

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-516>

### Reviewer A

The authors examined the US database called SEER. Like all national databases, the data collected may not be fully adherent to the clinical reality but the authors have recognized this limitation.

The subject of the manuscript is very interesting and the conclusions may have a real impact on the conduct of the multi-disciplinary meetings.

My only request is to mention immunotherapy in the limitations section.

Author response:

Thank you for the valuable suggestions. Following your advice, we have added a discussion on immunotherapy in the limitation section of the revised manuscript. We acknowledge the significance of immunotherapy in cancer treatment, and our data in this study do not comprehensively involve this aspect. By incorporating this information in the limitation section, we aim to provide a more comprehensive presentation of our research, catering to the readers' needs and enhancing the quality of the paper.

### Reviewer B

This study is a large retrospective analysis comparing treatment modalities. The authors state that chemotherapy plus surgery is more beneficial than other treatment modalities for single and multiple extrathoracic metastases. There are several unclear points in this manuscript.

1) Performance Status (PS) is known to be one of the most influential prognostic factors for survival. However, this study does not present data on PS. The decision to undergo surgery is strongly related to PS. The authors should present data on PS.

2) The authors concluded that patients who underwent lobectomy/bilobectomy/pneumonectomy for both single and multiple EM had longer survival compared to sublobectomy. These surgical procedures are also significantly associated with PS. Again, PS data are important here. Patients who underwent lobectomy/bilobectomy/pneumonectomy likely had better PS.

Author response:

We appreciate your valuable suggestions. PS (performance status) is indeed a crucial prognostic factor for survival, and we acknowledge that surgical approaches are often influenced by patients' PS. Unfortunately, due to limitations in the available data source (SEER database), we could only analyze treatment patterns and survival outcomes, and specific PS data for the patients included in this study were not available. We

acknowledge the lack of PS data as a limitation of our research and have discussed this in the limitation section of the manuscript. Although we cannot directly analyze the impact of PS in our study, we believe that the association between surgical approaches and survival outcomes still provides valuable insights. Thank you once again for your valuable suggestions.

### **Reviewer C**

Most, if not all, treatment guidelines currently recommend systemic chemotherapy for patients with Stage IV NSCLC, regardless of whether there are multiple sites of metastatic disease or when systemic spread is oligometastatic. In the absence of progression, guidelines recommend definitive treatment of the intrathoracic disease, and in the presence of oligometastases definitive treatment of the limited metastatic disease. What is unclear is whether and under what circumstances surgery should be favored over radiation therapy usually in the form of SBRT. Viewed with this background, the study by He and colleagues has a major shortcoming to be addressed namely the outcome in patients treated with chemotherapy and radiation which is from a clinical perspective the major competing therapy to chemotherapy along with surgery. Unless the authors include this in their analysis, the impact of the study will be quite limited.

Additional comments and suggestions for revision:

1. The authors use the term pneumectomy throughout the manuscript which is not a commonly used or well understood term. It would be more clear if they used the term lung resection which encompasses all of the various procedures described in this study.

Author response:

Thank you for the valuable feedback on the guidance provided in the NSCLC treatment guidelines. We appreciate your concern regarding the absence of patient radiation therapy information in our study, which is indeed an important aspect that requires careful consideration. In the revised manuscript, we have incorporated the information about patient radiation therapy in the analysis, aiming to provide a more comprehensive perspective for comparing the effectiveness of different treatment methods, thereby expanding the scope and impact of our research.

Additionally, we have seriously considered your suggestion regarding the term “lung resection” for clarity and better understanding throughout the manuscript. We have adopted your advice and used “lung resection” in the revised version to improve the accuracy and readability of the article. Once again, thank you for your valuable feedback.

1. The number of patients with positive N2 and N3 nodes included in the study group is quite high accounting for 66% of the patients with a single metastatic site and more than 75% of patients with multiple sites of metastatic disease. These patients typically receive definitive chemoradiation and are not considered candidates for surgery in the presence of stage IV disease. If the question is which patients with metastatic disease

should be considered for surgical resection as stated in the introduction, it seems that the study group should exclude N2/N3 patients to focus the analysis on the group of patients who could reasonably be expected to be offered surgery. This could either be done by adding N2/N3 disease as an exclusion criterion or by performing a subgroup analysis for N0, N1 and N2/3 patients.

