INPLASY PROTOCOL

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The authors have no conflicts of interest to disclose.

Vein-First vs Artery-First Surgical Technique For Lobectomy of Non–Small Cell Lung Cancer: a protocol for systematic review and meta analysis

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Review question / Objective: **The operation of lung cancer may squeeze the tumor and further promote the spread of tumor cells to the circulation, which may be one of the reasons for the metastasis and recurrence of lung cancer. The potential risk of tumor cell dissemination can theoretically be minimized if the effluent veins were ligated first (via the vein-first [V-first] technique), instead of having the artery ligated first (via the artery-first [A-first] technique). However, this technical concept has not yet been widely accepted as a standard of surgical oncology in current guidelines owing to a lack of sufficient evidence. This systematic review and meta-analysis will be performed to determine which technique during lobectomy will achieve longer patient survival and be more beneficial for patients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 May 2020 and was last updated on 14 May 2020 (registration number INPLASY202050060).

INTRODUCTION

Review question / Objective: **The operation of lung cancer may squeeze the tumor and further promote the spread of tumor cells to the circulation, which may be one of the reasons for the metastasis and recurrence of lung cancer. The potential risk of tumor cell dissemination can theoretically be minimized if the effluent veins were ligated first (via the vein-first [V-first] technique), instead of having the artery ligated first (via the artery-first [A-first] technique). However, this technical concept has not yet been widely accepted as a standard of surgical oncology in current guidelines**

owing to a lack of sufficient evidence. This systematic review and meta-analysis will be performed to determine which technique during lobectomy will achieve longer patient survival and be more beneficial for patients.

Rationale: This systematic review and meta-analysis will be performed to determine which technique during lobectomy will achieve longer patient survival and be more beneficial for patients.

Condition being studied: The potential risk of tumor cell dissemination can theoretically be minimized if the effluent veins were ligated first (via the vein-first [V-first] technique), instead of having the artery ligated first (via the artery-first [A-first] technique). However, this technical concept has not yet been widely accepted as a standard of surgical oncology in current guidelines owing to a lack of sufficient evidence. This systematic review and meta-analysis will be performed to determine which technique during lobectomy will achieve longer patient survival and be more beneficial for patients with resectable non–small cell lung cancer (NSCLC).

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 lobectomy, 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 lobectomy for patients diagnosed with resectable non–small cell lung cancer will be studied.

Comparator: The efficacy and safety of the vein-first and artery-first surgical technique of lobectomy for patients diagnosed 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, published o.

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

Information sources: Two reviewers (LG 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 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 surgery.

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 (LG 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[17]. 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[18].

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[19].

Language: Without any language restrictions.

Country(ies) involved: China.

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

Dissemination plans: This systematic review and meta-analysis was conducted through analysis of published or unpublished studies or records, there is no demand for ethics approval. We will publish the results in a peer-reviewed journal.

Contributions of each author:
Author 1 - Lei Gao - Author 1 drafted the manuscript.
Author 2 - Zhimin Shen - The author provided statistical expertise.

Author 3 - Hui Xu - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Fei Luo - The author read, provided feedback and approved the final manuscript.
Author 5 - Peipei Zhang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 6 - Tianci Chai - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 7 - Sui Chen - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 8 - Mingqiang Kang - The author read, provided feedback and approved the final manuscript.