Comparison between video-assisted thoracoscopic lung cancer resection and robot-assisted lung cancer resection

Protocol for a systematic review and meta-analysis

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1. Introduction

Lung cancer is the second frequent cancer and the leading common cause of cancer death among men worldwide in 2015.[1]

The incidence of lung cancer in women has increased significantly in recent years.[2] Nowadays, surgical resection is one of the main treatments for lung cancer which brings potential healing opportunities to these patients.

In recent years, the techniques of video-assisted thoracoscopic lung cancer resection have made great progress and become the main surgical procedure for lung cancer resection worldwide[3,4] which possesses the advantages of less postoperative pain,[5,6] shorter hospital stay, fewer complications, and lower mortality rates compared with open techniques.[7–12] With advances in science and technology, robotic surgery systems have been invented to extend the surgeon’s eyes and hands through computers, which have the advantage of traditional minimally invasive surgery, The utilization rate of robotic surgery technology is rising year by year.[13,14] Compared with video-assisted thoracoscopic surgery (VATS), robotic lung resection has shorter hospital days, more radical lymph node dissection, fewer bleeding, and more accurate surgical incisions.[11–18]

However many clinical studies have shown that there is no difference between the time of surgery, nodal harvests, blood loss, and 30-day mortality rate.[19–21] Moreover, the costs of robot-assisted lung cancer resection are higher than video-assisted thoracoscopic lung cancer resection,[22,23] making the promotion of robotic surgery controversial. Emerging technologies need time to improve and evolve so that they can be widely adopted.
because some high-quality (Hi-Q) studies have been published, in recent years we will conduct meta-analysis and a systematic review of these high quality evidence to evaluate the difference in the quality metrics of these 2 approaches of operation. If sufficient data are available, we will perform subgroup analysis in different operative types of lung cancer resection.

2. Objective
A meta-analysis and systematic review will be conducted to estimate the effects of robot-assisted thoracic surgery (RATS) versus VATS for patients with resectable lung cancer.

3. Methods
This protocol is conducted adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement. The results of this systematic review and meta-analysis will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA) guidelines. This protocol has been registered in the PROSPERO network (registration number: CRD42018111864).

3.1. Eligibility criteria
3.1.1. Types of studies. We will search and include studies that about comparisons between video-assisted thoracoscopic lung cancer resection and robot-assisted lung cancer resection. Propensity score matched comparative studies, prospective cohort studies; randomized controlled trials (RCTs) will be included, without publication type and language restrictions.

3.1.2. Types of participants. The participants included will be adults diagnosed with lung cancer cytologically or histologically confirmed and who were treated with surgical resection of lung cancer. No restrictions regarding race/ethnicity, sex, economic status, and education will be applied.

3.1.3. Types of interventions. All forms of video-assisted thoracoscopic lung cancer resection compared with robot-assisted lung cancer resection for patients with lung cancer.

3.1.4. Types of outcome measures. Comparison of length of hospitalization, complication rate, overall survival, and disease-free survival (DFS) between video-assisted thoracoscopic lung cancer resection and robot-assisted lung cancer resection.

3.1.5. Exclusion criteria. Case reports, case series, review articles, non-peer reviewed articles, animal studies, letters to the editor, editorials, meeting abstracts, commentaries, non-propensity-matched comparative studies, proceedings, and other non-related studies will be excluded.

3.2. Information sources
We will search Medline, Embase, Pubmed, Google Scholar, and the Cochrane Central Register of Controlled Trials for related literature published in any language before February 28, 2019.

3.3. Search strategy
The relevant keyword or combination subject terms of search will correspond to Medical Subject Heading terms. Before final analysis, the searching will be repeated to identify additional studies meeting the inclusion criteria. The search strategies for PubMed are shown in Table 1.

3.4. Data collection and analysis
3.4.1. Study selection. Two reviewers (TCC, YHL) will independently investigate titles and abstracts of all the literature searched and assess whether the studies conform to the inclusion criteria as described in the protocol. The full text of all possible eligible studies will be retrieved and 2 review authors (TCC, YHL) will separately screen the full text to identify the studies to be included. Two reviewers (TCC, JBL) will document the reasons for excluded studies that do not meet the inclusion criteria. Disagreement will be resolved by discussion or, if necessary, in consultation with the third reviewer (ZYX or WWL). Duplicate literature will be excluded and the multiple reports from the same study will be included in the review of 1 unit. The selection process will be recorded in detail and shown in the PRISMA flow chart.

3.4.2. Data extraction and management. The following data will be abstracted from the included studies: study characteristics (first author, country, publication date, study design, withdrawals, periods of data collection, blanking periods, follow-up duration, and outcomes of interest), and study results. The data will be extracted independently by 2 reviewers (TCC, YHL), and discrepancies will be resolved by discussion with a third reviewer (ZYZ or ZXY).

