## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Protocol for a systematic review and meta-analysis of recurrence and metastasis of different surgical techniques for non-small cell lung cancer |
| **AUTHORS** | Huang, Xiongfeng; Zhu, Donghong; Cao, Yaoxing; Li, Weijuan; Lai, Jinxing; Ren, Yuxi |

## VERSION 1 - REVIEW

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| **REVIEWER NAME** | Ghaderi, Sadegh |
| **REVIEWER AFFILIATION** | Tehran University of Medical Sciences, Department of Neuroscience and Addiction Studies |
| **REVIEWER CONFLICT OF INTEREST** | I do not have any potential competing interests. |
| **DATE REVIEW RETURNED** | 07-Apr-2024 |

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| **GENERAL COMMENTS** | I appreciate your invitation. I believe that this protocol study is thorough and appropriate for publication. I highly suggest that the author incorporate and compare previous meta-analyses and references in this study, following the preparation of a systematic review and meta-analysis study, such as https://doi.org/10.21037%2Ftcr.2020.02.15. In my view, I recommend that the authors include the term "systematic review" alongside "meta-analysis" in the title of the final article. |

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| **REVIEWER NAME** | Bertolaccini, Luca |
| **REVIEWER AFFILIATION** | European Institute of Oncology |
| **REVIEWER CONFLICT OF INTEREST** | None. |
| **DATE REVIEW RETURNED** | 24-Apr-2024 |

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| **GENERAL COMMENTS** | The meta-analysis protocol outlines a comprehensive plan for evaluating the recurrence and metastasis rates associated with lymph node dissection versus lymph node sampling in patients with early-stage non-small cell lung cancer (NSCLC). The study addresses the controversy surrounding the optimal surgical approach for lymph node assessment in NSCLC resection.<br>Several potential shortcomings should be considered.<br>1. Although the protocol intends to include randomized controlled trials (RCTs) and non-randomized studies, it acknowledges potential bias in non-randomized studies. This could introduce methodological limitations and affect the overall quality of evidence.<br>2. The inclusion criteria specify patients with stage I to IIIA NSCLC, potentially excluding patients with more advanced stages of the disease. This could limit the generalizability of the findings to the broader NSCLC population. |

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| | 3. Despite the comprehensive search strategy, including studies published in languages other than English may be limited, potentially leading to language bias.<br>4. The protocol mentions efforts to contact primary authors for additional data if needed. However, there may still be incomplete reporting or missing data in the included studies, which could impact the accuracy and completeness of the meta-analysis results.<br>5. The protocol states that there is no intention to involve patients or the general public in the planning, execution, reporting, or dissemination of the systematic review. Lack of patient and public involvement may limit the relevance and applicability of the findings to the end-users, including patients and healthcare providers.<br><br>While the statistical analysis appears comprehensive, several potential shortcomings warrant consideration:<br>1. Despite acknowledging the potential for substantial heterogeneity among the included studies, the protocol does not provide a detailed plan for addressing or exploring heterogeneity beyond subgroup analyses. Heterogeneity can significantly impact the validity of meta-analysis results and should be carefully assessed and accounted for using appropriate statistical methods.<br>2. While the protocol mentions using funnel plots and Egger's linear regression test to assess publication bias, these methods may have limitations, and additional approaches (e.g., trim-and-fill method, cumulative meta-analysis) could provide more robust insights into the presence of publication bias. A more comprehensive assessment of publication bias is necessary to ensure the reliability of the meta-analysis findings.<br>3. The protocol mentions conducting sensitivity analysis to assess the impact of studies with poorer methodological quality on the outcomes. However, the specific criteria for identifying poorer-quality studies and the methods for handling them in the analysis are unclear. A more detailed explanation of the sensitivity analysis approach is needed to ensure transparency and reproducibility of the results.<br>4. While the protocol mentions using the GRADE framework for grading the quality of evidence, it does not provide specific criteria or thresholds for determining the certainty of evidence. Clear and explicit criteria for assessing the risk of bias, consistency of effect, imprecision, indirectness, and publication bias are essential for accurately grading the quality of evidence and interpreting the findings. |

**VERSION 1 – AUTHOR RESPONSE**

Response to Reviewers

Reviewer: 1

Dr. Sadegh Ghaderi, Tehran University of Medical Sciences

Comment 1:

I appreciate your invitation. I believe that this protocol study is thorough and appropriate for publication. I highly suggest that the author incorporate and compare previous meta-analyses and references in this study, following the preparation of a systematic review and meta-analysis study, such as https://doi.org/10.21037/tcr.2020.02.15. In my view, I recommend that the authors include the term "systematic review" alongside "meta-analysis" in the title of the final article.

Response:

Thank you for your valuable suggestions. We have added this reference (No.17) and modified the title according to your request.

Reviewer: 2

Dr. Luca Bertolaccini, European Institute of Oncology

Comments to the Author:

The meta-analysis protocol outlines a comprehensive plan for evaluating the recurrence and metastasis rates associated with lymph node dissection versus lymph node sampling in patients with early-stage non-small cell lung cancer (NSCLC). The study addresses the controversy surrounding the optimal surgical approach for lymph node assessment in NSCLC resection.

Several potential shortcomings should be considered.

