Peer Review File
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Review Comments

Reviewer A

Comment 1: Despite the narrative review is a new type or literature overview lacking some systematic aspects, the paper has some interest for a rapid consultation especially for beginners. The focus of the review is wide. There is no question on specific matters of debate nor parameters for surgical planning, operative technique, surgical oncology and so on. The paper is actually easy and, being so wide, is a general report of really clearly established knowledge on the problem to be discussed.

Reply: Thank you very much for your encouragement and your valuable comments. Your constructive comments have improved the logic and scientific nature of this manuscript. We fully acknowledge the shortcomings of this review. Based on your comments, we have made detailed revisions to the manuscript and responded to your comments. Thank you very much.

Comment 2: Some specific chapters are by the way not so well tuned. I would suggest going into deep with more selected papers regarding the prognostic factors. The representative case is completely out of paper purposes.

Reply: We thank the reviewer for pointing these critical issues out. We admit that because the logic of our manuscript is not clear enough and the structure is not well adjusted, the reviewer feels that the presentation of this case in the review is completely unnecessary and deviates from the purpose. Based on this consideration, we agree with the reviewer and delete this case report. Thanks for your suggestions.

Comment 3: If you want to maintain the "future chapter", in that case, you need to expand the search out of the large patient series into single technique, materials innovation...

Reply: We are very grateful to the reviewer for this valuable comment, which has greatly helped improve our manuscript. Based on the comment, we do search out of the large series about the materials and surgery for chest wall reconstruction. Thank you!

Changes in the text: *"Table 3 summarized the most important series on the chest wall reconstruction (including the clinical outcomes)."* (See Lines 298-299, Page 11) Please review the details from Table 2.

Comment 4: Language revision is recommended and subtitles are better in more formal language.

Reply: I would like to thank you for your approval, as well as your suggestions and constructive comments. With your insightful comments, we have revised the manuscript and supplementary materials adequately. We are sorry for any grammatical errors in our previous manuscript, and we have improved the grammatical and logical level throughout our revised version. We have rearranged the relationships between paragraphs and added connectives to make the paper well-articulated and easier to understand.

Thanks for your suggestions.

Reviewer B

Comment: The authors searched the literature for surgical treatment of lung cancers invading the chest wall. Even if in the era of lung cancer screening, this is always a modern and important topic. The paper is very well written, and the final result is a narrative review comprising the whole topic (chest wall resection and reconstruction, indications, pre-op preparation, post-op complications, prognostic factors and so on). The most relevant literature has been extensively considered and discussed. English language is good.

Reply: Thank you very much for your encouragement and your valuable comments. We felt that the detailed comments of the reviewers improved our manuscript substantially. Thank you very much!

Reviewer C

Comment 1: I have no doubt that the authors have performed a tremendous amount of work to investigate this topic and ultimately write a draft of their manuscript with what they have learned. In very general terms, their concepts are possibly of interest, but their current version is very challenging to follow. The presentation of their topic requires a considerable amount of reworking. As one broad example, even though they have divided their review into different sections, many of their individual paragraphs do not have a clear focus. The ones that they may perceive as being concise read as though the data review was very cursory (which I am sure was much more in-depth). Therefore they should try to develop a summary statement to either end or start a lot of their paragraphs. On a larger scale, the natural progression of their sections is not intuitive to understand.

Reply: Thank you very much to the reviewer for your valuable comments and your encouragement. We apologize for the lack of readability in our last version of the manuscript and acknowledge the lack of clear focus between paragraphs. In response to the reviewer's suggestion that our data review was cursory, we provide Table 1 summarizing the search strategy. At the same time, we have rearranged and optimized the paragraphs, and improved the summary and logical connection between each paragraph, so that the review can be intuitively understood. Thank you so much!

Comment 2: What exactly is the central thesis of their review? They seem to be presenting several random aspects of many studies. Having a clearer overarching point to which sections can point toward would be advantageous. The description of their methodology is not entirely comprehensive. It does not highlight how their review is relative to the other published data or even comparatively to the other reviews on this topic. Similarly, there is no quantitative assessment of any aspect of their review.