Author response:

Thank you for your valuable suggestion. We greatly appreciate your highlighting the need for our study to pay more attention to patients who might be considered for surgery. Taking your suggestion into careful consideration, we have reanalyzed the data and excluded patients with N2/N3 lymph node positivity from the study cohort. This narrows our research focus to those patients who are likely to undergo surgical treatment. We are grateful for your valuable advice, which undoubtedly enhances the quality and relevance of our study.

2. Current treatment guidelines recommend systemic chemotherapy for patients with Stage IV lung cancer, regardless of whether there are multiple metastatic sites or the systemic disease is limited to a single site. In the setting of oligometastatic disease, treatment guidelines also recommend some form of local therapy along with definitive treatment of the limited metastatic disease either with surgical resection or SBRT. Data regarding the choice of local therapy (surgery vs SBRT) in these patients is limited. Viewed in this context, the manuscript by He and colleagues has a major shortcoming that must be addressed for the study to be of value in achieving the stated goal of "identifying NSCLC patients with extrathoracic metastases who could benefit from primary tumor resection". They must include patients treated with chemotherapy and radiation to the primary tumor since this is from the clinical perspective the major competing therapy. This need for revision and other comments and suggestions are outlined in the comments to the authors section of this review.

Author response:

Thank you very much for your suggestions. We understand your concerns about the absence of patient radiation therapy information in our study, which is indeed an important aspect that needs careful consideration. In the revised Table 1 of our manuscript, we have included information about patients undergoing radiation therapy. Furthermore, we have incorporated data of this indicator in the subsequent analysis. We aimed at providing a more comprehensive perspective to compare the effectiveness of different treatment methods, thereby expanding the scope and impact of our research. For specific modifications, please refer to the revised manuscript. Once again, thank you for your guidance.

#### **Reviewer D**

The authors provide a retrospective study on patients with non-small cell lung cancer (NSCLC) with extrathoracic metastases extracted from the Surveillance, Epidemiology,

and End results (SEER) database. They conclude that primary tumour surgery could improve survival in NSCLC patients with single extrathoracic metastasis on the condition that at least a lobectomy is performed.

Comments:

- this is a retrospective study with its inherent selection bias resulting in exclusion of a large number of patients. No valid comparative analysis is presented.

Author response:

Thank you very much for the comments. We appreciate the issues you have pointed out. As a retrospective study, we do indeed face inherent selection bias that may result in the exclusion of some patients. The focus of our article is on "identifying NSCLC patients with extrathoracic metastasis who may benefit from primary tumor resection," primarily investigating the optimal treatment strategies for patients with extrathoracic metastases. While the data may be influenced by inherent selection bias, it does not compromise the stability and accuracy of our data analysis results. Once again, thank you for your guidance. We will closely address the concerns you raised to ensure the quality and reliability of the study.

- only the years 2010 till 2015 were considered although a new TNM classification was introduced in 2016 where category M1b was redefined as a single metastasis in one extrathoracic organ; this is not mentioned or discussed by the authors.

Author response:

Thank you for your feedback. The AJCC staging system was updated to the 8th edition(<https://theoncologist.onlinelibrary.wiley.com/doi/full/10.1634/theoncologist.2017-0659>) in 2016, defining M1b as a single extrathoracic metastasis (EM). However, the patient cohort selected for this study spans from 2010 to 2015, and M1b staging in our study was based on the AJCC 7th([https://www.facs.org/media/j30havyf/ajcc\\_7thed\\_cancer\\_staging\\_manual.pdf](https://www.facs.org/media/j30havyf/ajcc_7thed_cancer_staging_manual.pdf)) edition, referring to patients with distant metastases outside the thoracic cavity, without specifying the number of metastases. This discrepancy may have led to some patients who were not suitable candidates for surgery undergoing the procedure, introducing bias into the data. We have addressed this difference by including a clarification in the limitation section of the discussion. Please refer to the manuscript for specific details. Once again, we appreciate your valuable input.

