BMJ Open

Protocol for a meta-analysis of recurrence and metastasis of different surgical techniques for early stage non-small cell lung cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086503
Article Type:	Protocol
Date Submitted by the Author:	16-Mar-2024
Complete List of Authors:	Huang, Xiongfeng; Fuzhou Medical College of Nanchang University Ren, Yuxi; Jiangxi University of Chinese Medicine Cao, Yaoxing; Jiangxi College of Traditional Chinese Medicine Li, Weijuan; Fuzhou Medical College of Nanchang University Lai, Jinxing; Nanchang University Affiliated Ganzhou Hospital
Keywords:	Lung Diseases, ONCOLOGY, SURGERY, Meta-Analysis

Protocol for a meta-analysis of recurrence and metastasis of different surgical techniques for early stage non-small cell lung cancer

Xiongfeng Huang[1], Yuxi Ren[2], Yaoxing Cao[3], Weijuan Li[1], Jinxing Lai[4]*

1. Fuzhou Medical College of Nanchang University, Fuzhou, China.

2. Jiangxi University of Chinese Medicine, Nanchang, China.

3. Jiangxi College of Traditional Chinese Medicine, Fuzhou, China.

4. Affiliated Ganzhou Hospital of Nanchang University, Ganzhou, China.

***Correspondence:** Jinxing Lai

*E-mail: laijingxing990@163.com

ABSTRACT

Introduction

Lung cancer remains the primary cause of cancer-related deaths on a global scale. Surgery is the main therapeutic option for early stage non-small cell lung cancer (NSCLC). However, the optimal surgical approach for lymph node assessment in NSCLC resection remains controversial, and it's still uncertain whether lymph node dissection (LND) is more effective in reducing recurrence and metastasis rates in NSCLC compared to lymph node sampling (LNS). Therefore, we will conduct a meta-analysis to evaluate the recurrence and metastasis of LND versus LNS in patients with early stage NSCLC.

Methods and analysis

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement. According to the predefined inclusion criteria, we will conduct a comprehensive search for randomized controlled trials (RCTs) and non-randomized studies examining the recurrence and metastasis of LND compared to LNS in patients with stage I-IIIA NSCLC. A literature search from inception in PubMed, EMBASE, the Cochrane Library, CNKI, WanFang, Sinomed, VIP, and Web of Science. There will be no limitations on language, and the search will be undertaken on 1 May 2024 with regular search for new studies.

Additionally, relevant literature references will be retrieved and hand searching of pertinent journals will be conducted. The main outcomes include overall recurrence rate, local recurrence rate, and distant metastasis rate. The supplementary outcomes encompass the rates of regional recurrence and lymph node metastasis. Two independent reviewers will perform screening, data extraction, and quality assessment. Our reviewers will perform subgroup analysis, sensitivity analysis, and publication bias analysis to evaluate the heterogeneity and robustness. Review Manager 5.4 will be applied in analyzing and synthesizing. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to assess the quality of evidence for the whole study.

Ethics and dissemination

Ethical approval is dispensable for this study since no private information of the participants will be involved. The findings of the present study will be disseminated through a peer-reviewed journal or conference presentation.

Study registration

The protocol of the systematic review has been registered on Open Science Framework, with a registration DOI https://doi.org/10.17605/OSF.IO/S2FT5.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This protocol adheres to the guidelines established by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
- This is a comprehensive review of lymph node dissection versus lymph node sampling in early stage non-small cell lung cancer patients.
- To minimize the risk of bias, two researchers will independently carry out the study selection, data extraction, and quality assessment.
- Non-randomized studies may pose a significant risk of selection bias.
- The potential existence of significant heterogeneity among various studies could hinder the derivation of causal conclusions from their combined findings.

INTRODUCTION

Non-small cell lung cancer (NSCLC), the predominant form of lung malignancy, continues to pose a significant threat to global health. In 2024, the American Cancer Society estimated that lung cancer is the leading cause of cancer death, with an estimated 340 people dying from lung cancer every day, almost 2.5 times more than colorectal cancer, which ranks second in cancer deaths.[1] Lung cancer remains the primary cause of cancer-related deaths on a global scale.[2-5]

Surgical resection plays a crucial role in the management of NSCLC, and lymph node staging is essential for accurate prognostication and treatment planning. Lymph node dissection (LND) and lymph node sampling (LNS) are two surgical techniques used for NSCLC, but their relative effectiveness remains controversial.[6-15] LNS involves the removal of a smaller number of lymph nodes for pathological examination. This approach is generally less invasive, leading to shorter operative times and potentially fewer postoperative complications.[16] However, it may not provide as comprehensive nodal staging as dissection, leading to potential underestimation of the disease stage. LND, conversely, involves the complete removal of lymph nodes and surrounding tissue in specific anatomic regions.[17] This approach offers a comprehensive assessment of nodal involvement, allowing for more accurate staging and potentially improving long-term outcomes. However, it is a more invasive procedure that may increase the risk of post-operative complications, which may result in a reduction in postoperative quality of life for patients. Furthermore, for some patients with early NSCLC, the incidence of lymph node metastasis is not very high, and most patients may not have regional lymph node metastasis. Thus, the necessity of performing complete and systematic lymph node dissection in patients with early-stage NSCLC and whether the expected clinical effect can be achieved remains controversial.

Patients with NSCLC continue to experience a notable rate of recurrence and metastasis following surgical intervention, thereby impacting their overall survival outcomes. Several studies have compared the recurrence and metastasis of LND and LNS in NSCLC surgery. Based on three previous studies,[18-20] LND has been shown

to reduce the incidence of recurrence and metastasis in early stage NSCLC. And Meng et al.[21] have posited in their meta-analysis that the use of LND may be effective in eliminating hidden micrometastases to reduce the risk of both local recurrence and distant metastases. However, the results of our previous meta-analysis indicated that in individuals with early-stage NSCLC, LND and LNS yielded similar rates of recurrence and metastasis.[22] Additionally, other studies have also shown that lymph node dissection conducted in early-stage lung cancer does not impact the occurrence of recurrence and metastasis.[23-25]

The optimal surgical approach for lymph node assessment in NSCLC resection remains controversial, and it's still uncertain whether LND is more effective in reducing recurrence and metastasis rates in NSCLC compared to LNS. Clearly, newer systematic review and meta-analyses are required to resolve this issue, and definitive analyses can provide stronger rationales for the choice of a specific therapy. Consequently, we will perform a meta-analysis of relevant randomized controlled trials (RCTs) and non-randomized studies to evaluate the recurrence and metastasis of LND versus LNS in early stage NSCLC patients. We hope this meta-analysis will offer strong evidence for the surgical treatment of patients with early stage NSCLC and guide future clinical practice.

MATERIALS AND METHODS

Registration and reporting

This review protocol has been officially registered in the Open Science Framework (OSF) database (DOI https://doi.org/10.17605/OSF.IO/S2FT5). And designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (supplemental File 1).[26] If there is a change to this protocol, details of the amendment and the reasons for it will be added to OSF.

Eligibility criteria

Types of studies

All relevant published RCTs and non-randomized studies will be included. The review

will not include certain types of studies, such as methodological papers, editorials, qualitative research, individual case reports, and secondary studies like narrative reviews, systematic reviews and meta-analyses. There will be no restrictions on the language used or the time of publication.

Types of participants

Individuals with stage I to IIIA non-small cell lung cancer who received either LND or LNS will be eligible for inclusion, with no limitations based on country, race, ethnicity, age, gender, or occupation.

Type of outcomes

The main outcomes are as follows: overall recurrence rate, local recurrence rate (ipsilateral lung, ipsilateral pleura, trachea, etc.), and distant metastasis rate (contralateral lung, contralateral pleura, bone, liver, etc.). The supplementary outcomes encompass the rates of regional recurrence and lymph node metastasis.

Information source and search strategy

A literature search from inception in PubMed, EMBASE, the Cochrane Library, CNKI, WanFang, Sinomed, VIP, and Web of Science. The Gray Journal includes annual meetings of the American Society of Clinical Oncology and the American Society of Thoracic Surgery (chest surgery), using combinations of the search terms: lymph node dissection, LND, lymph node sampling, LNS, and non–small cell lung cancer, NSCLC. Detailed search strategies are shown in supplemental File 2. There will be no limitations on language, and the search will be undertaken on 1 May 2024 with regular search for new studies. The bibliography of all articles obtained will be examined to identify additional publications that may be pertinent. In addition, abstracts from the American Society of Clinical Oncology and the European Society of Medical Oncology will be searched for potential studies. In order to gather thorough information from qualifying studies, we will contact primary authors to request any pertinent data, such as supplementary materials that may not have been fully disclosed or reported, and information from informal sources related to the research. Two reviewers will examine the reference list and individually choose the studies.

Study Selection

The chosen articles will undergo a dual review process by two separate authors. Following the initial screening of titles and abstracts of papers found through the search strategy, the papers will be sorted into two categories: potentially relevant or not relevant based on the eligibility criteria. Subsequently, efforts will be made to obtain the full texts of all potentially relevant papers, which will then be reviewed against the eligibility criteria. In the event of disagreements during the full-text screening, they will be resolved through discussion. If a consensus cannot be reached, a third author will step in to settle the dispute. The study selection process is illustrated in Figure 1.

Data extraction process

The data will be taken from each full-text article that meets the eligibility criteria: study design; country of study; interventions; outcomes; number and general characteristics of participants, for example, age, and gender. If data is missing, we will reach out to the original author to request additional information. The process of data extraction will be conducted by two reviewers, with Microsoft Excel being employed as the tool for data collection. Any disagreements between the two reviewers will be resolved by discussion or by consulting with the third reviewer, the characteristics of the study are attached as Supplemental File 3.

Study risk of bias assessment

Two reviewers will assess the quality of the included studies. Disagreement between the two reviewers will be resolved by discussion with the third reviewer.

We will evaluate the included RCTs' quality using the Cochrane Handbook's "risk of bias" technique.[27] Sequence generation, allocation concealment, blinding, incomplete data, and selective reporting were assessed, and each of them was graded as “yes(+)”, “no(-)” or “unclear(?)”, which reflected low risk of bias, high risk of bias, and uncertain risk of bias, respectively.[28] The Newcastle-Ottawa scale will be used to evaluate the methodological rigor of non-randomized studies. The Newcastle-Ottawa Scale consists of eight items that are divided into three categories: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each).[29] One star will be given for each item in the selection and

outcome domains, and up to two stars will be given for the comparability domain, when a primary study satisfies the methodological required standard. Studies with star values between 0 and 4 will ultimately be classified as having a high risk of bias, studies with scores between 5 and 6 as having a moderate risk of bias, and studies with scores between 7 and 9 as having a low risk of bias.[30]

DATA ANALYSIS

Statistical analysis

Meta-analysis will be planned with sufficient clinically and statistically homogeneous and comparable reported outcomes among studies by pooling data using Review Manager V.5.4 software by The Cochrane Collaboration. Dichotomous data will be compared using a risk ratio (RR) or odds ratio (OR). Respective 95% confidence intervals (CI) will be calculated for each estimate and presented in forest plots. Statistical heterogeneity will be assessed visually by Q and I^2 statistics.[31] For the Q statistic, a P value<0.10 Will be regarded as statistically significant for heterogeneity. For the I^2 statistic,[32] if there is heterogeneity among the study results (I^2>50%), the heterogeneity source will be further examined. After the exclusion of effects exerted by significant clinical heterogeneity, the random-effects model will be employed for the meta-analysis.[33 34] If there is no heterogeneity between the study results (I^2< 50%), this study will use the fixed-effect model in terms of meta-analysis.[35 36] All reported P-values are 2-sided and values of P<0.05 will be regarded as significant for all included studies. A narrative synthesis will be carried out if insufficient homogeneous studies make meta-analysis impractical.

Assessment of publication bias

The funnel plot will be used to assess reporting bias. A symmetrical funnel shape will suggest the absence of publication bias, whereas an asymmetrical funnel plot will indicate the presence of such bias. An objective assessment of publication bias will be conducted employing Egger's linear regression test, where a p-value less than 0.1 is considered statistically significant, indicating the presence of publication bias.[37 38]

Subgroup and sensitivity analyses

Subgroup analyses will be conducted based on study and population variables, including age, gender, intervention approaches, sample size, and other factors. For sensitivity analysis, studies of poorer methodological quality will be removed to see if their deletion alters the outcomes of the analyses. When heterogeneity is substantial, the leave-one-out method is employed to ascertain whether it arises from a specific study. For instance, to ascertain whether heterogeneity diminishes, we eliminate one study. This approach is employed to investigate each study individually, in order to identify the root cause of heterogeneity.

Grading the quality of evidence

The evaluation of the evidence's quality throughout the entire study will be conducted utilizing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework.[39-41] This system is frequently employed to evaluate the credibility of evidence and determine the level of recommendations. Two independent reviewers will employ the five GRADE considerations, including the risk of bias, consistency of effect, imprecision, indirectness, and publication bias, to meticulously evaluate the certainty of the evidence and arrive at sound conclusions.[42 43]

Updates to study protocol

If modifications to the review protocol are deemed necessary, these adjustments will be thoroughly documented and incorporated as supplementary material alongside the final manuscript. Additionally, these updates will be reflected on the OSF register for future reference.

Patient and public involvement

We do not have any intention to involve patients or the general public in the planning, execution, reporting, or dissemination of our systematic review.

Ethics and dissemination

Ethical approval is dispensable for this study since no private information of the participants will be involved. The findings of the present study will be disseminated through a peer-reviewed journal or conference presentation.