Reply: Thank you so much for your valuable insights. We acknowledge the shortcomings of quantitative assessment in the review. Based on your valuable comments, we summarized the important research series on the topic of induction therapy and chest wall reconstruction surgery and presented them in the manuscript and Table 2.3. We also re-summarize the central arguments of the review.

We acknowledge the shortcomings of the research process and disclose them in the Shortcomings section at the end of the manuscript. Thank you so much!

Changes in the text:

"2. Methods

This narrative review was based on a literature search of three databases from January 1984 to September 2023. The literature databases included PubMed, Embase, and ScienceDirect, searched in English. Some groundbreaking or historically significant literature was also included. Search topics focused on the management of patients with NSCLC that invaded the chest wall, particularly surgery (chest wall resection and chest wall reconstruction). The specific entity of Pancoast tumor or superior sulcus tumor (SST) and the role of the different surgical approaches for these tumors will be not addressed here. Studies with lower levels of evidence or single case reports were excluded. Table 1 summarizes the search strategy of this review." (See Lines 98-106, Page 4)

"i. Limitations: Based on the nature of Narrative Review, this review did not conduct a quantitative analysis of the specific literature searched. It only conducted basic screening based on the evidence level of the literature and did not implement strict quality control assessment." (See Lines 365-367, Page 13)

Comment 3: The authors also need to present their material in a more analytical fashion. Presently their sections read as a listing of studies, almost as if the abstract of the studies were placed together sequentially. Also, they present several variables, factors, or elements independently which renders the overall message difficult to follow. As an example, when they present depth of chest wall involvement they also introduce the issue of tumor size. The general topic of tumor size would lend itself to more quantitative analysis. Given that they have done the work, their review would be complemented with some type of meta-analysis. If they choose not to be more analytic, then they would do well to have a more processed or digested version of all the studies and provide a more synthesized interpretation of the studies. In other words, describing the common themes or distinctly different themes and why they are different is of more use rather than simply listing each study's important findings.

Reply: Thanks to the reviewer for these important comments. We apologize for the unclear description of the manuscript and for making the reviewer feel that the manuscript is difficult to understand. Based on your comments, we have reformatted and subdivided the paragraphs to make them easier to read and improve the logical relationship between paragraphs. Thank you so much!

Comment 4: I do not understand the value of adding a case report to this review. Even the multidisciplinary team section is extraneous. We all believe in its value, but this review is not the forum in which to describe its value. This approach uses additional text unnecessarily when they could use this space to expand upon other areas.

Reply: We thank the reviewer for raising such a valuable question. We strongly agree that MDT should not be placed as a separate part of this review, but we also believe that lung cancer patients with CWI need to be treated with MDT because of their disease heterogeneity to obtain a better prognosis. Therefore, we eliminated the separate chapters of MDT in the manuscript and instead allowed them to appear only in small necessary sentences. Thank you!

Comment 5: Although minor, when citing references, including the first name or the initial of the first name is not necessary. Using the last name will suffice. Overall, this narrative review seems somewhat early in its production and requires a substantial amount of revising and refinement. I

understand that it is supposed to be a more qualitative review, but the style in which they have presented their research betrays what must have been a tremendous amount of work. They must revise their manuscript to one that should be easier to understand and follow.

Reply: Thank you for the guidance on literature citations, and we have modified the references of the review according to your suggestion. We apologize for any shortcomings in the manuscript and do our best to revise it accordingly. Thanks for your comments.

Reviewer D

Comment: The authors reported a review of literature with regard to patients with non-small cell lung cancer complicated with chest wall invasion. They concluded that surgery plays an important role in treating NSCLC patients with chest wall invasion, and a 42-cooperative multidisciplinary team is required for successful treatment with adequate outcome data. this report is valuable for publication in the Journal of Thoracic Disease. After the analyses including one more article treating long observation for those patients, it should be accepted for publication; Neoadjuvant Therapy for Patients With Non-small Cell Lung Cancer Complicated With Chest Wall Invasion. Anticancer Res. 2022 Nov;42(11):5539-5546. doi: 10.21873/anticanres.16059. PMID: 36288862.

