuvant therapy after the operation (types of chemotherapeutic drugs and whether or not radiotherapy is accepted). Otherwise, we will adopt a fixed-effect model to analyse the data. We will adopt the Mantel-Haenszel method to pool the binary data, and the results will be reported in the form of relative risk with a 95% CI. An inverse variance analysis method will be used to pool the continuous data, and the results will be reported in the form of a standardised mean difference with a 95% CI.

Subgroup analysis

If there is substantial heterogeneity and if the available data are sufficient, then we will perform subgroup analysis to search for potential origins of heterogeneity. If the extracted data are enough, then we will conduct subgroup analysis of the type of operation, type of tumour, tumour stage, age and postoperative adjuvant treatment.

Sensitivity analysis

We will conduct a sensitivity analysis to evaluate the robustness and reliability of the aggregation results by eliminating trials with a high bias risk. If a reporting bias exists, then we will use the methods of fill and trim to analyse for publication bias.²³

Publication bias

Funnel charts and Egger test will be adopted to assess for publication bias if there are no < 10 eligible trials. If reporting bias is suspected in a trial, we will contact the corresponding author via email to determine whether there are additional outcome data that were not reported.

Evidence evaluation

We will classify the quality of all the evidence into four levels (high, medium, low and very low) in accordance with the criteria of Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (study limitations, imprecision, publication bias, indirectness bias, and effect consistency).²⁴

DISCUSSION

Oesophageal cancer is one of the worst malignant digestive neoplasms and has poor treatment outcomes. Oesophagectomy is a major part of the treatment strategy for locally resectable oesophageal cancer and plays an important role in the treatment of patients with oesophageal cancer, providing a potentially curable opportunity for these patients.^{5-7 25} Video-assisted thoracoscopic oesophagectomy for patients with oesophageal cancer has been used worldwide, but controversy about the

surgical approaches for thoracic oesophageal cancer and the scope of lymph node dissection persists.

The superiority of the right thoracic approach during oesophagectomy in radical lymphadenectomy of oesophageal carcinoma has been widely accepted. However, because of the lack of prospective evidence, whether patients benefit from radical lymphadenectomy remains controversial. Two studies in the UK and Sweden report that radical lymph node removal may not improve patient survival.^{18 26} However, some trials have shown that expanding the scope of lymphadenectomy can extend survival and significantly benefit patients with a limited number of positive lymph nodes.^{27–29} The advantages of the left thoracic approach during oesophagectomy include simple incision and adequate exposure of the hiatus, but inadequate upper mediastinal lymph node resection also occurs. In contrast, the right thoracic approach during oesophagectomy was designed to improve survival by providing more extensive radial lymphadenectomy.^{15–17}

As far as we know, this study will be the first systematic review and meta-analysis to compare the efficacy and outcome of the two different surgical methods to determine which is more likely to benefit patients with oesophageal cancer and to provide a basis for clinicians to develop optimal treatment strategies for patients.

Contributors LJ and KM: are the guarantors of the article; have strictly reviewed this protocol and approved the publication. CT and LY: conceived of and designed the study. CT and SZ: drafted this protocol; contributed equally to this work. CT, CS, ZZ, HJ, YC and LW: will perform the search, screening and extraction.

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Competing interests None declared.

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