Author contributions

XH conceived the study. XH and YC registered the protocol. XH and WL drafted the protocol. YC and JL revised it. XH and YR developed the search strategies and will run them. JL and YC will select studies and extract data. XH will analyze the data. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Jiangxi Province key research and development program (No.2020YBBGWL001); and the Jiangxi Provincial Department of Education Science and Technology research key project (No.GJJ208902).

Competing interests

The authors declare no conflict of interest.

Word count

2072 words

REFERENCES

1. Siegel RL, Giaquinto AN. Cancer statistics, 2024. 2024;74(1):12-49. doi: 10.3322/caac.21820
2. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. *Clinics in chest medicine* 2020;41(1):1-24. doi: 10.1016/j.ccm.2019.10.001 [published Online First: 2020/02/06]
3. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *The New England journal of medicine* 2008;359(13):1367-80. doi: 10.1056/NEJMra0802714 [published Online First: 2008/09/26]
4. Gridelli C, Rossi A, Maione P, et al. Vaccines for the treatment of non-small cell lung cancer: a renewed anticancer strategy. *The oncologist* 2009;14(9):909-20. doi: 10.1634/theoncologist.2009-0017 [published Online First: 2009/09/04]
5. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA: a cancer journal for clinicians* 2011;61(2):69-90. doi: 10.3322/caac.20107 [published Online First: 2011/02/08]
6. Xu J, Lai J, Huang X. Survival outcomes following complete mediastinal lymphadenectomy or selective mediastinal lymphadenectomy in patients with stage I-IIIA non-small cell lung cancer: protocol for a systematic review and meta-analysis. 2024;14(3):e084520. doi:

10.1136/bmjopen-2024-084520

7. Zhang Y, Deng C, Zheng Q, et al. Selective Mediastinal Lymph Node Dissection Strategy for Clinical T1N0 Invasive Lung Cancer: A Prospective, Multicenter, Clinical Trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2023;18(7):931-39. doi: 10.1016/j.jtho.2023.02.010 [published Online First: 2023/02/26]

8. Wang Y, Darling GE. Complete mediastinal lymph node dissection versus systematic lymph node sampling in surgical treatment of non-small cell lung cancer: do we have the answer? *Journal of thoracic disease* 2017;9(11):4169-70. doi: 10.21037/jtd.2017.10.39 [published Online First: 2017/12/23]

9. Xu F, Qi L, Yue D, et al. The effect of the extent of lymph node dissection for stage IA non-small-cell lung cancer on patient disease-free survival. *Clinical lung cancer* 2013;14(2):181-7. doi: 10.1016/j.cllc.2012.09.002 [published Online First: 2012/12/01]

10. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in medicine* 1998;17(24):2815-34. doi: 10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8 [published Online First: 1999/01/28]

11. Ou SH, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2008;3(8):880-6. doi: 10.1097/JTO.0b013e31817dfced [published Online First: 2008/08/02]

12. Wang Z, Qi Z, Cheng D, et al. Lobe-Specific Node Dissection Can Be a Suitable Alternative to Systematic Lymph Node Dissection in Highly Selective Early-Stage Non-Small-Cell Lung Cancer Patients: A Meta-Analysis. *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia* 2021;27(3):143-50. doi: 10.5761/atcs.oa.20-00136 [published Online First: 2020/12/08]

13. Tantraworasin A, Saeteng S, Siwachat S, et al. Impact of lymph node management on resectable non-small cell lung cancer patients. *Journal of thoracic disease* 2017;9(3):666-74. doi: 10.21037/jtd.2017.02.90 [published Online First: 2017/04/30]

14. Yang M, Cao H, Guo X, et al. The number of resected lymph nodes (nLNs) combined with

tumor size as a prognostic factor in patients with pathologic N0 and Nx non-small cell lung cancer. *PloS one* 2013;8(9):e73220. doi: 10.1371/journal.pone.0073220 [published Online First: 2013/09/12]

15. Wang W, Chen D, Xi K, et al. Impact of Different Types of Lymphadenectomy Combined With Different Extents of Tumor Resection on Survival Outcomes of Stage I Non-small-cell Lung Cancer: A Large-Cohort Real-World Study. *Frontiers in oncology* 2019;9:642. doi: 10.3389/fonc.2019.00642 [published Online First: 2019/08/10]
16. Dezube AR, Mazzola E, Bravo-Iñiguez CE, et al. Analysis of Lymph Node Sampling Minimums in Early Stage Non-Small-Cell Lung Cancer. *Seminars in thoracic and cardiovascular surgery* 2021;33(3):834-45. doi: 10.1053/j.semtcvs.2020.11.007 [published Online First: 2020/11/13]
17. Kim K. Video-Assisted Thoracic Surgery Mediastinal Lymph Node Dissection in Lung Cancer Surgery. *Journal of chest surgery* 2021;54(4):258-62. doi: 10.5090/jcs.21.054 [published Online First: 2021/08/07]
18. Wu Y, Huang ZF, Wang SY, et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung cancer (Amsterdam, Netherlands)* 2002;36(1):1-6. doi: 10.1016/s0169-5002(01)00445-7 [published Online First: 2002/03/14]
19. Su X, Wang X, Long H, et al. Mediastinal lymph node dissection affects survival in patients with stage I non-small cell lung cancer. *The Thoracic and cardiovascular surgeon* 2008;56(4):226-30. doi: 10.1055/s-2007-989494 [published Online First: 2008/05/16]
20. Lardinois D, Suter H, Hakki H, et al. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. *The Annals of thoracic surgery* 2005;80(1):268-74; discussion 74-5. doi: 10.1016/j.athoracsur.2005.02.005 [published Online First: 2005/06/25]
21. Meng D, Zhou Z, Wang Y, et al. Lymphadenectomy for clinical early-stage non-small-cell lung cancer: a systematic review and meta-analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2016;50(4):597-604. doi: 10.1093/ejcts/ezw083 [published Online First: 2016/04/24]
22. Huang X, Wang J, Chen Q, et al. Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis. *PloS one* 2014;9(10):e109979. doi: 10.1371/journal.pone.0109979 [published Online First:

2014/10/09]

23. Mokhles S, Macbeth F, Treasure T, et al. Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small-cell lung cancer: a systematic review of randomized trials and a meta-analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2017;51(6):1149-56. doi: 10.1093/ejcts/ezw439 [published Online First: 2017/02/06]
24. Luo J, Yang S, Dong S. Selective Mediastinal Lymphadenectomy or Complete Mediastinal Lymphadenectomy for Clinical Stage I Non-Small Cell Lung Cancer: A Meta-Analysis. 2021;38(12):5671-83. doi: 10.1007/s12325-021-01954-w
25. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *The Journal of thoracic and cardiovascular surgery* 2011;141(3):662-70. doi: 10.1016/j.jtcvs.2010.11.008 [published Online First: 2011/02/22]
26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4(1):1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]
27. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). *Cochrane* 2023
28. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)* 2011;343:d5928. doi: 10.1136/bmj.d5928 [published Online First: 2011/10/20]
29. Wells G, Shea B, O'Connell D, et al. The newcastle-ottawa scale(NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2020
30. Luchini C, Stubbs B, Solmi M, et al. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017(4):80-84.
31. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. *Jama* 2006;295(6):676-80. doi: 10.1001/jama.295.6.676 [published Online First: 2006/02/10]
32. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*

(Clinical research ed) 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]

33. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemporary clinical trials* 2015;45(Pt A):139-45. doi: 10.1016/j.cct.2015.09.002 [published Online First: 2015/09/08]
34. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemporary clinical trials* 2007;28(2):105-14. doi: 10.1016/j.cct.2006.04.004 [published Online First: 2006/06/30]
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]
36. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;22(4):719-48. [published Online First: 1959/04/01]
37. Cumpston MS, McKenzie JE, Welch VA, et al. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. *Journal of public health (Oxford, England)* 2022;44(4):e588-e92. doi: 10.1093/pubmed/fdac036 [published Online First: 2022/03/31]
38. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ (Clinical research ed)* 2001;323(7304):101-5. doi: 10.1136/bmj.323.7304.101 [published Online First: 2001/07/14]
39. Langer G, Meerpohl JJ, Perleth M, et al. [GRADE guidelines: 12. Developing Summary of Findings tables - dichotomous outcomes]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen* 2013;107(9-10):646-64. doi: 10.1016/j.zefq.2013.10.034 [published Online First: 2013/12/10]
40. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)* 2008;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE [published Online First: 2008/05/06]
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of clinical epidemiology* 2011;64(4):395-400. doi: 10.1016/j.jclinepi.2010.09.012 [published Online First: 2011/01/05]
42. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of

evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]

43. H S, Brozek J, Oxman AE. GRADE handbook for grading quality of evidence and strength of recommendation. 2009

Appendices

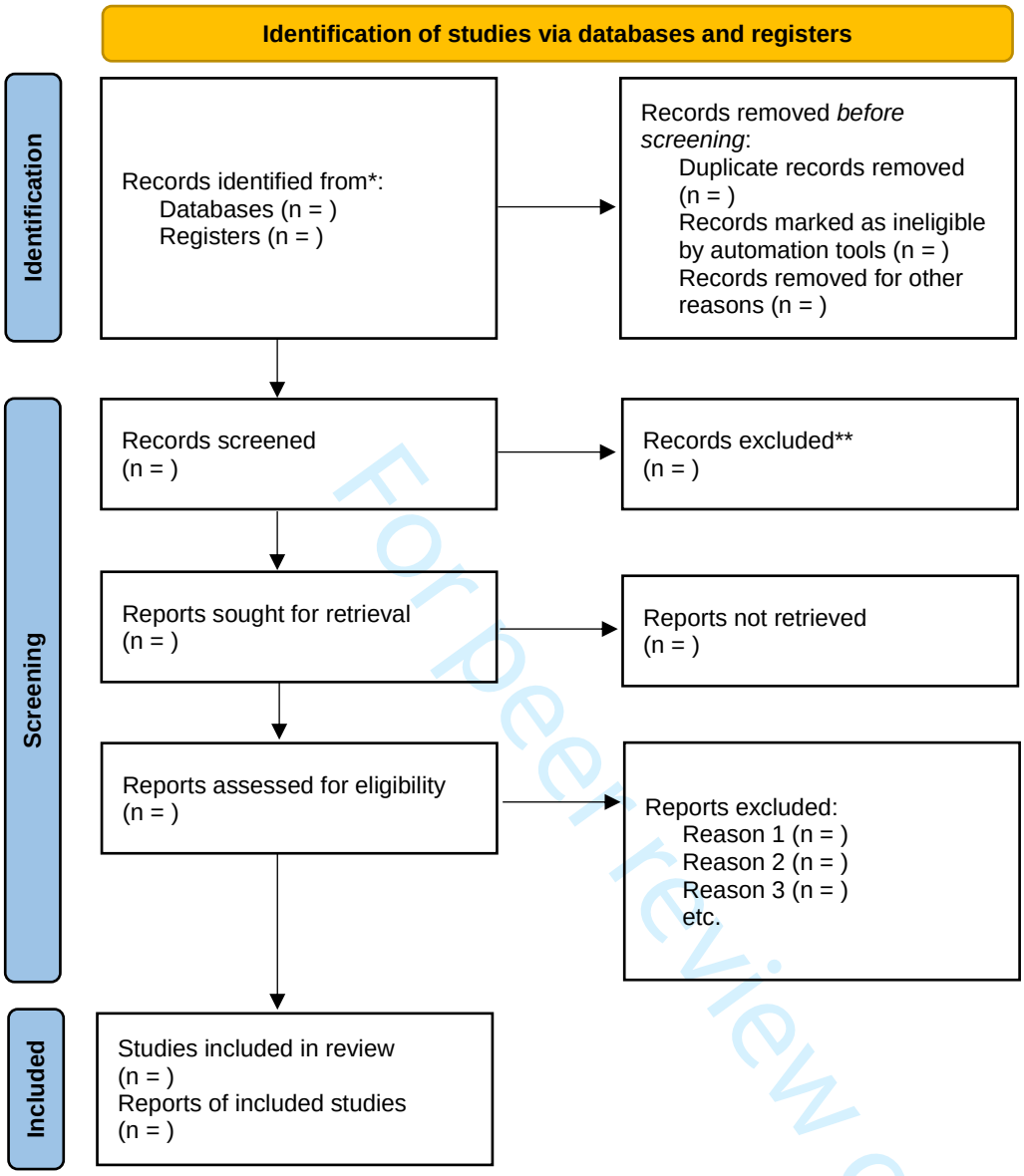
Fig 1. Flow diagram showing the selection process of articles.

Supplemental File 1. PRISMA-P-checklist.

Supplemental File 2. Search strategy.

