INPLASY PROTOCOL

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Review Stage at time of this submission: The review has not yet started.

Conflicts of interest:
The authors have no conflicts of interest to disclose.

Artery-first vs vein-first surgical technique for segmentectomy of non–small cell lung cancer: a protocol for systematic review and meta analysis

Tong, Z[1]; Qian, J[2]; Yang, X[3]; Lin, J[4].

Review question / Objective: Surgery is the first choice for many solid tumors, such as non-small cell lung cancer, esophageal cancer, liver cancer and so on. However, even after radical resection, about 50% of patients will develop local recurrence or distant metastasis within 3 years[1-4]. Many studies have shown that surgical procedures can promote the spread of tumor cells into the circulatory system[5-9]. In the process of lung cancer surgery, the tumor can be squeezed and further promote the tumor cells to the circulation, which may be one of the reasons for lung cancer metastasis and recurrence. McCulloch et al reported that tumor cells could be detected in venous blood during operation[10]. In addition, lung cancer is also common tumor vascular invasion, which may be the reason for the high incidence of hematogenous dissemination of tumor cells[11-13]. One surgical technique to prevent tumor cells from spreading into the bloodstream is to ligate the outflow vein[14]. In theory, the potential risk of tumor cell proliferation can be minimized if the outflow vein is ligated first (via v-first) rather than the artery (via a-first). However, due to the lack of sufficient evidence, this technical concept has not been widely accepted as a standard in surgical oncology in the current guidelines. This systematic review and meta-analysis will be used to determine which techniques can prolong the survival time of patients undergoing segmentectomy and are more beneficial to patients with resectable non-small cell lung cancer (NSCLC).

INTRODUCTION

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promote the tumor cells to the circulation, which may be one of the reasons for lung cancer metastasis and recurrence. McCulloch et al reported that tumor cells could be detected in venous blood during operation[10]. In addition, lung cancer is also common tumor vascular invasion, which may be the reason for the high incidence of hematogenous dissemination of tumor cells[11-13]. One surgical technique to prevent tumor cells from spreading into the bloodstream is to ligate the outflow vein[14]. In theory, the potential risk of tumor cell proliferation can be minimized if the outflow vein is ligated first (via v-first) rather than the artery (via a-first). However, due to the lack of sufficient evidence, this technical concept has not been widely accepted as a standard in surgical oncology in the current guidelines. This systematic review and meta-analysis will be used to determine which techniques can prolong the survival time of patients undergoing segmentectomy and are more beneficial to patients with resectable non-small cell lung cancer (NSCLC).

Rationale: Surgery for lung cancer squeezes the tumor, further promoting the circulation of tumor cells, which may be one of the reasons for lung cancer metastasis and recurrence. In theory, the potential risk of tumor cell proliferation can be minimized if the outflow veins are ligated first (via veins first [V-first]) rather than arteries first (via arteries first [A-first]).

Condition being studied: Surgery for lung cancer squeezes the tumor, further promoting the circulation of tumor cells, which may be one of the reasons for lung cancer metastasis and recurrence. In theory, the potential risk of tumor cell proliferation can be minimized if the outflow veins are ligated first (via veins first [V-first]) rather than arteries first (via arteries first [A-first]). However, due to the lack of sufficient evidence, this technical concept has not been widely accepted as a standard in surgical oncology in the current guidelines. This systematic review and meta-analysis will be used to determine which techniques will yield longer patient survival and benefit patients during segmentectomy.

METHODS

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.

Participant or population: The participants will be patients diagnosed with resectable, pathologically confirmed non–small cell lung cancer who were treated with segmentectomy, and there will be no restrictions on sex, ethnicity, economic status, or education.

Intervention: All types of vein-first or artery-first surgical technique of segmentectomy for patients diagnosed with resectable non–small cell lung cancer will be studied.

Comparator: The efficacy and safety of venous advance and arterial surgical techniques in segmentectomy for patients with resectable non-small cell lung cancer.

Study designs to be included: Randomized controlled trials (RCTs), quasi-RCTs, propensity score matched comparative studies and prospective cohort studies of interest.

Eligibility criteria: Randomized 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 vein-first vs artery-first surgical technique of segmentectomy for patients diagnosed with resectable non–small cell lung cancer.

Information sources: Two reviewers (ZWT and JKQ) will search PubMed, Web of Science, Cancerlit, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases for relevant

trials published before October 1, 2020, without any language restrictions.

Main outcome(s): The primary outcome will be overall survival of patients with resectable non–small cell lung cancer after surgery.

Additional outcome(s): 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 non–small cell lung cancer after segmentectomy.

Data 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 study. · Population characteristics: age, sex, pathology diagnosis, tumour stage, pathologic 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 pre-designed 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.

Quality assessment / Risk of bias analysis: The Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias of each trial included. The two authors (ZWT and JKQ) 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. 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. EPOC guidelines will be used to assess the risks of the non-randomized controlled trials included.

Strategy of data synthesis: 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 Chi2 and I2 statistical tests to evaluate statistical heterogeneity among the studies. If there is high heterogeneity (p50%), 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 (RR) with a 95% confidence interval (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 standardized mean difference (SMD) with a 95% confidence interval (CI).

Subgroup analysis: If there is substantial heterogeneity and if the available data are sufficient, we will perform subgroup analysis to search for potential origins of heterogeneity. If the extracted data are enough, we will conduct subgroup analysis of the type of operation, type of tumour,

tumour stage, age, and postoperative adjuvant treatment.

Sensibility 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, we will use the methods of fill and trim to analyse for publication bias.

Language: without any language restrictions.

Country(ies) involved: China.

Keywords: Vein-first surgical technique, artery-first surgical technique, segmentectomy, non–small cell lung cancer.

Contributions of each author:
Author 1 - Zhangwei Tong - drafted the manuscript.
Author 2 - Jiekun Qian - provided statistical expertise.
Author 3 - Xiaojie Yang - contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Jiangbo Lin - read, provided feedback and approved the final manuscript.