### Table 1: PubMed search strategies.

| Query | Search term |
|-------|-------------|
| #1 | Pulmonary Neoplasms OR Neoplasms, Lung OR Lung Neoplasm OR Neoplasm, Lung OR Neoplasms, Pulmonary OR Neoplasm, Pulmonary OR Pulmonary Neoplasm OR Lung Cancer OR Cancer, Lung OR Cancers, Lung OR Lung Cancers OR Pulmonary Cancer OR Cancer, Pulmonary OR Cancers, Pulmonary OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell OR Lung Carcinomas,Non-Small-Cell OR Non-Small-Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Non Small Cell Lung OR Lung Neoplasms |
| #2 | Procedure, Robotic Surgica OR Procedures, Robotic Surgical OR Robotic Surgical Procedure OR Surgical Procedure, Robotic OR Surgical Procedures, Robotic OR "Robotic Surgical Procedures" |
| #3 | Surgeries, Video-Assisted Thoracic[Title/Abstract] OR Surgery, Video-Assisted Thoracic OR Thoracic Surgeries, Video-Assisted OR Thoracic Surgery, Video Assisted OR Video-Assisted Thoracic Surgeries OR Video-Assisted Thoracic Surgery OR Surgeries, Video-Assisted Thoracoscopic OR Surgery Video-Assisted Thoracoscopic OR Thoracoscopic Surgery, Video-Assisted OR Video Assisted Thoracoscopic OR Thoracoscopic Surgery, Video-Assisted Thoracoscopic OR OR Thoracic Surgery, Video-Assisted Thoracoscopic Surgeries OR Video-Assisted Thoracic Surgery OR Surgery, Thoracic, Video-Assisted OR VATS OR “Thoracic Surgery, Video-Assisted” |
| #4 | Randomized controlled trial OR Controlled clinical trial OR Randomized OR Randomly OR Trial OR Groups NOT Animals |
| #5 | #1 AND #2 AND #3 AND #4 |
total duration of study, et al); characteristics of participants (sex, age, height, weight, smoking and dust exposure, diabetes, hypertension, diagnostic criteria, pathological confirmation, staging of lung cancer according to the TNM classification, etc); intervention characteristics (surgical approach, bleeding, transfusion, duration, thoracotomy conversion, number of lymph nodes retrieved, etc); outcome and other date (length of hospitalization, length of intensive care unit (ICU) stay, complication rate, overall survival, disease-free survival (DFS), etc). All the extracted data will be recorded in a pre-designed excel table and if the relevant data was lost or unclear, we will consult the authors by email before the study are excluded because the data is unavailable.

3.5. Assessment of risk of bias

The Cochrane Handbook for Systematic Reviews will be used to evaluate the risk of bias of each study. Two reviewers will assess the risk of bias which based on the following ranges: 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); other bias. The assessment results and details will be shown in the risk of bias graph.

3.6. Data analysis

We will use Review Manager 5.3 software to synthesize the data extracted. If the data extracted from the included studies are evaluated as highly homogeneous. We will conduct meta-analysis on them for the purpose of obtaining a clinically meaningful result, in order to carry out a standard meta-analysis. Higgins I² statistic and Cochran Q will be used to assess heterogeneity between studies. If the I² or Chi² statistic>50% will be considered to be highly heterogeneous and the data will be analyzed by a random effect model. Otherwise, we will adopt the fixed effect model to analysis the data. Mantel–Haenszel method will be used in the pooling of binary data and the results will be presented in the form of relative risk (RR) about 95% confidence interval (CI) of the dates. The inverse variance method will be applied in pooling of continuous data. The results will be given in the form of standardized mean difference (SMD) with 95% CI.

3.6.1. Subgroup analysis. Subgroup analysis will be conducted to search potential sources of heterogeneity and if sufficient data are available, we will perform subgroup analysis in different operative types of lung cancer resection.

3.6.2. Sensitivity analysis. To determine whether the aggregation results are robust and reliable, sensitivity analysis will be conducted by excluding highly biased studies.

3.7. Publication bias

We will use funnel plots and Egger tests to qualitatively analyze publication bias of the studies included. When publication bias does exist, we will use trim and fill method to analyze publication bias in the studies. [26]

3.8. Evidence evaluation

The overall evidence will be assessed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and the quality of evidence will be assessed as 4 levels—high, moderate, low, and very low [27]

4. Discussion

The latest studies show that the incidence of lung cancer is increasing year by year worldwide, which has become the first frequent cancer and the leading common cause of cancer death in human worldwide. [2] Lung cancer resection plays an important role in providing a potentially curable chance for lung cancer patients. Robot-assisted lung cancer resection has an indisputable technological advantage over traditional video-assisted lung surgery. Robot surgery has better accuracy, comfort, and stereoscopic vision. RATS is a safe and promising alternative to VATS for difficult lobectomy. Early studies have shown that robotic surgery has no advantage versus VATS on postoperative outcomes and the cost of robotic surgery is very high, so the promotion of robotic surgery technology is controversial.

Due to the latest high-quality clinical studies published, we will use the advantages of this high-quality evidence for systematic review and meta-analysis to obtain objective results. This result will provide a reference for clinical decision making. There is still a long way to go before the popularization of robotic surgery. We hope that robotic surgery technology will be further improved and the cost reduced to make a great contribution to human health.