Supplemental File 3. General information of the included studies.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	P7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. Search strategy

1. PubMed

Number	Search terms
#1	Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung OR Non-Small Cell Lung Cancer OR Lung Neoplasms OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Non-Small-Cell Lung OR Lung Carcinoma OR Non-Small-Cell OR Lung Carcinomas OR NSCLC [Title/Abstract]
#2	Surgical Procedures OR Operative OR surgery OR surgery OR surgical OR operative OR postoperative [Title/Abstract]
#3	lymphadenectomy OR lymphadenectomy OR complete mediastinal lymphadenectomy OR mediastinal lymph node excision OR lobe-specific lymph node dissection OR mediastinal lymph node dissection OR mediastinal lymph node sampling OR lymph node dissection OR lymph node OR dissect OR sample OR selective mediastinal lymphadenectomy OR systematic lymph node dissection OR selective lymph node dissection OR LND OR LNS [Title/Abstract]
#4	randomly OR randomized OR RCT OR trials OR cohort OR longitudinal OR prospective OR survival [Title/Abstract]
#5	#1 AND #2 AND #3 AND #4 [Title/Abstract]

2. Embase

Number	Search terms
#1	Non-Small-Cell:ti,ab,kw OR Non-Small-Cell Lung Carcinomas:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Non-Small-Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Lung Neoplasms:ti,ab,kw OR Pulmonary Neoplasms:ti,ab,kw OR Lung Neoplasm:ti,ab,kw OR Pulmonary Neoplasm:ti,ab,kw OR Lung Cancer:ti,ab,kw OR Lung Cancers:ti,ab,kw OR Pulmonary Cancer:ti,ab,kw OR Pulmonary Cancers:ti,ab,kw OR Cancer of the Lung:ti,ab,kw OR Cancer of Lung:ti,ab,kw OR Non-Small-Cell Lung:ti,ab,kw OR Lung Carcinoma:ti,ab,kw OR Non-Small-Cell:ti,ab,kw OR Lung Carcinomas:ti,ab,kw OR NSCLC:ti,ab,kw
#2	Surgical Procedures:ti,ab,kw OR Operative OR surgery:ti,ab,kw OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR operative:ti,ab,kw OR postoperative:ti,ab,kw

#3	lymphadenectomy:ti,ab,kw OR lymphadenectomy:ti,ab,kw OR complete mediastinal lymphadenectomy:ti,ab,kw OR mediastinal lymph node excision:ti,ab,kw OR lobe-specific lymph node dissection:ti,ab,kw OR mediastinal lymph node dissection:ti,ab,kw OR mediastinal lymph node sampling:ti,ab,kw OR lymph node dissection:ti,ab,kw OR lymph node:ti,ab,kw OR dissect:ti,ab,kw OR sample:ti,ab,kw OR selective mediastinal lymphadenectomy:ti,ab,kw OR systematic lymph node dissection:ti,ab,kw OR selective lymph node dissection:ti,ab,kw OR LND:ti,ab,kw OR LNS:ti,ab,kw
#4	randomly:ti,ab,kw OR randomized:ti,ab,kw OR RCT:ti,ab,kw OR trials:ti,ab,kw OR cohort:ti,ab,kw OR longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR survival:ti,ab,kw
#5	#1 AND #2 AND #3 AND #4

3. Cochrane Library

Number	Search terms
#1	Non-Small-Cell:ti,ab,kw OR Non-Small-Cell Lung Carcinomas:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Non-Small-Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Lung Neoplasms:ti,ab,kw OR Pulmonary Neoplasms:ti,ab,kw OR Lung Neoplasm:ti,ab,kw OR Pulmonary Neoplasm:ti,ab,kw OR Lung Cancer:ti,ab,kw OR Lung Cancers:ti,ab,kw OR Pulmonary Cancer:ti,ab,kw OR Pulmonary Cancers:ti,ab,kw OR Cancer of the Lung:ti,ab,kw OR Cancer of Lung:ti,ab,kw OR Non-Small-Cell Lung:ti,ab,kw OR Lung Carcinoma:ti,ab,kw OR Non-Small-Cell:ti,ab,kw OR Lung Carcinomas:ti,ab,kw OR NSCLC:ti,ab,kw
#2	Surgical Procedures:ti,ab,kw OR Operative OR surgery:ti,ab,kw OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR operative:ti,ab,kw OR postoperative:ti,ab,kw
#3	lymphadenectomy:ti,ab,kw OR lymphadenectomy:ti,ab,kw OR complete mediastinal lymphadenectomy:ti,ab,kw OR mediastinal lymph node excision:ti,ab,kw OR lobe-specific lymph node dissection:ti,ab,kw OR mediastinal lymph node dissection:ti,ab,kw OR mediastinal lymph node sampling:ti,ab,kw OR lymph node dissection:ti,ab,kw OR lymph node:ti,ab,kw OR dissect:ti,ab,kw OR sample:ti,ab,kw OR selective mediastinal lymphadenectomy:ti,ab,kw OR systematic lymph node dissection:ti,ab,kw OR selective lymph node dissection:ti,ab,kw OR LND:ti,ab,kw OR LNS:ti,ab,kw
#4	randomly:ti,ab,kw OR randomized:ti,ab,kw OR RCT:ti,ab,kw OR trials:ti,ab,kw OR cohort:ti,ab,kw OR longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR survival:ti,ab,kw

#5	#1 AND #2 AND #3 AND #4

4. Web of Science

Number	Search terms
#1	TS=(Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung OR Non-Small Cell Lung Cancer OR Lung Neoplasms OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Non-Small-Cell Lung OR Lung Carcinoma OR Non-Small-Cell OR Lung Carcinomas OR NSCLC)
#2	TS=(Surgical Procedures OR Operative OR surgery OR surgery OR surgical OR operative OR postoperative)
#3	TS=(lymphadenectomy OR lymphadenectomy OR complete mediastinal lymphadenectomy OR mediastinal lymph node excision OR lobe-specific lymph node dissection OR mediastinal lymph node dissection OR mediastinal lymph node sampling OR lymph node dissection OR lymph node OR dissect OR sample OR selective mediastinal lymphadenectomy OR systematic lymph node dissection OR selective lymph node dissection OR LND OR LNS)
#4	TS=(randomly OR randomized OR RCT OR trials OR cohort OR longitudinal OR prospective OR survival)
#5	#1 AND #2 AND #3 AND #4

5. China National Knowledge Infrastructure (CNKI) (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

6. WANFANG DATA (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

7. Chinese biomedical literature service system (Sinomed) (Chinese)

Search terms
("非小细胞肺癌" [常用字段:智能] OR "肺癌" [常用字段:智能]) AND ("肺癌"[常用字段:智能]) AND ("随机对照试验"[常用字段:智能]) AND ("淋巴结清扫方式"[全部字段:智能] OR "系统性淋巴结清扫"[全部字段:智能]OR "选择性淋巴结清扫"[全部字段:智能] OR "叶特异性淋巴结清扫"[全部字段:智能] OR "纵膈淋巴结采样"[全部字段:智能])

8. VIP database (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

Supplemental File 3. General information of the included studies.

First author		
Country, year		
Sample size (males/females)		
Median age, y (range)		
Design		
Include or exclude		
Reason(s) for exclusion		
Follow-up (mean and range) (months)		
Tumor location		
Tumor size(cm)		
Tumor stage		
Surgery procedure		
Adjuvant treatment		
Primary outcomes: 1. Overall recurrence rate 2. Local recurrence rate (ipsilateral lung, ipsilateral pleura, trachea, etc.) 3. Distant metastasis rate (contralateral lung, contralateral pleura, bone, liver, etc.)		
Second outcomes: 1. Regional recurrence rate 2. Lymph node metastasis rate		

BMJ Open

Protocol for a systematic review and meta-analysis of recurrence and metastasis of different surgical techniques for non-small cell lung cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086503.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Jul-2024
Complete List of Authors:	Huang, Xiongfeng; Fuzhou Medical College, Nanchang University Zhu, Donghong; The Ninth Hospital of Nanchang, Department of Respiratory Cao, Yaoxing; Jiangxi College of Traditional Chinese Medicine Li, Weijuan; Fuzhou Medical College, Nanchang University Lai, Jinxing; Affiliated Ganzhou Hospital of Nanchang University Ren, Yuxi; Jiangxi University of Traditional Chinese Medicine
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	Lung Diseases, ONCOLOGY, SURGERY, Meta-Analysis

Protocol for a systematic review and meta-analysis of recurrence and metastasis of different surgical techniques for non-small cell lung cancer

Xiongfeng Huang[1], Donghong Zhu[2], Yaoxing Cao[3], Weijuan Li[1], Jinxing Lai[4], Yuxi Ren[5]*

1. Fuzhou Medical College, Nanchang University, Fuzhou, China.
2. Department of Respiratory, The Ninth Hospital of Nanchang, Nanchang, China.
3. Jiangxi College of Traditional Chinese Medicine, Fuzhou, China.
4. Affiliated Ganzhou Hospital of Nanchang University, Ganzhou, China.
5. Jiangxi University of Traditional Chinese Medicine, Nanchang, China.

***Correspondence:** Yuxi Ren. E-mail: renyuxi009@163.com

ABSTRACT

Introduction

Lung cancer remains the primary cause of cancer-related deaths on a global scale. Surgery is the main therapeutic option for non-small cell lung cancer (NSCLC). However, the optimal surgical approach for lymph node assessment in NSCLC resection remains controversial, and it's still uncertain whether lymph node dissection (LND) is more effective in reducing recurrence and metastasis rates in NSCLC compared to lymph node sampling (LNS). Therefore, we will conduct a meta-analysis to evaluate the recurrence and metastasis of LND versus LNS in patients with NSCLC.

Methods and analysis

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement. According to the predefined inclusion criteria, we will conduct a comprehensive search for randomized controlled trials (RCTs) and non-randomized studies examining the recurrence and metastasis of LND compared to LNS in patients with NSCLC. A literature search from inception in PubMed, EMBASE, the Cochrane Library, CNKI, WanFang, Sinomed, VIP, and Web of Science. There will be no limitations on language, and the search will

be undertaken on 30 August 2024 with regular search for new studies. Additionally, relevant literature references will be retrieved and hand searching of pertinent journals will be conducted. The main outcomes include overall recurrence rate, local recurrence rate, and distant metastasis rate. The supplementary outcomes encompass the rates of regional recurrence and lymph node metastasis. Two independent reviewers will perform screening, data extraction, and quality assessment. Our reviewers will perform subgroup analysis, sensitivity analysis, and publication bias analysis to evaluate the heterogeneity and robustness. Review Manager 5.4 will be applied in analyzing and synthesizing. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to assess the quality of evidence for the whole study.

Ethics and dissemination

Ethical approval is dispensable for this study since no private information of the participants will be involved. The findings of the present study will be disseminated through a peer-reviewed journal or conference presentation.

Study registration

The protocol of the systematic review has been registered on Open Science Framework, with a registration DOI https://doi.org/10.17605/OSF.IO/S2FT5.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
- To minimize the risk of bias, two researchers will independently carry out the study selection, data extraction, and quality assessment.
- Non-randomized studies may introduce methodological limitations and affect the overall quality of evidence.
- The potential existence of significant heterogeneity among various studies could hinder the derivation of causal conclusions from their combined findings.
- Because our search will focus primarily on English and Chinese databases, there is a possibility of overlooking studies in other languages, which could result in language bias.

INTRODUCTION

Non-small cell lung cancer (NSCLC), the predominant form of lung malignancy, continues to pose a significant threat to global health. In 2024, the American Cancer Society estimated that lung cancer is the leading cause of cancer death, with an estimated 340 people dying from lung cancer every day, almost 2.5 times more than colorectal cancer, which ranks second in cancer deaths.[1] Lung cancer remains the primary cause of cancer-related deaths on a global scale.[2-5]

Surgical resection plays a crucial role in the management of NSCLC, and lymph node staging is essential for accurate prognostication and treatment planning. Lymph node dissection (LND) and lymph node sampling (LNS) are two surgical techniques used for NSCLC, but their relative effectiveness remains controversial.[6-15] LNS involves the removal of a smaller number of lymph nodes for pathological examination. This approach is generally less invasive, leading to shorter operative times and potentially fewer postoperative complications.[16] However, it may not provide as comprehensive nodal staging as dissection, leading to potential underestimation of the disease stage. LND, conversely, involves the complete removal of lymph nodes and surrounding tissue in specific anatomic regions. This approach offers a comprehensive assessment of nodal involvement, allowing for more accurate staging and potentially improving long-term outcomes. However, it is a more invasive procedure that may increase the risk of post-operative complications, which may result in a reduction in postoperative quality of life for patients. Furthermore, for some patients with early NSCLC, the incidence of lymph node metastasis is not very high, and most patients may not have regional lymph node metastasis. Thus, the necessity of performing complete and systematic lymph node dissection in patients with NSCLC and whether the expected clinical effect can be achieved remains controversial.

Patients with NSCLC continue to experience a notable rate of recurrence and metastasis following surgical intervention, thereby impacting their overall survival outcomes. A meta-analysis of 11 observational studies showed that surgery decreased the risk of NSCLC recurrence in stage I−IV. [17] And several studies have compared

the recurrence and metastasis of LND and LNS in NSCLC surgery. Based on three previous studies,[18-20] LND has been shown to reduce the incidence of recurrence and metastasis in NSCLC. And Meng et al.[21] have posited in their meta-analysis that the use of LND may be effective in eliminating hidden micrometastases to reduce the risk of both local recurrence and distant metastases. However, the results of our previous meta-analysis indicated that in individuals with NSCLC, LND and LNS yielded similar rates of recurrence and metastasis.[22] Additionally, other studies have also shown that lymph node dissection conducted in lung cancer does not impact the occurrence of recurrence and metastasis.[23-25]

The optimal surgical approach for lymph node assessment in NSCLC resection remains controversial, and it's still uncertain whether LND is more effective in reducing recurrence and metastasis rates in NSCLC compared to LNS. Clearly, newer systematic review and meta-analyses are required to resolve this issue, and definitive analyses can provide stronger rationales for the choice of a specific therapy. Consequently, we will perform a meta-analysis of relevant randomized controlled trials (RCTs) and non-randomized studies to evaluate the recurrence and metastasis of LND versus LNS in NSCLC patients. We hope this meta-analysis will offer strong evidence for the surgical treatment of patients with NSCLC and guide future clinical practice.