Reply: Thank you very much for your encouragement and your valuable comments. You provided us with a very important study, which we carefully read and included in our review. Thank you so much!

Changes in the text: *"For definite hilar/mediastinal lymph node and rib invasion, NAT is recommended for patients after discussion with an MDT. The purpose is to improve the radical rate of resection, obtain a reliable safety margin, preserve important structures, and eradicate micrometastases, and extend the patient's survival benefit (22)."* (See Lines 150-153, Page 6)

22. Sato K, Nakamura S, Kadomatsu Y, et al. Neoadjuvant Therapy for Patients With Non-small Cell Lung Cancer Complicated With Chest Wall Invasion. Anticancer Res. 2022;42:5539–46. (See Lines 430-431, Page 15)

Reviewer E

Comment 1: I appreciate the effort of the authors in writing this manuscript, but I fear that the paper doesn't have much to add to the Literature. The majority of what is written is very generic, with little insight, and also from a methodologic point of view there are many shortcomings, such that the article should be rewritten altogether. I write down some of the major issues here: The title should be added with "a literature review"

Reply: Thank you so much for this important comment! We are very grateful to the reviewers for providing us with very detailed comments because these comments made us aware of the shortcomings in the review writing, and we attach great importance to these valuable comments. At the same time, we acknowledge these shortcomings in the previous version of the manuscript. Therefore, we revised the manuscript in response to these comments and added necessary sections or tables.

We agree that the title should be further modified and optimized. Thank you very much.

Changes in the text: ***Title:*** *Chest Wall Resections for Non-small Cell Lung Cancer, a literature review* (See Line 2, Page 1)

Comment 2: The background section of the abstract fails to make a point as to why NSCLC with CWI is something that deserves a review.

Reply: We are very grateful to the reviewer for this comment. We apologize for not highlighting the importance of the topic of this review in context and have revised it. Thank you very much!

Changes in the text: *"A rare clinical entity, chest wall invasion (CWI) accounts for 3% to 8% (2–6) of all resected non-small cell lung cancer (NSCLC) cases and approximately 45% of T3 tumors (7). However, the optimal treatment strategy for such advanced tumors remains controversial as to the role of neoadjuvant therapy (NAT), surgical strategies/ techniques and reconstruction of the chest wall."* (See Lines 66-69, Page 3)

Comment 3: The introduction is chaotic. It is not clear what the guidelines say since from lines 73-75 it seems that upfront surgery is recommended, while from lines 76-78, it seems that patients should undergo induction treatment first.

Reply: Thanks to the reviewer for these important comments. We apologize for the unclear description of the role of surgery and treatment guidelines in the introduction, so we have revised this section and subsequently added relevant paragraphs on induction therapy. Thanks!

Changes in the text: "The most recent National Comprehensive Cancer Network (NCCN) 2023 guidelines recommend en-bloc resection as the predominant treatment for patients with T3 N0-1 or resectable T4 N0-1 disease for patients with CWI. In the absence of functional limitations, there are no absolute contraindications to chest wall resection and reconstruction.

For IIIA tumors (T4, N0-1), it is preferred to re-evaluate the possibility of surgery after preoperative systemic therapy (concurrent chemoradiotherapy or chemotherapy) on a planned basis, and then consider further treatment options (redo-operation and chemotherapy or chemoradiation therapy) based on the status of the postoperative margins. For patients with positive surgical margins (R1/R2), reoperation combined with adjuvant chemotherapy or radiotherapy and chemotherapy is recommended." (See Lines 70-79, Page 3)

Comment 4: The organization and naming of paragraphs is questionable. After "Methods" it appears "1. Whether the operation achieves the radical goal." First of all, either all paragraphs are numbered or none of them is.Secondary, some paragraph names can be improved (e.g. "Whether the operation achieves the radical goal" could be renamed "The impact of resection margins" or even "resection margins" if that was a subparagraph of a "prognostic factors" paragraph, consider this).