Comment 1:

1. Although the protocol intends to include randomized controlled trials (RCTs) and non-randomized studies, it acknowledges potential bias in non-randomized studies. This could introduce methodological limitations and affect the overall quality of evidence.

Response:

Thank you for your helpful comment. To gather a more thorough collection of literature, we plan to explore both randomized controlled trials (RCTs) and non-randomized studies, although it is important to note that non-randomized trials may impact the overall quality of the study. Therefore, we will use the subgroup analysis method to conduct meta-analysis statistics for RCTS and non-randomized studies respectively, and of course, we will also conduct an overall meta-analysis. In addition, we will exclude some studies with poor quality in the sensitivity analysis to verify the robustness of the results. What's more, this limitation is also indicated in article 3 of the STRENGTHS AND LIMITATIONS OF THIS STUDY section---"Non-randomized studies may introduce methodological limitations and affect the overall quality of evidence". (Page 2; line 52-53).

Comment 2:

2. The inclusion criteria specify patients with stage I to IIIA NSCLC, potentially excluding patients with more advanced stages of the disease. This could limit the generalizability of the findings to the broader NSCLC population.

Response:

Thank you for your helpful advice. We have eliminated the restriction pertaining to stages I to IIIA and intend to encompass all stages of NSCLC as you suggested.

Comment 3:

3. Despite the comprehensive search strategy, including studies published in languages other than English may be limited, potentially leading to language bias.

Response:

Thank you for your helpful comment. We will make every effort to gather all the research available, without restricting the language. However, it is still possible to overlook research that is not in English, as you mentioned. So we wrote that into the STRENGTHS AND LIMITATIONS OF THIS STUDY section—"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." (Page 2; line 56-58).

Comment 4:

4. The protocol mentions efforts to contact primary authors for additional data if needed. However, there may still be incomplete reporting or missing data in the included studies, which could impact the accuracy and completeness of the meta-analysis results.

Response:

Thank you for your valuable suggestions. We have added relevant contents in the Dealing with missing data section according to your suggestion, as follows: 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. (Page 6; line 65-70).

Comment 5:

5. The protocol states that there is no intention to involve patients or the general public in the planning, execution, reporting, or dissemination of the systematic review. Lack of patient and public involvement may limit the relevance and applicability of the findings to the end-users, including patients and healthcare providers.

Response:

Thank you for your helpful advice. We have made the necessary adjustments to the Patient and public involvement section as you suggested. –"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." (Page 9; line 261-264).

Comment 6:

While the statistical analysis appears comprehensive, several potential shortcomings warrant consideration:

1. Despite acknowledging the potential for substantial heterogeneity among the included studies, the protocol does not provide a detailed plan for addressing or exploring heterogeneity beyond subgroup

analyses. Heterogeneity can significantly impact the validity of meta-analysis results and should be carefully assessed and accounted for using appropriate statistical methods.

Response:

Thank you for your helpful comment. We have added corresponding contents about these issues in the Statistical analysis part of our revised manuscript as you suggested.—"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." (Page 7-8; line 203-211).

Comment 7:

2. While the protocol mentions using funnel plots and Egger's linear regression test to assess publication bias, these methods may have limitations, and additional approaches (e.g., trim-and-fill method, cumulative meta-analysis) could provide more robust insights into the presence of publication bias. A more comprehensive assessment of publication bias is necessary to ensure the reliability of the meta-analysis findings.

Response:

Thank you for your helpful advice. We have added relevant contents in the Assessment of publication bias section as you suggested.—"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." (Page 8; line 218-220).

Comment 8:

3. The protocol mentions conducting sensitivity analysis to assess the impact of studies with poorer methodological quality on the outcomes. However, the specific criteria for identifying poorer-quality studies and the methods for handling them in the analysis are unclear. A more detailed explanation of the sensitivity analysis approach is needed to ensure transparency and reproducibility of the results.

Response:

Thank you for your helpful comment. The detailed explanation of the sensitivity analysis approach has been added to the Subgroup and sensitivity analyses section as you suggested.— "In particular, we will omit 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." (Page 8; line 225-229).

Comment 9:

4. While the protocol mentions using the GRADE framework for grading the quality of evidence, it does not provide specific criteria or thresholds for determining the certainty of evidence. Clear and explicit criteria for assessing the risk of bias, consistency of effect, imprecision, indirectness, and

publication bias are essential for accurately grading the quality of evidence and interpreting the findings.

Response:

Thank you for your helpful advice. We have added corresponding contents about these issues in the Grading the quality of evidence section as you suggested.—"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." (Page 9; line 243-254).

## VERSION 2 – REVIEW

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| **REVIEWER NAME** | Bertolaccini, Luca |
| **REVIEWER AFFILIATION** | European Institute of Oncology |
| **REVIEWER CONFLICT OF INTEREST** | None |
| **DATE REVIEW RETURNED** | 30-Jul-2024 |

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| **GENERAL COMMENTS** | No further comments. |

## VERSION 2 – AUTHOR RESPONSE

Response to Reviewers

Reviewer: 2

Dr. Luca Bertolaccini, European Institute of Oncology

Comments to the Author:

No further comments.

Response:

Thank you very much for your kindly comments.