MATERIALS AND METHODS

Registration and reporting

This review protocol has been officially registered in the Open Science Framework (OSF) database (DOI https://doi.org/10.17605/OSF.IO/S2FT5). And the results will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (supplemental File 1).[26] If there is a change to this protocol, details of the amendment and the reasons for it will be added to OSF. The systematic review and meta-analysis is anticipated to commence on August 30th and conclude on December 30th.

Eligibility criteria

Types of studies

All relevant published RCTs and non-randomized studies will be included. The review will not include certain types of studies, such as methodological papers, editorials, qualitative research, individual case reports, and secondary studies like narrative reviews, systematic reviews and meta-analyses. There will be no restrictions on the language used or the time of publication.

Types of participants

Individuals with NSCLC who received either LND or LNS will be eligible for inclusion, with no limitations based on country, race, ethnicity, age, gender, or occupation.

Type of outcomes

The main outcomes are as follows: overall recurrence rate, local recurrence rate (ipsilateral lung, ipsilateral pleura, trachea, etc.), and distant metastasis rate (contralateral lung, contralateral pleura, bone, liver, etc.). The supplementary outcomes encompass the rates of regional recurrence and lymph node metastasis.

Information source and search strategy

A literature search from inception in PubMed, EMBASE, the Cochrane Library, CNKI, WanFang, Sinomed, VIP, and Web of Science. The Gray Journal includes annual meetings of the American Society of Clinical Oncology and the American Society of Thoracic Surgery (chest surgery), using combinations of the search terms: lymph node dissection, LND, lymph node sampling, LNS, and non–small cell lung cancer, NSCLC. Detailed search strategies are shown in supplemental File 2. There will be no limitations on language, and the search will be undertaken on 30 August 2024 with regular search for new studies. The bibliography of all articles obtained will be examined to identify additional publications that may be pertinent. In addition, abstracts from the American Society of Clinical Oncology and the European Society of Medical Oncology will be searched for potential studies. In order to gather thorough information from qualifying studies, we will contact primary authors to request any pertinent data, such as supplementary materials that may not have been fully disclosed or reported, and information from informal sources related to the research. Two reviewers will examine the reference list and individually choose the studies.

Study Selection

The chosen articles will undergo a dual review process by two separate authors. Following the initial screening of titles and abstracts of papers found through the search strategy, the papers will be sorted into two categories: potentially relevant or not relevant based on the eligibility criteria. Subsequently, efforts will be made to obtain the full texts of all potentially relevant papers, which will then be reviewed against the eligibility criteria. In the event of disagreements during the full-text screening, they will be resolved through discussion. If a consensus cannot be reached, a third author will step in to settle the dispute. The study selection process is illustrated in Figure 1.

Data extraction process

The data will be taken from each full-text article that meets the eligibility criteria: study design; country of study; interventions; outcomes; number and general characteristics of participants, for example, age, and gender. The process of data extraction will be conducted by two reviewers, with Microsoft Excel being employed as the tool for data collection. Any disagreements between the two reviewers will be resolved by discussion or by consulting with the third reviewer, the characteristics of the study are attached as Supplemental File 3.

Dealing with missing data

In cases where data is unavailable, two reviewers will make efforts to contact the original authors via email or phone to request supplementary information. Should the data remain unattainable, the study will be omitted from the analysis. The potential influence of missing data on the comprehensive analysis will be evaluated through sensitivity analysis.

Study risk of bias assessment

Two reviewers will assess the quality of the included studies. Disagreement between the two reviewers will be resolved by discussion with the third reviewer.

We will evaluate the included RCTs' quality using the Cochrane Handbook's "risk of bias" technique.[27] Sequence generation, allocation concealment, blinding, incomplete data, and selective reporting were assessed, and each of them was graded as “yes(+)”, “no(-)” or “unclear(?)”, which reflected low risk of bias, high risk of bias,

and uncertain risk of bias, respectively.[28] The Newcastle-Ottawa scale will be used to evaluate the methodological rigor of non-randomized studies. The Newcastle-Ottawa Scale consists of eight items that are divided into three categories: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each).[29] One star will be given for each item in the selection and outcome domains, and up to two stars will be given for the comparability domain, when a primary study satisfies the methodological required standard. Studies with star values between 0 and 4 will ultimately be classified as having a high risk of bias, studies with scores between 5 and 6 as having a moderate risk of bias, and studies with scores between 7 and 9 as having a low risk of bias.[30]

Patient and public involvement

Since this study will focus on reviewing existing literature, there will be no direct participation of patients or the public. While patients will not be engaged in data collection or analysis for this review, their input, along with that of the public, will be considered in shaping future research stemming from this study.

DATA ANALYSIS

Statistical analysis

Meta-analysis will be planned with sufficient clinically and statistically homogeneous and comparable reported outcomes among studies by pooling data using Review Manager V.5.4 software by The Cochrane Collaboration. Dichotomous data will be compared using a risk ratio (RR) or odds ratio (OR). Respective 95% confidence intervals (CI) will be calculated for each estimate and presented in forest plots.

Statistical heterogeneity will be assessed visually by Q and I^2 statistics.[31] For the Q statistic, a P value<0.10 Will be regarded as statistically significant for heterogeneity. For the I^2 statistic,[32] if there is heterogeneity among the study results (I^2>50%), the heterogeneity source will be further examined. After the exclusion of effects exerted by significant clinical heterogeneity, the random-effects model will be employed for the meta-analysis.[33, 34] If there is no heterogeneity between the study results (I^2< 50%), this study will use the fixed-effect model in terms of meta-analysis.[35, 36] All reported

P-values are 2-sided and values of $P<0.05$ will be regarded as significant for all included studies. In cases of significant heterogeneity encountered during the meta-analysis procedure, several strategies will be implemented. Firstly, a subgroup analysis will be conducted to classify studies according to potential sources of heterogeneity, leading to separate meta-analyses for each subgroup. Secondly, meta-regression techniques will be employed to examine study attributes and pinpoint factors that may be influencing the observed heterogeneity. Lastly, if challenges with high heterogeneity persist, the option of transforming the meta-analysis into a systematic review will be considered, allowing for a qualitative synthesis of studies without quantitative amalgamation.

Assessment of publication bias

The funnel plot will be used to assess reporting bias. A symmetrical funnel shape will suggest the absence of publication bias, whereas an asymmetrical funnel plot will indicate the presence of such bias. An objective assessment of publication bias will be conducted employing Egger's linear regression test, where a p-value less than 0.1 is considered statistically significant, indicating the presence of publication bias.[37, 38] And we will conduct a trim and fill analysis to address any potential publication bias. This method involves excluding outlier studies and estimating hypothetical missing studies to create a balanced funnel plot.

Subgroup and sensitivity analyses

Subgroup analyses will be conducted based on study and population variables, including study type, age, gender, intervention approaches, sample size, and other factors. For sensitivity analysis, studies of poorer methodological quality will be removed to see if their deletion alters the outcomes of the analyses. In particular, we will exclude non-randomized studies deemed to be of low quality (rated between 0 and 4 stars) and those RCTs identified as having a high risk of bias. This methodology will enable us to evaluate the reliability of our findings and pinpoint any potential sources of bias. When heterogeneity is substantial, the leave-one-out method is employed to ascertain whether it arises from a specific study. For instance, to ascertain whether

heterogeneity diminishes, we eliminate one study. This approach is employed to investigate each study individually, in order to identify the root cause of heterogeneity.

Grading the quality of evidence

The evaluation of the evidence's quality throughout the entire study will be conducted utilizing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework.[39-41] This system is frequently employed to evaluate the credibility of evidence and determine the level of recommendations. Two independent reviewers will employ the five GRADE considerations, including the risk of bias, consistency of effect, imprecision, indirectness, and publication bias, to meticulously evaluate the certainty of the evidence and arrive at sound conclusions.[42, 43] Verification will be carried out upon completion, and any uncertainties will be deliberated among reviewers or escalated to a third expert for guidance.

The level of evidence will be assessed and categorized as high, moderate, low, or very low. RCT evidence is initially considered to have a high level of certainty, but this evaluation may be adjusted downwards if factors such as risk of bias, indirectness, inconsistency, imprecision, and publication bias are identified. On the other hand, evidence from observational studies is typically assigned a low level of certainty, but this rating may be elevated if there is evidence for a large magnitude of effect, mitigation of potential bias or confounding factors, leading to an upgrade from the initial low rating. Strong recommendations are made when there is a high level of evidence, while practice considerations are given when there is a moderate level of evidence. When the evidence level is below moderate, it is stated that there is insufficient evidence from scientific literature to provide guidance to policymakers, clinicians, and patients.

Updates to study protocol

If modifications to the review protocol are deemed necessary, these adjustments will be thoroughly documented and incorporated as supplementary material alongside the final manuscript. Additionally, these updates will be reflected on the OSF register for future reference.

Ethics and dissemination

Ethical approval is dispensable for this study since no private information of the participants will be involved. The findings of the present study will be disseminated through a peer-reviewed journal or conference presentation.

Author contributions

XH conceived the study. XH and YC registered the protocol. XH and WL drafted the protocol. YC and JL revised it. XH and YR developed the search strategies and will run them. XH and YR will select studies and extract data. XH and DZ will analyze the data. All authors contributed to the article and approved the submitted version. XH is the guarantor.

Funding

Science and technology project of Fuzhou Medical College of Nanchang University (fykj202404); Science and technology project of Jiangxi Provincial Administration of Traditional Chinese Medicine (2023A0289); Science and technology project of Jiangxi Provincial Administration of Traditional Chinese Medicine (2022B1103); Jiangxi Province key research and development program (2020YBBGWL001), Jiangxi Provincial Department of Education Science and Technology research key project (GJJ208902).

Competing interests

The authors declare no conflict of interest.

Word count

2314 words

REFERENCES

1. Siegel RL, Giaquinto AN. Cancer statistics, 2024. *CA: a cancer journal for clinicians* 2024;74(1):12-49. doi: 10.3322/caac.21820

2. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. *Clinics in chest medicine* 2020;41(1):1-24. doi: 10.1016/j.ccm.2019.10.001 [published Online First: 2020/02/06]

3. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *The New England journal of medicine*

2008;359(13):1367-80. doi: 10.1056/NEJMra0802714 [published Online First: 2008/09/26]

4. Gridelli C, Rossi A, Maione P, et al. Vaccines for the treatment of non-small cell lung cancer: a renewed anticancer strategy. *The oncologist* 2009;14(9):909-20. doi: 10.1634/theoncologist.2009-0017 [published Online First: 2009/09/04]

5. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA: a cancer journal for clinicians* 2011;61(2):69-90. doi: 10.3322/caac.20107 [published Online First: 2011/02/08]

6. Xu J, Lai J, Huang X. Survival outcomes following complete mediastinal lymphadenectomy or selective mediastinal lymphadenectomy in patients with stage I-IIIA non-small cell lung cancer: protocol for a systematic review and meta-analysis. *BMJ Open* 2024;14(3):e084520. doi: 10.1136/bmjopen-2024-084520

7. Zhang Y, Deng C, Zheng Q, et al. Selective Mediastinal Lymph Node Dissection Strategy for Clinical T1N0 Invasive Lung Cancer: A Prospective, Multicenter, Clinical Trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2023;18(7):931-39. doi: 10.1016/j.jtho.2023.02.010 [published Online First: 2023/02/26]

8. Wang Y, Darling GE. Complete mediastinal lymph node dissection versus systematic lymph node sampling in surgical treatment of non-small cell lung cancer: do we have the answer? *Journal of thoracic disease* 2017;9(11):4169-70. doi: 10.21037/jtd.2017.10.39 [published Online First: 2017/12/23]

9. Xu F, Qi L, Yue D, et al. The effect of the extent of lymph node dissection for stage IA non-small-cell lung cancer on patient disease-free survival. *Clinical lung cancer* 2013;14(2):181-7. doi: 10.1016/j.cllc.2012.09.002 [published Online First: 2012/12/01]

10. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in medicine* 1998;17(24):2815-34. doi: 10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8 [published Online First: 1999/01/28]

11. Ou SH, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2008;3(8):880-6. doi: 10.1097/JTO.0b013e31817dfced [published Online First: 2008/08/02]

12. Wang Z, Qi Z, Cheng D, et al. Lobe-Specific Node Dissection Can Be a Suitable Alternative to Systematic Lymph Node Dissection in Highly Selective Early-Stage Non-Small-Cell Lung Cancer Patients: A Meta-Analysis. *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia* 2021;27(3):143-50. doi: 10.5761/atcs.oa.20-00136 [published Online First: 2020/12/08]

13. Tantraworasin A, Saeteng S, Siwachat S, et al. Impact of lymph node management on resectable non-small cell lung cancer patients. *Journal of thoracic disease* 2017;9(3):666-74. doi: 10.21037/jtd.2017.02.90 [published Online First: 2017/04/30]

14. Yang M, Cao H, Guo X, et al. The number of resected lymph nodes (nLNs) combined with tumor size as a prognostic factor in patients with pathologic N0 and Nx non-small cell lung cancer. *PloS one* 2013;8(9):e73220. doi: 10.1371/journal.pone.0073220 [published Online First: 2013/09/12]

15. Wang W, Chen D, Xi K, et al. Impact of Different Types of Lymphadenectomy Combined With Different Extents of Tumor Resection on Survival Outcomes of Stage I Non-small-cell Lung Cancer: A Large-Cohort Real-World Study. *Frontiers in oncology* 2019;9:642. doi: 10.3389/fonc.2019.00642 [published Online First: 2019/08/10]