Reply: Thank you so much for this helpful comment! We agree with you that the paragraphs should be improved to make them more precise. Based on your comments, we have reformatted and subdivided the paragraphs to make them easier to read and improve the logical relationship between paragraphs. Thank you!

Changes in the text:

E. Clinical factors associated with prognosis

1. The impact of resection margins

As early as 1999(65), the need for complete surgery was articulated. Even R1

resection with minimal residual disease is unfavorable for the patient's prognosis. There is a significant difference in five-year survival between patients with complete resection and those with incomplete resection (24%-32% vs. 4%-13%) (65–67). (See Lines 306-311, Page 11)

Comment 5: Third, the organization of the paragraphs should follow some criteria. Why start from resection margins, depth of chest wall involvement, lymph node assessment (which are discussed as a prognostic factor), then continue with pre-operative assessment, then, extent of surgical resection, then complications (those associated with resection and those with reconstruction…, does it make sense to split these two?)… and then materials for reconstruction? This makes the whole read very chaotic, difficult to follow.Ideally, a logical way to organize this would be to start from pre-operative assessment, then surgical planning (approach, extent of resection…), materials for reconstructions (which is something that has to do with the surgical procedure), and then, at the end, prognostic factors for survival. Organizing the body of the review in paragraphs and subparagraphs would also help (example: pre-operative assessment, surgical issues, outcomes, prognostic factors, each of these with their subparagraphs).

Reply: We greatly appreciate and thank the reviewer for pointing out the problems in the structure and logic of our review writing. We acknowledge these errors and have made corresponding modifications in the review based on the reviewers' comments, including renumbering the paragraphs and restructuring the review. (See Lines 108-355, Pages 4-13) Thank you!

Comment 6: The biggest flaw of this paper is that it really does not help the reader in providing a knowledge about the most important issues concerning NSCLC with CWI. I make some examples:There's not even one paragraph discussing exactly when and if an induction treatment is indicated. There is only a vague citation of the guidelines in the introduction section, which is not clear at all. This issue has been the subject of many trials. I would expect a paragraph, or even a table, comparing outcomes between different induction treatments (or induction vs no induction), and indications and level of evidence to suggest an induction treatment in patients with CWI. There's nothing about that.

Reply: We are very grateful to the reviewer for these critical comments. We apologize for the insufficient description of important clinical issues in the review. Based on this comment, we have added a section on induction therapy for patients with CWI. Thank you very much!

Changes in the text:

"B. ***Evaluation and implementation of induction/neoadjuvant therapy (NAT)***

As shown in the background, there is currently a lack of clinical guidance on the indications and contraindications for NAT in patients with CWI. Indications for NAT are based on multidisciplinary team (MDT) discussions and no clear criteria are established.

The status of lymph nodes is one of the factors that should be considered whether to use neoadjuvant therapy. In NSCLC patients with suspected severe nodal involvement, mediastinoscopy should be used to assess nodal status preoperatively. If hilar or mediastinal involvement is found preoperatively, NAT is one of the treatment options that should be discussed by the MDT(19).

Another factor to consider is whether the tumor has invaded the ribs. A propensity score-

matched retrospective study of 521 patients with pT3-T4 NSCLC from Zhao et al.(20)demonstrated that patients in the pathological rib invasion subgroup had similar 5-year overall survival rates as patients with pT4 tumors. Another study (21)demonstrated that rib invasion is a poor prognostic factor, in which three patients who did not receive preoperative treatment were confirmed to have insufficient surgical margins. Postoperative local and distant recurrences were more common in patients with pathological rib invasion.

For definite hilar/mediastinal lymph node and rib invasion, NAT is recommended for patients after discussion with an MDT. The purpose is to improve the radical rate of resection, obtain a reliable safety margin, preserve important structures, and eradicate micrometastases, and extend the patient's survival benefit (22).