- line 224: the authors could only stratify for metastatic organs and not number of lesions; this is confusing as in daily practice the number of lesions is mainly considered. In their analysis, patients with 1, 3 or 6 lesions in one organ were grouped together making interpretation of results more difficult

Author response:

Thank you for your suggestion. Due to limitations in the SEER database, specific

quantities of lesions are not recorded. As a result, we are unable to conduct a stratified analysis based on the number of lesions. In addressing this limitation, we have added it in the discussion section of the manuscript. Please refer to the manuscript for more details.

- no precise information is provided on preoperative staging: how many patients had PET scanning? In how many cases was there a histologic proof of metastatic disease?
- which follow-up examinations were performed, at what time intervals?
- the use of chemotherapy is listed as a single entity: which regimens were given, how many cycles? What is currently recommended?
- what was role of radiotherapy in treating metastatic lesions?

Author response:

Thank you very much for the suggestions. However, due to limitations in the SEER database, the currently available data do not include specific information about patient preoperative staging, whether they underwent PET scans, histology, or other details mentioned above. The published follow-up data currently only include survival status and overall survival. There is no specific data available regarding the examination and intervals of follow-up. Nevertheless, the role of radiation therapy in treating metastatic lesions, as you mentioned, has been addressed and supplemented in the discussion. Please refer to the manuscript for specific details.

- line 55 definition of oligometastatic disease: this was provided by the EORTC (European Organisation for Research and Treatment of Cancer) in the paper by Dingemans AM. *J Thorac Oncol* 2019; 14:2109 which is not mentioned, applied or discussed by the authors

Author response:

Thank you for the reviewer's suggestion. We have now added a supplement in the introduction regarding the definition of oligometastasis in the EORTC: "According to a consensus published by the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group, oligometastasis is defined as a maximum of five metastases and involvement of three organs (PMID: 31398540)."

- other essential references are missing as European Society of Medical Oncology (ESMO) guidelines (Planchard D. *Ann Oncol* 2019; 30:863) and the randomised phase II trial by Gomez D (*J Clin Oncol* 2019; 30:863)

Author response:

Thank you for your valuable feedback. We greatly appreciate your mention of the important references we missed in our initial draft, such as the European Society for Medical Oncology (ESMO) guidelines and the randomized phase II clinical trial conducted by Gomez D (*J Clin Oncol* 2019; 30:863). In our revised manuscript, we have included these significant references from the journals you mentioned in our

introduction section. This will provide a more comprehensive and robust discussion in the relevant sections of the paper. For specific details, please refer to the revised manuscript.

- lines 165-167 first study to identify patients for aggressive surgery: this not correct as this is also evaluated by Mitchell K (ref. 9 of the authors, not discussed as such)

Author response:

Thank you for your feedback. We have revised the description of the relevant content in the revised manuscript to ensure that the current research status is accurately reflected. Your comments are essential to improve the clarity and accuracy of the paper. If you have any further suggestions or concerns, please feel free to let us know.

- lines 223 - 231: immunotherapy is not mentioned by the authors although over the last years, it has become a cornerstone in the treatment of (oligo)metastatic disease

Author response:

Thank you for your suggestion. We have supplemented the relevant research of immunotherapy in oligometastatic diseases in the discussion section, please refer to the manuscript for details.

- throughout the manuscript the term pneumectomy is used which literally means removal of air; the correct term is pneumonectomy

Author response:

Thank you for your valuable suggestions. This is a clerical error. pneumonectomy is correct, and we have corrected the formulation in the manuscript.

- in summary, although the authors report a fairly large series, patients were treated between 2010 and 2015 while diagnostic and treatments algorithms have changed substantially over the last years. No in-depth analysis is provided according to recent literature data. For this reason, the conclusions of the authors are too strong and cannot be applied to current clinical practice.

Author response:

Thank you for your advice. We agree with you that knowledge and technology in the medical field have developed rapidly in the past few years, and new research and treatment methods are constantly emerging. Indeed, our research cannot fully cover these latest advances. Therefore, following your suggestion, we have made modifications to the conclusion, avoiding excessive exaggeration of our research results. Additionally, in the revised manuscript, we have included citations to the latest relevant literature to ensure that our study is practical and has guiding value.