16. Dezube AR, Mazzola E, Bravo-Iñiguez CE, et al. Analysis of Lymph Node Sampling Minimums in Early Stage Non-Small-Cell Lung Cancer. *Seminars in thoracic and cardiovascular surgery* 2021;33(3):834-45. doi: 10.1053/j.semtcvs.2020.11.007 [published Online First: 2020/11/13]

17. Hu J, Miao H, Li R, et al. Surgery and subsequent risk of non-small cell lung cancer recurrence: a meta-analysis of observational studies. *Translational cancer research* 2020;9(3):1960-68. doi: 10.21037/tcr.2020.02.15

18. Wu Y, Huang ZF, Wang SY, et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung cancer (Amsterdam, Netherlands)* 2002;36(1):1-6. doi: 10.1016/s0169-5002(01)00445-7 [published Online First: 2002/03/14]

19. Su X, Wang X, Long H, et al. Mediastinal lymph node dissection affects survival in patients with stage I non-small cell lung cancer. *The Thoracic and cardiovascular surgeon* 2008;56(4):226-30. doi: 10.1055/s-2007-989494 [published Online First: 2008/05/16]

20. Lardinois D, Suter H, Hakki H, et al. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell

lung cancer. *The Annals of thoracic surgery* 2005;80(1):268-74; discussion 74-5. doi: 10.1016/j.athoracsur.2005.02.005 [published Online First: 2005/06/25]

21. Meng D, Zhou Z, Wang Y, et al. Lymphadenectomy for clinical early-stage non-small-cell lung cancer: a systematic review and meta-analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2016;50(4):597-604. doi: 10.1093/ejcts/ezw083 [published Online First: 2016/04/24]
22. Huang X, Wang J, Chen Q, et al. Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis. *PloS one* 2014;9(10):e109979. doi: 10.1371/journal.pone.0109979 [published Online First: 2014/10/09]
23. Mokhles S, Macbeth F, Treasure T, et al. Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small-cell lung cancer: a systematic review of randomized trials and a meta-analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2017;51(6):1149-56. doi: 10.1093/ejcts/ezw439 [published Online First: 2017/02/06]
24. Luo J, Yang S, Dong S. Selective Mediastinal Lymphadenectomy or Complete Mediastinal Lymphadenectomy for Clinical Stage I Non-Small Cell Lung Cancer: A Meta-Analysis. 2021;38(12):5671-83. doi: 10.1007/s12325-021-01954-w
25. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *The Journal of thoracic and cardiovascular surgery* 2011;141(3):662-70. doi: 10.1016/j.jtcvs.2010.11.008 [published Online First: 2011/02/22]
26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4(1):1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]
27. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). *Cochrane* 2023
28. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)* 2011;343:d5928. doi:

10.1136/bmj.d5928 [published Online First: 2011/10/20]

29. Wells G, Shea B, O'Connell D, et al. The newcastle-ottawa scale(NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2020

30. Luchini C, Stubbs B, Solmi M, et al. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017(4):80-84.

31. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. *Jama* 2006;295(6):676-80. doi: 10.1001/jama.295.6.676 [published Online First: 2006/02/10]

32. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]

33. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemporary clinical trials* 2015;45(Pt A):139-45. doi: 10.1016/j.cct.2015.09.002 [published Online First: 2015/09/08]

34. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemporary clinical trials* 2007;28(2):105-14. doi: 10.1016/j.cct.2006.04.004 [published Online First: 2006/06/30]

35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]

36. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;22(4):719-48. [published Online First: 1959/04/01]

37. Cumpston MS, McKenzie JE, Welch VA, et al. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. *Journal of public health (Oxford, England)* 2022;44(4):e588-e92. doi: 10.1093/pubmed/fdac036 [published Online First: 2022/03/31]

38. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ (Clinical research ed)* 2001;323(7304):101-5. doi: 10.1136/bmj.323.7304.101 [published Online First: 2001/07/14]

39. Langer G, Meerpohl JJ, Perleth M, et al. [GRADE guidelines: 12. Developing Summary of Findings tables - dichotomous outcomes]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im*

Gesundheitswesen 2013;107(9-10):646-64. doi: 10.1016/j.zefq.2013.10.034 [published Online First: 2013/12/10]

40. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)* 2008;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE [published Online First: 2008/05/06]
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of clinical epidemiology* 2011;64(4):395-400. doi: 10.1016/j.jclinepi.2010.09.012 [published Online First: 2011/01/05]
42. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]
43. H S, Brozek J, Oxman AE. GRADE handbook for grading quality of evidence and strength of recommendation. 2009

Appendices

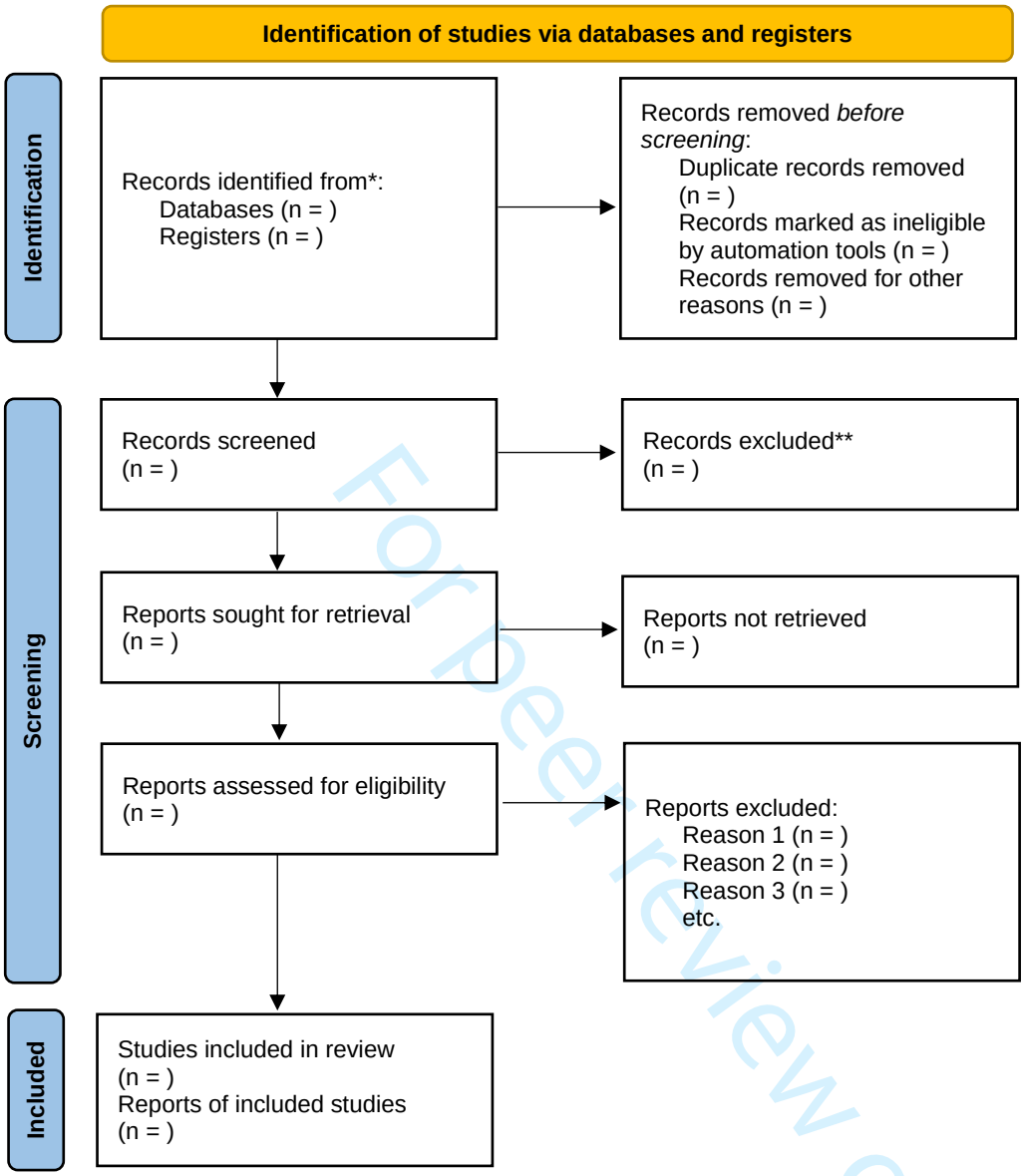
Fig 1. Flow diagram showing the selection process of articles.

Supplemental File 1. PRISMA-P-checklist.

Supplemental File 2. Search strategy.

Supplemental File 3. General information of the included studies.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	P8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. Search strategy

1. PubMed

Number	Search terms
#1	Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung OR Non-Small Cell Lung Cancer OR Lung Neoplasms OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Non-Small-Cell Lung OR Lung Carcinoma OR Non-Small-Cell OR Lung Carcinomas OR NSCLC [Title/Abstract]
#2	Surgical Procedures OR Operative OR surgery OR surgery OR surgical OR operative OR postoperative [Title/Abstract]
#3	lymphadenectomy OR lymphadenectomy OR complete mediastinal lymphadenectomy OR mediastinal lymph node excision OR lobe-specific lymph node dissection OR mediastinal lymph node dissection OR mediastinal lymph node sampling OR lymph node dissection OR lymph node OR dissect OR sample OR selective mediastinal lymphadenectomy OR systematic lymph node dissection OR selective lymph node dissection OR LND OR LNS [Title/Abstract]
#4	randomly OR randomized OR RCT OR trials OR cohort OR longitudinal OR prospective OR survival [Title/Abstract]
#5	#1 AND #2 AND #3 AND #4 [Title/Abstract]

2. Embase

Number	Search terms
#1	Non-Small-Cell:ti,ab,kw OR Non-Small-Cell Lung Carcinomas:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Non-Small-Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Lung Neoplasms:ti,ab,kw OR Pulmonary Neoplasms:ti,ab,kw OR Lung Neoplasm:ti,ab,kw OR Pulmonary Neoplasm:ti,ab,kw OR Lung Cancer:ti,ab,kw OR Lung Cancers:ti,ab,kw OR Pulmonary Cancer:ti,ab,kw OR Pulmonary Cancers:ti,ab,kw OR Cancer of the Lung:ti,ab,kw OR Cancer of Lung:ti,ab,kw OR Non-Small-Cell Lung:ti,ab,kw OR Lung Carcinoma:ti,ab,kw OR Non-Small-Cell:ti,ab,kw OR Lung Carcinomas:ti,ab,kw OR NSCLC:ti,ab,kw
#2	Surgical Procedures:ti,ab,kw OR Operative OR surgery:ti,ab,kw OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR operative:ti,ab,kw OR postoperative:ti,ab,kw

#3	lymphadenectomy:ti,ab,kw OR lymphadenectomy:ti,ab,kw OR complete mediastinal lymphadenectomy:ti,ab,kw OR mediastinal lymph node excision:ti,ab,kw OR lobe-specific lymph node dissection:ti,ab,kw OR mediastinal lymph node dissection:ti,ab,kw OR mediastinal lymph node sampling:ti,ab,kw OR lymph node dissection:ti,ab,kw OR lymph node:ti,ab,kw OR dissect:ti,ab,kw OR sample:ti,ab,kw OR selective mediastinal lymphadenectomy:ti,ab,kw OR systematic lymph node dissection:ti,ab,kw OR selective lymph node dissection:ti,ab,kw OR LND:ti,ab,kw OR LNS:ti,ab,kw
#4	randomly:ti,ab,kw OR randomized:ti,ab,kw OR RCT:ti,ab,kw OR trials:ti,ab,kw OR cohort:ti,ab,kw OR longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR survival:ti,ab,kw
#5	#1 AND #2 AND #3 AND #4

3. Cochrane Library

Number	Search terms
#1	Non-Small-Cell:ti,ab,kw OR Non-Small-Cell Lung Carcinomas:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Non-Small-Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Lung Neoplasms:ti,ab,kw OR Pulmonary Neoplasms:ti,ab,kw OR Lung Neoplasm:ti,ab,kw OR Pulmonary Neoplasm:ti,ab,kw OR Lung Cancer:ti,ab,kw OR Lung Cancers:ti,ab,kw OR Pulmonary Cancer:ti,ab,kw OR Pulmonary Cancers:ti,ab,kw OR Cancer of the Lung:ti,ab,kw OR Cancer of Lung:ti,ab,kw OR Non-Small-Cell Lung:ti,ab,kw OR Lung Carcinoma:ti,ab,kw OR Non-Small-Cell:ti,ab,kw OR Lung Carcinomas:ti,ab,kw OR NSCLC:ti,ab,kw
#2	Surgical Procedures:ti,ab,kw OR Operative OR surgery:ti,ab,kw OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR operative:ti,ab,kw OR postoperative:ti,ab,kw
#3	lymphadenectomy:ti,ab,kw OR lymphadenectomy:ti,ab,kw OR complete mediastinal lymphadenectomy:ti,ab,kw OR mediastinal lymph node excision:ti,ab,kw OR lobe-specific lymph node dissection:ti,ab,kw OR mediastinal lymph node dissection:ti,ab,kw OR mediastinal lymph node sampling:ti,ab,kw OR lymph node dissection:ti,ab,kw OR lymph node:ti,ab,kw OR dissect:ti,ab,kw OR sample:ti,ab,kw OR selective mediastinal lymphadenectomy:ti,ab,kw OR systematic lymph node dissection:ti,ab,kw OR selective lymph node dissection:ti,ab,kw OR LND:ti,ab,kw OR LNS:ti,ab,kw
#4	randomly:ti,ab,kw OR randomized:ti,ab,kw OR RCT:ti,ab,kw OR trials:ti,ab,kw OR cohort:ti,ab,kw OR longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR survival:ti,ab,kw

#5	#1 AND #2 AND #3 AND #4

4. Web of Science

Number	Search terms
#1	TS=(Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung OR Non-Small Cell Lung Cancer OR Lung Neoplasms OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Non-Small-Cell Lung OR Lung Carcinoma OR Non-Small-Cell OR Lung Carcinomas OR NSCLC)
#2	TS=(Surgical Procedures OR Operative OR surgery OR surgery OR surgical OR operative OR postoperative)
#3	TS=(lymphadenectomy OR lymphadenectomy OR complete mediastinal lymphadenectomy OR mediastinal lymph node excision OR lobe-specific lymph node dissection OR mediastinal lymph node dissection OR mediastinal lymph node sampling OR lymph node dissection OR lymph node OR dissect OR sample OR selective mediastinal lymphadenectomy OR systematic lymph node dissection OR selective lymph node dissection OR LND OR LNS)
#4	TS=(randomly OR randomized OR RCT OR trials OR cohort OR longitudinal OR prospective OR survival)
#5	#1 AND #2 AND #3 AND #4

5. China National Knowledge Infrastructure (CNKI) (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

6. WANFANG DATA (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

7. Chinese biomedical literature service system (Sinomed) (Chinese)

Search terms
("非小细胞肺癌" [常用字段:智能] OR "肺癌" [常用字段:智能]) AND ("肺癌"[常用字段:智能]) AND ("随机对照试验"[常用字段:智能]) AND ("淋巴结清扫方式"[全部字段:智能] OR "系统性淋巴结清扫"[全部字段:智能]OR "选择性淋巴结清扫"[全部字段:智能] OR "叶特异性淋巴结清扫"[全部字段:智能] OR "纵膈淋巴结采样"[全部字段:智能])

8. VIP database (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

Supplemental File 3. General information of the included studies.