Table 2 shows the status of neoadjuvant therapy research for patients with potentially operable NSCLC. A phase 2 trial in Japan (23,24)demonstrated that the survival advantage for patients who received NAT was most pronounced when they achieved complete pathological response, compared with patients who had residual disease. However, this study included superior sulcus tumors, and the proportion of CWI among patients is unknown. Lack of radiographic response to NAT is associated with a significantly increased risk of poor overall survival (OS), which helps select patients who may benefit from subsequent adjuvant therapy(25). For patients who do not respond radiologically to induction therapy, additional adjuvant therapy should be considered, as surgery alone may not provide long-term benefits. MDT discussion should be carried out throughout the entire course of patient treatment, including subsequent adjuvant therapy, because in another Japanese study(21), even though five of the patients achieved pathological complete response (PCR) after induction therapy, two developed brain metastases.

An international, open-label, phase 3 trial from Forde et al.(26)shows that preoperative immunotherapy using checkpoint inhibitors can improve pathological response and OS compared with neoadjuvant chemotherapy alone, which provides a new option for neoadjuvant therapy.

Currently, there is still a lack of high-level evidence on whether and which type of NAT patients with CWI should receive." (See Lines 135-170, Pages 5-6 and Table 2)

Comment 7: Prosthetic materials… first of all should be divided depending on the tissue to be reconstructed: sternum, ribs, or diaphragm? It is not all the same, prostheses have different requirements based on the tissue to replace. Secondary, a simple list of all possible bioprosthetic materials is really not enough. Maybe a table detailing pros and cons of each material, as well as the place that is supposed to go, would help; moreover, the reader should get an idea of what is used the most in surgical series. While I understand that this is a narrative review, tables are still fundamental. There's not even one table listing the most relevant case-series, with a number of included patients, type and % of pre-operative treatment, and outcomes. This is a minimal expectation from such a type of review. It is really hard for any reader to catch what is the overall experience and what are the outcomes with this kind of surgery.

Reply: We are very grateful to the reviewer for your insightful and valuable comments. In response to these comments, we have tried our best to make targeted modifications to the existing problems in the review. The main topic of the article is chest wall resection for patients with CWI. In our early assumptions, chest wall reconstruction was a smaller topic that may not

be necessary, but it is undeniable that chest wall reconstruction plays a role in preoperative planning and patient prognosis.

We strongly agree that the selection of reconstruction materials should be based on relevant factors such as the surgical site and reconstructed tissue. We would like to ask the reviewers to forgive us for the incomplete review of this section on chest wall reconstruction surgery (especially the materials section). The reviewer's question regarding surgical series is important, and in response to this comment, we have reviewed and provided tables of important patient series with surgical reconstruction. Thank you very much!

Changes in the text: *"Table 3 summarized the most important series on the chest wall reconstruction (including the clinical outcomes)."* (See Lines 298-299, Page 11)

Comment 8: There's no "Outcomes" paragraph. Overall, I believe that the paper fails in what the aim of a narrative review is. Focusing on main issues, summarizing evidence, and, possibly, giving some insight on a topic.

Reply: Thanks for this valuable comment. Based on the "Narrative-Reviews-Structure-template" given by the journal, we modified the "Outcomes" to present the "Strengths and limitations" of this review and the conclusion section. Thank you very much!

Changes in the text:

"F. Strengths and limitations

Strengths: This review focuses on NSCLC patients (non-SST tumors) that invade the chest wall, and comprehensively covers preoperative diagnosis, preoperative treatment, surgical planning, technical points of resection and reconstruction surgery, and prognostic factors for patients. discussion. It may provide readers with a basic understanding of the historical development and latest clinical advances in the diagnosis and treatment (chest wall resection and possible chest wall reconstruction) of a subset of NSCLC patients that invade the chest wall.

i. *Limitations: Based on the nature of the Narrative Review, this review did not conduct a quantitative analysis of the specific literature searched. It only conducted basic screening based on the evidence level of the literature and did not implement strict quality control assessment.*

4. Conclusion

Surgery plays an important role in treating NSCLC patients with CWI, and a collaborative, experienced (MDT is an essential component of a patient's successful treatment process. In the future, more high-quality clinical research is needed to focus on the CWI patients so that patients can receive more effective treatment options and better clinical prognosis." (See Lines 357-373, Page 13)