Author contributions

Jiangbo Lin and Mingqiang Kang is the guarantor of the article. Tianci Chai, Yuhan Lin, and Jiangbo Lin conceived and designed the study. Tianci Chai, Yuhan Lin, Zhimin Shen, and Sui Chen drafted this protocol. Zhenyang Zhang, Wenwei Lin, Peipei Zhang, and Zhimin Shen will perform the search, screening, and extraction. Jiangbo Lin and Mingqiang Kang have strictly reviewed this protocol and approved of publication. Tianci Chai and Yuhan Lin contributed equally to this work.

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References

[1] Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017;3:524-48.

[2] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018.
[3] Shaw JP, Dembitzer FR, Wisnivesky JP, et al. Video-assisted thoracoscopic lobectomy: state of the art and future directions. Ann Thorac Surg 2008;85:5705–9.

[4] Lewis RJ, Caccavale R, Sider GE, et al. Video-assisted thoracic surgical resection of malignant lung tumors. J Thorac Cardiovasc Surg 1992;104:1679–85.

[5] Landreneau RJ. Video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 1993;56.

[6] Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. JSLS J Soc Laparoendosc Surg 2007;11:368–74.

[7] Jawitz OK, Wang Z, Boffa DJ, et al. The differential impact of preoperative comorbidity on perioperative outcomes following thoracoscopic and open lobectomies. Eur J Cardiothorac Surg Off J Eur Assoc Cardiothorac Surg 2017;51:169–74.

[8] Whitson BA, Andrade RS, Boettcher A, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. Ann Thorac Surg 2007;83:1965–70.

[9] Cattaneo SM, Park BJ, Wilton AS, et al. Use of video-assisted thoracic surgery for lobectomy in the elderly results in fewer complications. Ann Thorac Surg 2008;85:231–5.

[10] Mathisen DJ. Re: video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg Off J Eur Assoc Cardiothorac Surg 2016;49:609–10.

[11] Nwogu CE, D’Cunha J, Pang H, et al. VATS lobectomy has better perioperative outcomes than open lobectomy: CALGB 31001, an ancillary analysis of CALGB 140202 (Alliance). Ann Thorac Surg 2015;99:399–405.

[12] Paul S, Altorki NK, Sheng S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg 2010;139:366–78.

[13] Veronesi G, Novellis P, Voulaz E, et al. Robot-assisted surgery for lung cancer: state of the art and perspectives. Lung Cancer (Amsterdam, Netherlands) 2016;101:28–34.

[14] Paul S, Jalbert J, Isaacs AJ, et al. Comparative effectiveness of robotic-assisted vs thoracoscopic lobectomy. Chest 2014;146:1505–12.

[15] Louie BE, Farivar AS, Aye RW, et al. Early experience with robotic lung resection results in similar operative outcomes and morbidity when compared with matched video-assisted thoracoscopic surgery cases. Ann Thorac Surg 2012;93:1598–604.

[16] Wilson JL, Louie BE, Cerfolio RJ, et al. The prevalence of nodal upstaging during robotic lung resection in early stage non-small cell lung cancer. Ann Thorac Surg 2014;97:1901–6.

[17] Farivar AS, Cerfolio RJ, Knight AW, et al. Comparing robotic lung resection with thoracotomy and video-assisted thoracoscopic surgery cases entered into the Society of Thoracic Surgeons database. Innovations 2014;9:10–5.

[18] Yang HX, Woo KM, Sima CS, et al. Long-term survival based on the surgical approach to lobectomy for clinical stage I nonsmall cell lung cancer: comparison of robotic, video-assisted thoracic surgery, and thoracotomy lobectomy. Ann Surg 2017;265:431–7.

[19] Jang HJ, Lee HS, Park SY, et al. Comparison of the early robot-assisted lobectomy experience to video-assisted thoracic surgery lobectomy for lung cancer: a single-institution case series matching study. Innovations (Philadelphia, Pa) 2011;6:305–10.

[20] Kent M, Wang T, Whyte R, et al. Open, video-assisted thoracic surgery, and robotic lobectomy: review of a national database. Ann Thorac Surg 2014;97:236–42.

[21] Farivar AS, Cerfolio RJ, Vallieres E, et al. Comparing robotic lung resection with thoracotomy and video-assisted thoracoscopic surgery cases entered into the Society of Thoracic Surgeons database. Innovations (Philadelphia, Pa) 2014;9:10–5.

[22] Deen SA, Wilson JL, Wilshire CL, et al. Defining the cost of care for lobectomy and segmentectomy: a comparison of open, video-assisted thoracoscopic, and robotic approaches. Ann Thorac Surg 2014;97:1000–7.

[23] Swanson SJ, Miller DL, McKenna RJJr, et al. Comparing robot-assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: results from a multiinstitutional study. Innovations (Philadelphia, Pa) 2011;6:305–10.

[24] Prefered reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ (Clinical research ed) 2016;354:i4086.

[25] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clin Res ed) 2009;339:b2700.

[26] Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. Res Synth Methods 2012;3:161–76.

[27] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ (Clin Res ed) 2011;343:d5928.