First author		
Country, year		
Sample size (males/females)		
Median age, y (range)		
Design		
Include or exclude		
Reason(s) for exclusion		
Follow-up (mean and range) (months)		
Tumor location		
Tumor size(cm)		
Tumor stage		
Surgery procedure		
Adjuvant treatment		
Primary outcomes: 1. Overall recurrence rate 2. Local recurrence rate (ipsilateral lung, ipsilateral pleura, trachea, etc.) 3. Distant metastasis rate (contralateral lung, contralateral pleura, bone, liver, etc.)		
Second outcomes: 1. Regional recurrence rate 2. Lymph node metastasis rate		

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	P8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Protocol for a systematic review and meta-analysis of recurrence and metastasis of different surgical techniques for non-small cell lung cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-086503.R2
Article Type:	Protocol
Date Submitted by the Author:	31-Jul-2024
Complete List of Authors:	Huang, Xiongfeng; Fuzhou Medical College, Nanchang University Zhu, Donghong; The Ninth Hospital of Nanchang, Department of Respiratory Cao, Yaoxing; Jiangxi College of Traditional Chinese Medicine Li, Weijuan; Fuzhou Medical College, Nanchang University Lai, Jinxing; Affiliated Ganzhou Hospital of Nanchang University Ren, Yuxi; Jiangxi University of Traditional Chinese Medicine
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	Lung Diseases, ONCOLOGY, SURGERY, Meta-Analysis

Protocol for a systematic review and meta-analysis of recurrence and metastasis of different surgical techniques for non-small cell lung cancer

Xiongfeng Huang[1], Donghong Zhu[2], Yaoxing Cao[3], Weijuan Li[1], Jinxing Lai[4], Yuxi Ren[5]*

1. Fuzhou Medical College, Nanchang University, Fuzhou, China.
2. Department of Respiratory, The Ninth Hospital of Nanchang, Nanchang, China.
3. Jiangxi College of Traditional Chinese Medicine, Fuzhou, China.
4. Affiliated Ganzhou Hospital of Nanchang University, Ganzhou, China.
5. Jiangxi University of Traditional Chinese Medicine, Nanchang, China.

***Correspondence:** Yuxi Ren. E-mail: renyuxi009@163.com

ABSTRACT

Introduction

Lung cancer remains the primary cause of cancer-related deaths on a global scale. Surgery is the main therapeutic option for non-small cell lung cancer (NSCLC). However, the optimal surgical approach for lymph node assessment in NSCLC resection remains controversial, and it's still uncertain whether lymph node dissection (LND) is more effective in reducing recurrence and metastasis rates in NSCLC compared to lymph node sampling (LNS). Therefore, we will conduct a meta-analysis to evaluate the recurrence and metastasis of LND versus LNS in patients with NSCLC.

Methods and analysis

This systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement. According to the predefined inclusion criteria, we will conduct a comprehensive search for randomized controlled trials (RCTs) and non-randomized studies examining the recurrence and metastasis of LND compared to LNS in patients with NSCLC. A literature search from inception in PubMed, EMBASE, the Cochrane Library, CNKI, WanFang, Sinomed, VIP, and Web of Science. There will be no limitations on language, and the search will

be undertaken on 30 August 2024 with regular search for new studies. Additionally, relevant literature references will be retrieved and hand searching of pertinent journals will be conducted. The main outcomes include overall recurrence rate, local recurrence rate, and distant metastasis rate. The supplementary outcomes encompass the rates of regional recurrence and lymph node metastasis. Two independent reviewers will perform screening, data extraction, and quality assessment. Our reviewers will perform subgroup analysis, sensitivity analysis, and publication bias analysis to evaluate the heterogeneity and robustness. Review Manager 5.4 will be applied in analyzing and synthesizing. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) will be used to assess the quality of evidence for the whole study.

Ethics and dissemination

Ethical approval is dispensable for this study since no private information of the participants will be involved. The findings of the present study will be disseminated through a peer-reviewed journal or conference presentation.

Study registration

The protocol of the systematic review has been registered on Open Science Framework, with a registration DOI https://doi.org/10.17605/OSF.IO/S2FT5.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system will be utilized to evaluate the quality of the evidence.
- To minimize the risk of bias, two researchers will independently carry out the study selection, data extraction, and quality assessment.
- Non-randomized studies may introduce methodological limitations and affect the overall quality of evidence.
- The potential existence of significant heterogeneity among various studies could hinder the derivation of causal conclusions from their combined findings.
- Because our search will focus primarily on English and Chinese databases, there is a possibility of overlooking studies in other languages, which could result in language bias.

INTRODUCTION

Non-small cell lung cancer (NSCLC), the predominant form of lung malignancy, continues to pose a significant threat to global health. In 2024, the American Cancer Society estimated that lung cancer is the leading cause of cancer death, with an estimated 340 people dying from lung cancer every day, almost 2.5 times more than colorectal cancer, which ranks second in cancer deaths.[1] Lung cancer remains the primary cause of cancer-related deaths on a global scale.[2-5]

Surgical resection plays a crucial role in the management of NSCLC, and lymph node staging is essential for accurate prognostication and treatment planning. Lymph node dissection (LND) and lymph node sampling (LNS) are two surgical techniques used for NSCLC, but their relative effectiveness remains controversial.[6-15] LNS involves the removal of a smaller number of lymph nodes for pathological examination. This approach is generally less invasive, leading to shorter operative times and potentially fewer postoperative complications.[16] However, it may not provide as comprehensive nodal staging as dissection, leading to potential underestimation of the disease stage. LND, conversely, involves the complete removal of lymph nodes and surrounding tissue in specific anatomic regions. This approach offers a comprehensive assessment of nodal involvement, allowing for more accurate staging and potentially improving long-term outcomes. However, it is a more invasive procedure that may increase the risk of post-operative complications, which may result in a reduction in postoperative quality of life for patients. Furthermore, for some patients with early NSCLC, the incidence of lymph node metastasis is not very high, and most patients may not have regional lymph node metastasis. Thus, the necessity of performing complete and systematic lymph node dissection in patients with NSCLC and whether the expected clinical effect can be achieved remains controversial.

Patients with NSCLC continue to experience a notable rate of recurrence and metastasis following surgical intervention, thereby impacting their overall survival outcomes. A meta-analysis of 11 observational studies showed that surgery decreased the risk of NSCLC recurrence in stage I−IV. [17] And several studies have compared

the recurrence and metastasis of LND and LNS in NSCLC surgery. Based on three previous studies,[18-20] LND has been shown to reduce the incidence of recurrence and metastasis in NSCLC. And Meng et al.[21] have posited in their meta-analysis that the use of LND may be effective in eliminating hidden micrometastases to reduce the risk of both local recurrence and distant metastases. However, the results of our previous meta-analysis indicated that in individuals with NSCLC, LND and LNS yielded similar rates of recurrence and metastasis.[22] Additionally, other studies have also shown that lymph node dissection conducted in lung cancer does not impact the occurrence of recurrence and metastasis.[23-25]

The optimal surgical approach for lymph node assessment in NSCLC resection remains controversial, and it's still uncertain whether LND is more effective in reducing recurrence and metastasis rates in NSCLC compared to LNS. Clearly, newer systematic review and meta-analyses are required to resolve this issue, and definitive analyses can provide stronger rationales for the choice of a specific therapy. Consequently, we will perform a meta-analysis of relevant randomized controlled trials (RCTs) and non-randomized studies to evaluate the recurrence and metastasis of LND versus LNS in NSCLC patients. We hope this meta-analysis will offer strong evidence for the surgical treatment of patients with NSCLC and guide future clinical practice.

MATERIALS AND METHODS

Registration and reporting

This review protocol has been officially registered in the Open Science Framework (OSF) database (DOI https://doi.org/10.17605/OSF.IO/S2FT5). The checklist for the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) can be found in Supplemental File 1. [26] If there is a change to this protocol, details of the amendment and the reasons for it will be added to OSF. The systematic review and meta-analysis is anticipated to commence on August 30th and conclude on December 30th.

Eligibility criteria

Types of studies

All relevant published RCTs and non-randomized studies will be included. The review will not include certain types of studies, such as methodological papers, editorials, qualitative research, individual case reports, and secondary studies like narrative reviews, systematic reviews and meta-analyses. There will be no restrictions on the language used or the time of publication.

Types of participants

Individuals with NSCLC who received either LND or LNS will be eligible for inclusion, with no limitations based on country, race, ethnicity, age, gender, or occupation.

Type of outcomes

The main outcomes are as follows: overall recurrence rate, local recurrence rate (ipsilateral lung, ipsilateral pleura, trachea, etc.), and distant metastasis rate (contralateral lung, contralateral pleura, bone, liver, etc.). The supplementary outcomes encompass the rates of regional recurrence and lymph node metastasis.

Information source and search strategy

A literature search from inception in PubMed, EMBASE, the Cochrane Library, CNKI, WanFang, Sinomed, VIP, and Web of Science. The Gray Journal includes annual meetings of the American Society of Clinical Oncology and the American Society of Thoracic Surgery (chest surgery), using combinations of the search terms: lymph node dissection, LND, lymph node sampling, LNS, and non–small cell lung cancer, NSCLC. Detailed search strategies are shown in supplemental File 2. There will be no limitations on language, and the search will be undertaken on 30 August 2024 with regular search for new studies. The bibliography of all articles obtained will be examined to identify additional publications that may be pertinent. In addition, abstracts from the American Society of Clinical Oncology and the European Society of Medical Oncology will be searched for potential studies. In order to gather thorough information from qualifying studies, we will contact primary authors to request any pertinent data, such as supplementary materials that may not have been fully disclosed or reported, and information from informal sources related to the research. Two reviewers will examine the reference list and individually choose the studies.

Study Selection

The chosen articles will undergo a dual review process by two separate authors. Following the initial screening of titles and abstracts of papers found through the search strategy, the papers will be sorted into two categories: potentially relevant or not relevant based on the eligibility criteria. Subsequently, efforts will be made to obtain the full texts of all potentially relevant papers, which will then be reviewed against the eligibility criteria. In the event of disagreements during the full-text screening, they will be resolved through discussion. If a consensus cannot be reached, a third author will step in to settle the dispute. The study selection process is illustrated in Figure 1.

Data extraction process

The data will be taken from each full-text article that meets the eligibility criteria: study design; country of study; interventions; outcomes; number and general characteristics of participants, for example, age, and gender. The process of data extraction will be conducted by two reviewers, with Microsoft Excel being employed as the tool for data collection. Any disagreements between the two reviewers will be resolved by discussion or by consulting with the third reviewer, the characteristics of the study are attached as Supplemental File 3.

Dealing with missing data

In cases where data is unavailable, two reviewers will make efforts to contact the original authors via email or phone to request supplementary information. Should the data remain unattainable, the study will be omitted from the analysis. The potential influence of missing data on the comprehensive analysis will be evaluated through sensitivity analysis.

Study risk of bias assessment

Two reviewers will assess the quality of the included studies. Disagreement between the two reviewers will be resolved by discussion with the third reviewer.

We will evaluate the included RCTs' quality using the Cochrane Handbook's "risk of bias" technique.[27] Sequence generation, allocation concealment, blinding, incomplete data, and selective reporting were assessed, and each of them was graded as “yes(+)”, “no(-)” or “unclear(?)”, which reflected low risk of bias, high risk of bias,

and uncertain risk of bias, respectively.[28] The Newcastle-Ottawa scale will be used to evaluate the methodological rigor of non-randomized studies. The Newcastle-Ottawa Scale consists of eight items that are divided into three categories: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each).[29] One star will be given for each item in the selection and outcome domains, and up to two stars will be given for the comparability domain, when a primary study satisfies the methodological required standard. Studies with star values between 0 and 4 will ultimately be classified as having a high risk of bias, studies with scores between 5 and 6 as having a moderate risk of bias, and studies with scores between 7 and 9 as having a low risk of bias.[30]

Patient and public involvement

Since this study will focus on reviewing existing literature, there will be no direct participation of patients or the public. While patients will not be engaged in data collection or analysis for this review, their input, along with that of the public, will be considered in shaping future research stemming from this study.