I would like to congratulate the authors for the amount of work behind this study but a

number of questions have come to my attention and prevent this manuscript from being published as it is.

Author response:

Thank you very much for the thorough review of our manuscript. We have made revisions based on your feedback. Additionally, despite some data limitations due to the database, we believe that this study provides valuable insights into the optimal treatment strategies for non-small cell lung cancer (NSCLC) with extrathoracic metastasis in clinical. We hope that our response and modifications meet with your approval.

### **Reviewer E**

1) The title of the article talks about extended resection. I would expect the authors to detail the surgeries and their extent: Pancoast resection, rib cage, superior vena cava, left atrium, aorta. By reading the manuscript, the authors talk about lobectomy, bilobectomy, pneumonectomy and sublobar resection but not extended resection. The title should be change because it is not appropriate.

Author response:

Thank you for the suggestions. We have modified the title to: "Optimal Therapeutic Strategy for Non-small Cell Lung Cancer with Thoracic Extrathoracic Metastasis: A Study Based on SEER Database."

1) How many metastasis did the patients who had multiple extra-thoracic metastasis have?

Author response:

Thank you very much for reviewing our manuscript. In this paper, single extrathoracic metastasis and multiple extrathoracic metastases are defined based on the number of involved organs. Single extrathoracic metastasis refers to involvement of a single organ, while multiple extrathoracic metastases indicate involvement of two or more organs ( $\geq 2$ ).

2) Treatment modalities such as surgery alone or no treatment doesn't reflect the guidelines of NCCN. Why such a huge amount of patients have those treatment?

Author response:

We apologize for the inconvenience. The SEER database only collects information on treatment methods, and the reasons for choosing these treatment approaches are not documented in the database. However, the SEER database is a public database and research resource created by the National Cancer Institute (NCI) in the United States. It collects and stores cancer incidence, mortality, and treatment data within 48% of the United States, supporting cancer research and epidemiological investigations. As a

highly authoritative cancer database, the SEER database offers large-scale sample data, encompassing various aspects such as demographics, treatment, and survival. The extensive patient population also allows for specific subset analyses based on patient characteristics, tumor staging, and treatment strategies. Therefore, we believe that the results of the data analysis in our study are reliable.

3) I am surprised there is no mention of radiotherapy as it is an option in adjuvant or Neo-adjuvant context for extended lung resection.

Author response:

Thank you for the suggestion. We have added information about patients undergoing radiation therapy in Table 1 and incorporated this indicator into subsequent data analyses. Descriptions have been included in both the Results and Discussion sections.

4) How were the metastasis treated?

Author response:

We are very sorry that the SEER database only collects treatment methods, and there is no specific treatment plan, so we cannot know the specific treatment plan for metastatic tumors. In order to make the article more comprehensive and powerful, we have added the relevant content about the treatment of metastatic tumors in the discussion section.

5) Why was sublobar resection considered in those patients as it is known that the gold standard is lobectomy? Were the patients not fit enough for a lobectomy?

Author response:

The SEER database retrospectively collects clinical information on patients every November and releases the data in April of the following year. While surgical procedures are recorded, the reasons for choosing a particular surgical approach are not documented. For more details about the SEER database, please refer to the website (<https://seer.cancer.gov/about/50-anniversary.html>).

6) Was an ethical committee contacted for this study? Was it registered under a specific number?

Author response:

Thank you for the question. The SEER (Surveillance, Epidemiology, and End Results) database is created and maintained by the National Cancer Institute (NCI) in the United States, with the aim of providing cancer epidemiological data. This database is open to researchers and medical professionals and can be accessed for free through the official SEER website (<https://seer.cancer.gov/>). Therefore, this study is exempt from local research ethics committee approval. We have provided additional explanations in the Methods section. Furthermore, access to the SEER database for data download can be obtained by registering an account with an email address and using the SEER\*Stat



software (<https://seer.cancer.gov/seerstat/>).