DATA ANALYSIS

Statistical analysis

Meta-analysis will be planned with sufficient clinically and statistically homogeneous and comparable reported outcomes among studies by pooling data using Review Manager V.5.4 software by The Cochrane Collaboration. Dichotomous data will be compared using a risk ratio (RR) or odds ratio (OR). Respective 95% confidence intervals (CI) will be calculated for each estimate and presented in forest plots.

Statistical heterogeneity will be assessed visually by Q and I^2 statistics.[31] For the Q statistic, a P value<0.10 Will be regarded as statistically significant for heterogeneity. For the I^2 statistic,[32] if there is heterogeneity among the study results (I^2>50%), the heterogeneity source will be further examined. After the exclusion of effects exerted by significant clinical heterogeneity, the random-effects model will be employed for the meta-analysis.[33, 34] If there is no heterogeneity between the study results (I^2< 50%), this study will use the fixed-effect model in terms of meta-analysis.[35, 36] All reported

P-values are 2-sided and values of $P<0.05$ will be regarded as significant for all included studies. In cases of significant heterogeneity encountered during the meta-analysis procedure, several strategies will be implemented. Firstly, a subgroup analysis will be conducted to classify studies according to potential sources of heterogeneity, leading to separate meta-analyses for each subgroup. Secondly, meta-regression techniques will be employed to examine study attributes and pinpoint factors that may be influencing the observed heterogeneity. Lastly, if challenges with high heterogeneity persist, the option of transforming the meta-analysis into a systematic review will be considered, allowing for a qualitative synthesis of studies without quantitative amalgamation.

Assessment of publication bias

The funnel plot will be used to assess reporting bias. A symmetrical funnel shape will suggest the absence of publication bias, whereas an asymmetrical funnel plot will indicate the presence of such bias. An objective assessment of publication bias will be conducted employing Egger's linear regression test, where a p-value less than 0.1 is considered statistically significant, indicating the presence of publication bias.[37, 38] And we will conduct a trim and fill analysis to address any potential publication bias. This method involves excluding outlier studies and estimating hypothetical missing studies to create a balanced funnel plot.

Subgroup and sensitivity analyses

Subgroup analyses will be conducted based on study and population variables, including study type, age, gender, intervention approaches, sample size, and other factors. For sensitivity analysis, studies of poorer methodological quality will be removed to see if their deletion alters the outcomes of the analyses. In particular, we will exclude non-randomized studies deemed to be of low quality (rated between 0 and 4 stars) and those RCTs identified as having a high risk of bias. This methodology will enable us to evaluate the reliability of our findings and pinpoint any potential sources of bias. When heterogeneity is substantial, the leave-one-out method is employed to ascertain whether it arises from a specific study. For instance, to ascertain whether

heterogeneity diminishes, we eliminate one study. This approach is employed to investigate each study individually, in order to identify the root cause of heterogeneity.

Grading the quality of evidence

The evaluation of the evidence's quality throughout the entire study will be conducted utilizing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework.[39-41] This system is frequently employed to evaluate the credibility of evidence and determine the level of recommendations. Two independent reviewers will employ the five GRADE considerations, including the risk of bias, consistency of effect, imprecision, indirectness, and publication bias, to meticulously evaluate the certainty of the evidence and arrive at sound conclusions.[42, 43] Verification will be carried out upon completion, and any uncertainties will be deliberated among reviewers or escalated to a third expert for guidance.

The level of evidence will be assessed and categorized as high, moderate, low, or very low. RCT evidence is initially considered to have a high level of certainty, but this evaluation may be adjusted downwards if factors such as risk of bias, indirectness, inconsistency, imprecision, and publication bias are identified. On the other hand, evidence from observational studies is typically assigned a low level of certainty, but this rating may be elevated if there is evidence for a large magnitude of effect, mitigation of potential bias or confounding factors, leading to an upgrade from the initial low rating. Strong recommendations are made when there is a high level of evidence, while practice considerations are given when there is a moderate level of evidence. When the evidence level is below moderate, it is stated that there is insufficient evidence from scientific literature to provide guidance to policymakers, clinicians, and patients.

Updates to study protocol

If modifications to the review protocol are deemed necessary, these adjustments will be thoroughly documented and incorporated as supplementary material alongside the final manuscript. Additionally, these updates will be reflected on the OSF register for future reference.

Ethics and dissemination

Ethical approval is dispensable for this study since no private information of the participants will be involved. The findings of the present study will be disseminated through a peer-reviewed journal or conference presentation.

Author contributions

XH conceived the study. XH and YC registered the protocol. XH and WL drafted the protocol. YC and JL revised it. XH and YR developed the search strategies and will run them. XH and YR will select studies and extract data. XH and DZ will analyze the data. All authors contributed to the article and approved the submitted version. XH is the guarantor.

Funding

Science and technology project of Fuzhou Medical College of Nanchang University (fykj202404); Science and technology project of Jiangxi Provincial Administration of Traditional Chinese Medicine (2023A0289); Science and technology project of Jiangxi Provincial Administration of Traditional Chinese Medicine (2022B1103); Jiangxi Province key research and development program (2020YBBGWL001), Jiangxi Provincial Department of Education Science and Technology research key project (GJJ208902).

Competing interests

The authors declare no conflict of interest.

Word count

2314 words

REFERENCES

1. Siegel RL, Giaquinto AN. Cancer statistics, 2024. *CA: a cancer journal for clinicians* 2024;74(1):12-49. doi: 10.3322/caac.21820

2. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. *Clinics in chest medicine* 2020;41(1):1-24. doi: 10.1016/j.ccm.2019.10.001 [published Online First: 2020/02/06]

3. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *The New England journal of medicine*

2008;359(13):1367-80. doi: 10.1056/NEJMra0802714 [published Online First: 2008/09/26]

4. Gridelli C, Rossi A, Maione P, et al. Vaccines for the treatment of non-small cell lung cancer: a renewed anticancer strategy. *The oncologist* 2009;14(9):909-20. doi: 10.1634/theoncologist.2009-0017 [published Online First: 2009/09/04]

5. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA: a cancer journal for clinicians* 2011;61(2):69-90. doi: 10.3322/caac.20107 [published Online First: 2011/02/08]

6. Xu J, Lai J, Huang X. Survival outcomes following complete mediastinal lymphadenectomy or selective mediastinal lymphadenectomy in patients with stage I-IIIA non-small cell lung cancer: protocol for a systematic review and meta-analysis. *BMJ Open* 2024;14(3):e084520. doi: 10.1136/bmjopen-2024-084520

7. Zhang Y, Deng C, Zheng Q, et al. Selective Mediastinal Lymph Node Dissection Strategy for Clinical T1N0 Invasive Lung Cancer: A Prospective, Multicenter, Clinical Trial. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2023;18(7):931-39. doi: 10.1016/j.jtho.2023.02.010 [published Online First: 2023/02/26]

8. Wang Y, Darling GE. Complete mediastinal lymph node dissection versus systematic lymph node sampling in surgical treatment of non-small cell lung cancer: do we have the answer? *Journal of thoracic disease* 2017;9(11):4169-70. doi: 10.21037/jtd.2017.10.39 [published Online First: 2017/12/23]

9. Xu F, Qi L, Yue D, et al. The effect of the extent of lymph node dissection for stage IA non-small-cell lung cancer on patient disease-free survival. *Clinical lung cancer* 2013;14(2):181-7. doi: 10.1016/j.cllc.2012.09.002 [published Online First: 2012/12/01]

10. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in medicine* 1998;17(24):2815-34. doi: 10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8 [published Online First: 1999/01/28]

11. Ou SH, Zell JA. Prognostic significance of the number of lymph nodes removed at lobectomy in stage IA non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2008;3(8):880-6. doi: 10.1097/JTO.0b013e31817dfced [published Online First: 2008/08/02]

12. Wang Z, Qi Z, Cheng D, et al. Lobe-Specific Node Dissection Can Be a Suitable Alternative to Systematic Lymph Node Dissection in Highly Selective Early-Stage Non-Small-Cell Lung Cancer Patients: A Meta-Analysis. *Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia* 2021;27(3):143-50. doi: 10.5761/atcs.oa.20-00136 [published Online First: 2020/12/08]

13. Tantraworasin A, Saeteng S, Siwachat S, et al. Impact of lymph node management on resectable non-small cell lung cancer patients. *Journal of thoracic disease* 2017;9(3):666-74. doi: 10.21037/jtd.2017.02.90 [published Online First: 2017/04/30]

14. Yang M, Cao H, Guo X, et al. The number of resected lymph nodes (nLNs) combined with tumor size as a prognostic factor in patients with pathologic N0 and Nx non-small cell lung cancer. *PloS one* 2013;8(9):e73220. doi: 10.1371/journal.pone.0073220 [published Online First: 2013/09/12]

15. Wang W, Chen D, Xi K, et al. Impact of Different Types of Lymphadenectomy Combined With Different Extents of Tumor Resection on Survival Outcomes of Stage I Non-small-cell Lung Cancer: A Large-Cohort Real-World Study. *Frontiers in oncology* 2019;9:642. doi: 10.3389/fonc.2019.00642 [published Online First: 2019/08/10]

16. Dezube AR, Mazzola E, Bravo-Iñiguez CE, et al. Analysis of Lymph Node Sampling Minimums in Early Stage Non-Small-Cell Lung Cancer. *Seminars in thoracic and cardiovascular surgery* 2021;33(3):834-45. doi: 10.1053/j.semtcvs.2020.11.007 [published Online First: 2020/11/13]

17. Hu J, Miao H, Li R, et al. Surgery and subsequent risk of non-small cell lung cancer recurrence: a meta-analysis of observational studies. *Translational cancer research* 2020;9(3):1960-68. doi: 10.21037/tcr.2020.02.15

18. Wu Y, Huang ZF, Wang SY, et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung cancer (Amsterdam, Netherlands)* 2002;36(1):1-6. doi: 10.1016/s0169-5002(01)00445-7 [published Online First: 2002/03/14]

19. Su X, Wang X, Long H, et al. Mediastinal lymph node dissection affects survival in patients with stage I non-small cell lung cancer. *The Thoracic and cardiovascular surgeon* 2008;56(4):226-30. doi: 10.1055/s-2007-989494 [published Online First: 2008/05/16]

20. Lardinois D, Suter H, Hakki H, et al. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell

lung cancer. *The Annals of thoracic surgery* 2005;80(1):268-74; discussion 74-5. doi: 10.1016/j.athoracsur.2005.02.005 [published Online First: 2005/06/25]

21. Meng D, Zhou Z, Wang Y, et al. Lymphadenectomy for clinical early-stage non-small-cell lung cancer: a systematic review and meta-analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2016;50(4):597-604. doi: 10.1093/ejcts/ezw083 [published Online First: 2016/04/24]
22. Huang X, Wang J, Chen Q, et al. Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis. *PloS one* 2014;9(10):e109979. doi: 10.1371/journal.pone.0109979 [published Online First: 2014/10/09]
23. Mokhles S, Macbeth F, Treasure T, et al. Systematic lymphadenectomy versus sampling of ipsilateral mediastinal lymph-nodes during lobectomy for non-small-cell lung cancer: a systematic review of randomized trials and a meta-analysis. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* 2017;51(6):1149-56. doi: 10.1093/ejcts/ezw439 [published Online First: 2017/02/06]
24. Luo J, Yang S, Dong S. Selective Mediastinal Lymphadenectomy or Complete Mediastinal Lymphadenectomy for Clinical Stage I Non-Small Cell Lung Cancer: A Meta-Analysis. 2021;38(12):5671-83. doi: 10.1007/s12325-021-01954-w
25. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *The Journal of thoracic and cardiovascular surgery* 2011;141(3):662-70. doi: 10.1016/j.jtcvs.2010.11.008 [published Online First: 2011/02/22]
26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4(1):1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]
27. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). *Cochrane* 2023
28. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)* 2011;343:d5928. doi:

10.1136/bmj.d5928 [published Online First: 2011/10/20]

29. Wells G, Shea B, O'Connell D, et al. The newcastle-ottawa scale(NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2020

30. Luchini C, Stubbs B, Solmi M, et al. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017(4):80-84.

31. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. *Jama* 2006;295(6):676-80. doi: 10.1001/jama.295.6.676 [published Online First: 2006/02/10]

32. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557 [published Online First: 2003/09/06]

33. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemporary clinical trials* 2015;45(Pt A):139-45. doi: 10.1016/j.cct.2015.09.002 [published Online First: 2015/09/08]

34. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemporary clinical trials* 2007;28(2):105-14. doi: 10.1016/j.cct.2006.04.004 [published Online First: 2006/06/30]

35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002;21(11):1539-58. doi: 10.1002/sim.1186 [published Online First: 2002/07/12]

36. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;22(4):719-48. [published Online First: 1959/04/01]

37. Cumpston MS, McKenzie JE, Welch VA, et al. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. *Journal of public health (Oxford, England)* 2022;44(4):e588-e92. doi: 10.1093/pubmed/fdac036 [published Online First: 2022/03/31]

38. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ (Clinical research ed)* 2001;323(7304):101-5. doi: 10.1136/bmj.323.7304.101 [published Online First: 2001/07/14]

39. Langer G, Meerpohl JJ, Perleth M, et al. [GRADE guidelines: 12. Developing Summary of Findings tables - dichotomous outcomes]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im*

Gesundheitswesen 2013;107(9-10):646-64. doi: 10.1016/j.zefq.2013.10.034 [published Online First: 2013/12/10]

40. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical research ed)* 2008;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE [published Online First: 2008/05/06]
41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of clinical epidemiology* 2011;64(4):395-400. doi: 10.1016/j.jclinepi.2010.09.012 [published Online First: 2011/01/05]
42. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)* 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26]
43. H S, Brozek J, Oxman AE. GRADE handbook for grading quality of evidence and strength of recommendation. 2009

Appendices

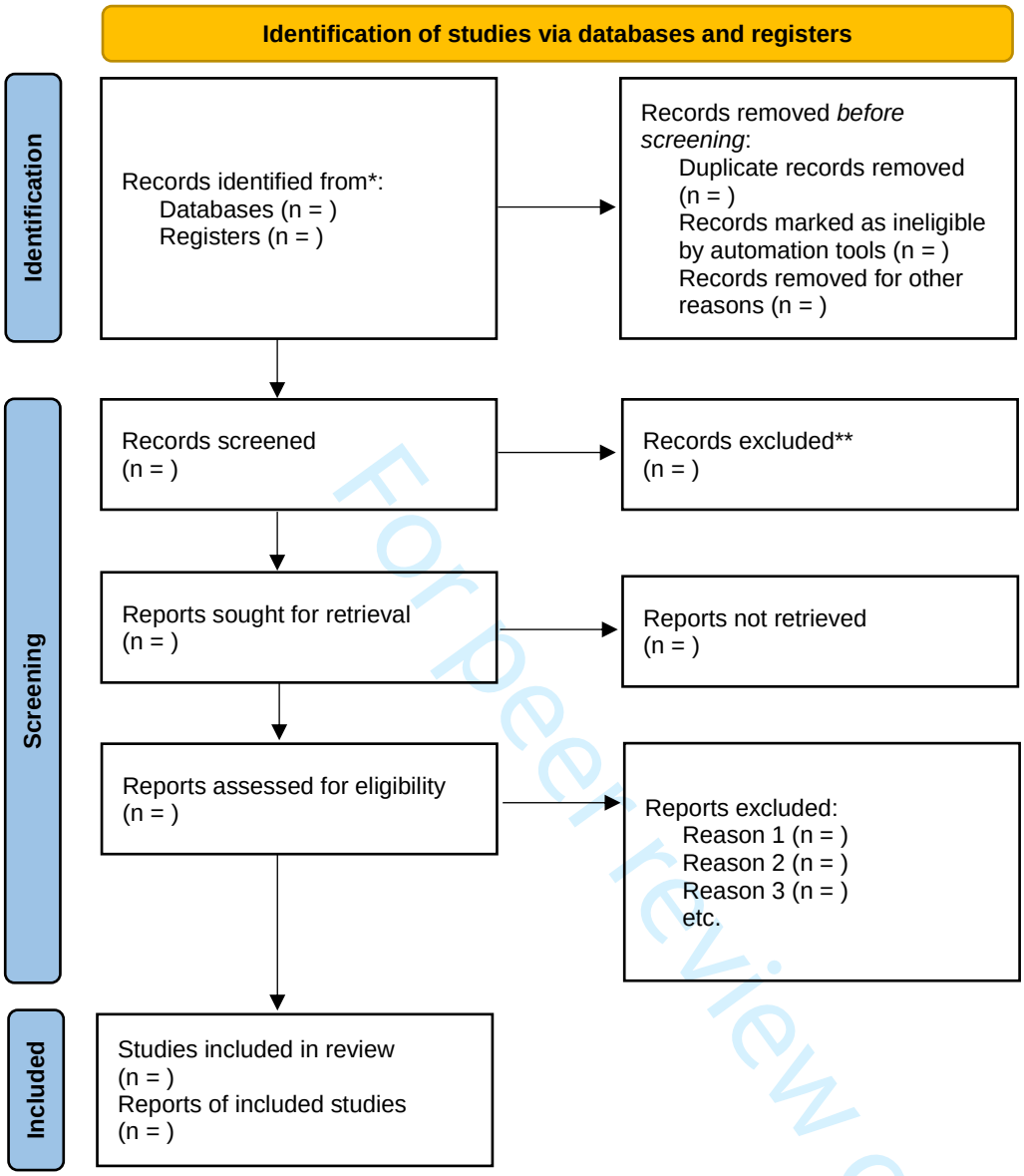
Fig 1. Flow diagram showing the selection process of articles.

Supplemental File 1. PRISMA-P-checklist.

Supplemental File 2. Search strategy.

Supplemental File 3. General information of the included studies.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	P8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. Search strategy

1. PubMed

Number	Search terms
#1	Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung OR Non-Small Cell Lung Cancer OR Lung Neoplasms OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Non-Small-Cell Lung OR Lung Carcinoma OR Non-Small-Cell OR Lung Carcinomas OR NSCLC [Title/Abstract]
#2	Surgical Procedures OR Operative OR surgery OR surgery OR surgical OR operative OR postoperative [Title/Abstract]
#3	lymphadenectomy OR lymphadenectomy OR complete mediastinal lymphadenectomy OR mediastinal lymph node excision OR lobe-specific lymph node dissection OR mediastinal lymph node dissection OR mediastinal lymph node sampling OR lymph node dissection OR lymph node OR dissect OR sample OR selective mediastinal lymphadenectomy OR systematic lymph node dissection OR selective lymph node dissection OR LND OR LNS [Title/Abstract]
#4	randomly OR randomized OR RCT OR trials OR cohort OR longitudinal OR prospective OR survival [Title/Abstract]
#5	#1 AND #2 AND #3 AND #4 [Title/Abstract]

2. Embase

Number	Search terms
#1	Non-Small-Cell:ti,ab,kw OR Non-Small-Cell Lung Carcinomas:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Non-Small-Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Lung Neoplasms:ti,ab,kw OR Pulmonary Neoplasms:ti,ab,kw OR Lung Neoplasm:ti,ab,kw OR Pulmonary Neoplasm:ti,ab,kw OR Lung Cancer:ti,ab,kw OR Lung Cancers:ti,ab,kw OR Pulmonary Cancer:ti,ab,kw OR Pulmonary Cancers:ti,ab,kw OR Cancer of the Lung:ti,ab,kw OR Cancer of Lung:ti,ab,kw OR Non-Small-Cell Lung:ti,ab,kw OR Lung Carcinoma:ti,ab,kw OR Non-Small-Cell:ti,ab,kw OR Lung Carcinomas:ti,ab,kw OR NSCLC:ti,ab,kw
#2	Surgical Procedures:ti,ab,kw OR Operative OR surgery:ti,ab,kw OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR operative:ti,ab,kw OR postoperative:ti,ab,kw

#3	lymphadenectomy:ti,ab,kw OR lymphadenectomy:ti,ab,kw OR complete mediastinal lymphadenectomy:ti,ab,kw OR mediastinal lymph node excision:ti,ab,kw OR lobe-specific lymph node dissection:ti,ab,kw OR mediastinal lymph node dissection:ti,ab,kw OR mediastinal lymph node sampling:ti,ab,kw OR lymph node dissection:ti,ab,kw OR lymph node:ti,ab,kw OR dissect:ti,ab,kw OR sample:ti,ab,kw OR selective mediastinal lymphadenectomy:ti,ab,kw OR systematic lymph node dissection:ti,ab,kw OR selective lymph node dissection:ti,ab,kw OR LND:ti,ab,kw OR LNS:ti,ab,kw
#4	randomly:ti,ab,kw OR randomized:ti,ab,kw OR RCT:ti,ab,kw OR trials:ti,ab,kw OR cohort:ti,ab,kw OR longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR survival:ti,ab,kw
#5	#1 AND #2 AND #3 AND #4

3. Cochrane Library

Number	Search terms
#1	Non-Small-Cell:ti,ab,kw OR Non-Small-Cell Lung Carcinomas:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Non-Small-Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung Carcinoma:ti,ab,kw OR Non-Small Cell Lung:ti,ab,kw OR Non-Small Cell Lung Cancer:ti,ab,kw OR Lung Neoplasms:ti,ab,kw OR Pulmonary Neoplasms:ti,ab,kw OR Lung Neoplasm:ti,ab,kw OR Pulmonary Neoplasm:ti,ab,kw OR Lung Cancer:ti,ab,kw OR Lung Cancers:ti,ab,kw OR Pulmonary Cancer:ti,ab,kw OR Pulmonary Cancers:ti,ab,kw OR Cancer of the Lung:ti,ab,kw OR Cancer of Lung:ti,ab,kw OR Non-Small-Cell Lung:ti,ab,kw OR Lung Carcinoma:ti,ab,kw OR Non-Small-Cell:ti,ab,kw OR Lung Carcinomas:ti,ab,kw OR NSCLC:ti,ab,kw
#2	Surgical Procedures:ti,ab,kw OR Operative OR surgery:ti,ab,kw OR surgery:ti,ab,kw OR surgical:ti,ab,kw OR operative:ti,ab,kw OR postoperative:ti,ab,kw
#3	lymphadenectomy:ti,ab,kw OR lymphadenectomy:ti,ab,kw OR complete mediastinal lymphadenectomy:ti,ab,kw OR mediastinal lymph node excision:ti,ab,kw OR lobe-specific lymph node dissection:ti,ab,kw OR mediastinal lymph node dissection:ti,ab,kw OR mediastinal lymph node sampling:ti,ab,kw OR lymph node dissection:ti,ab,kw OR lymph node:ti,ab,kw OR dissect:ti,ab,kw OR sample:ti,ab,kw OR selective mediastinal lymphadenectomy:ti,ab,kw OR systematic lymph node dissection:ti,ab,kw OR selective lymph node dissection:ti,ab,kw OR LND:ti,ab,kw OR LNS:ti,ab,kw
#4	randomly:ti,ab,kw OR randomized:ti,ab,kw OR RCT:ti,ab,kw OR trials:ti,ab,kw OR cohort:ti,ab,kw OR longitudinal:ti,ab,kw OR prospective:ti,ab,kw OR survival:ti,ab,kw

#5	#1 AND #2 AND #3 AND #4

4. Web of Science

Number	Search terms
#1	TS=(Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non-Small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non-Small Cell Lung Carcinoma OR Non-Small Cell Lung OR Non-Small Cell Lung Cancer OR Lung Neoplasms OR Pulmonary Neoplasms OR Lung Neoplasm OR Pulmonary Neoplasm OR Lung Cancer OR Lung Cancers OR Pulmonary Cancer OR Pulmonary Cancers OR Cancer of the Lung OR Cancer of Lung OR Non-Small-Cell Lung OR Lung Carcinoma OR Non-Small-Cell OR Lung Carcinomas OR NSCLC)
#2	TS=(Surgical Procedures OR Operative OR surgery OR surgery OR surgical OR operative OR postoperative)
#3	TS=(lymphadenectomy OR lymphadenectomy OR complete mediastinal lymphadenectomy OR mediastinal lymph node excision OR lobe-specific lymph node dissection OR mediastinal lymph node dissection OR mediastinal lymph node sampling OR lymph node dissection OR lymph node OR dissect OR sample OR selective mediastinal lymphadenectomy OR systematic lymph node dissection OR selective lymph node dissection OR LND OR LNS)
#4	TS=(randomly OR randomized OR RCT OR trials OR cohort OR longitudinal OR prospective OR survival)
#5	#1 AND #2 AND #3 AND #4

5. China National Knowledge Infrastructure (CNKI) (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

6. WANFANG DATA (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

7. Chinese biomedical literature service system (Sinomed) (Chinese)

Search terms
("非小细胞肺癌" [常用字段:智能] OR "肺癌" [常用字段:智能]) AND ("肺癌"[常用字段:智能]) AND ("随机对照试验"[常用字段:智能]) AND ("淋巴结清扫方式"[全部字段:智能] OR "系统性淋巴结清扫"[全部字段:智能]OR "选择性淋巴结清扫"[全部字段:智能] OR "叶特异性淋巴结清扫"[全部字段:智能] OR "纵膈淋巴结采样"[全部字段:智能])

8. VIP database (Chinese)

Search terms
(主题:“非小细胞肺癌”or“肺癌”) and (主题:“淋巴结清扫方式”or“系统性淋巴结清扫”or“选择性淋巴结清扫”or“叶特异性淋巴结清扫”or“纵膈淋巴结清扫”or“纵膈淋巴结采样”) and (全部:“随机对照试验”)

Supplemental File 3. General information of the included studies.

First author		
Country, year		
Sample size (males/females)		
Median age, y (range)		
Design		
Include or exclude		
Reason(s) for exclusion		
Follow-up (mean and range) (months)		
Tumor location		
Tumor size(cm)		
Tumor stage		
Surgery procedure		
Adjuvant treatment		
Primary outcomes: 1. Overall recurrence rate 2. Local recurrence rate (ipsilateral lung, ipsilateral pleura, trachea, etc.) 3. Distant metastasis rate (contralateral lung, contralateral pleura, bone, liver, etc.)		
Second outcomes: 1. Regional recurrence rate 2. Lymph node metastasis rate		

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	P1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	P2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	P1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	P10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	P3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	P4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	P5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	P5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	P6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	P6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	P6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	P6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	P7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	P7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	P8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	P8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	P8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	P9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.