Peer Review File

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Reviewer A

In this manuscript the Authors analyze the outcome of surgical treatment for stage III squamous cell lung cancer after neoadjuvant immunochemotherapy in a group of 17 patients (Stage IIIA in 7 and IIIB in 10). Favourable results were observed, with no postoperative mortality and minimally invasive procedures completed in 12 of the patients. A high rate of major pathological response (70.6%) was observed, with a 2-year disease-free survival of 76.6% and an overall survival of 82.5%. The study has some limitations as the retrospective design of the study, the relatively limited number of patients included, the relatively short follow-up and the heterogeneity of the type and duration of the neoadjuvant treatment, with different immunotherapy treatments and different number of cycles performed. Moreover, nodal involvement was also heterogeneous, and only 10 patients had an N2 nodal involvement. Nevertheless, the topic is of interest. The Authors should address in further detail some issues as specific technical points when performing surgery after induction immunochemotherapy, in particular with a minimally invasive surgery approach. The oncological results according to nodal status should also be reported.

Reply: Thank you for your comments. We have added a detailed description of the surgical techniques in the Methods, please see Page 5-6, Line 151-162. We also added the pathological T stage in the Table 2.

Reviewer B

This is an interesting report on an emerging new therapeutic strategy for stage III NSCLC. The patient outcome is good and confirms results of phase 2/3 trials in the real-world setting. However, some points could be improved before publishing:

1. Highlight box: neoadjuvant CRT is not the standard modality cyrrently. At least in Europe, we rarely performa radiotherapy before surgery (we mainly use neoadjuvant chemotherapy followed by surgery and postoperative radiotherapy). There are several clinical trials on that. Alos "late-stage resectable" is not appropriate. Please rephrase as "locally advanced resectable" or similar.

Reply 1: Thank you for your suggestion, we agree with you, in fact the neoadjuvant therapy in China is similar to that in Europe, so we have corrected our expression, we also modified the “late-stage” to “locally advanced resectable”. Please see Highlight box.

2. Could you please clarify whether stage IIIA/B was considered according to TNM8 or TNM7?

Reply 2: The staging of this study is in accordance with the TNM 8th edition, and we have illustrated it in Methods，please see Page 4, Line 117-118.

3. Could you please some more information on the type of N2 disease for the study patients? (single-level, bi-level, mulitlevel?). Could you also please provide a supplementary Table with all 17 patients and the type of surgery each received according to the N-status? This is relevant because of the current discussion how to handle multistation N2 disease

Reply 3: Thanks for your valuable comments, we have made an addition to the type of N2 disease, pleases see Table 1. We also provide supplementary table, summarizing all 17 patients and the type of surgery each received according to the N-status, please see supplementary table 1.

4. Could you please comment on the fact that no postoperative therapye was given in this study? (similar to CM-816, but different than KN-671, AEGEAN, Neotorch etc.)

Reply 4: Thank you for your comment. In fact, all patients have received adjuvant therapy after surgery. Generally, they received 2 cycles of chemotherapy before and after surgery and received immunotherapy for 1 to 2 years. Some patients achieved pCR, because of refusal to accept postoperative adjuvant chemotherapy, immunotherapy will be given for a period of 1 to 2 years. Since this is a real-world retrospective study, the treatment plan used is not uniform, so we did not describe this part of the content in the manuscript. We will try our best to achieve the treatment plan and provide more complete data for future research.

Changes in the text: None.

5. Were these patients treated in the routine setting (if yes, how, since there is no approval yet?) or within a clinical trial? Could you please provide the details about the ethical approval?

Reply 5: Thank you for your comment. Since this is a retrospective study, it is difficult to treat all the patient in the routine setting, resulting in high data heterogeneity, but this study was approved by the hospital ethics committee, and we illustrated it in Page 5, Line 137-140 and uploaded the Ethical Review Approval Document in Supplementary Material.

Reviewer C

I would like to congratulate the authors of the interesting manuscript entitled "Neoadjuvant immunotherapy combined with chemotherapy in the treatment of 3 stage III lung squamous cell carcinoma: a retrospective cohort study".

In their retrospective cohort study, the authors analyze the outcomes of neoadjuvant immunochemotherapy followed by surgery for stage III squamous cell lung cancer. The study is reported according to the STROBE guidelines. The manuscript is written in a clear and understandable manner in good quality English. The study is of great clinical

value and may be useful to oncologists and thoracic surgeons involved in the treatment of lung cancer.
I have no major comments on the article, but as a thoracic surgeon, I would be interested in a slightly broader discussion of the issues related to surgery. In the results, I would suggest specifying the type of minimally invasive approach used (VATS? RATS?), as well as the rate and reasons for conversion to thoracotomy. I would suggest adding a brief description of the impact of preoperative immunotherapy on intraoperative difficulties and complications in the discussion.
Other than that, I don't have any major comments. Once again, congratulations on a very interesting study.
Reply: Thanks to your comment. We have added a detailed description of the surgical techniques in the Methods, please see Page 5-6, Line 151-162. Also in Table 3, we have changed the "minimally invasive approach" to "VATS". In this study, 5 patients underwent thoracotomy due to anticipated complexity, no conversion to thoracotomy during operation, and we described it in Page 9, Line 262-263. We added some description and references (ref 24 and 25) of the impact of preoperative immunotherapy on intraoperative difficulties and complications in the Discussion, please see Page 9, Line 270-277.

Reviewer D

I have some comments and suggestions and I thank the authors for reading and considering them.
1. In your Introduction section (lines 95-97) you state that squamous cell type of NSCLC is rarely suitable for targeted therapy and (lines 99-100) that there is little evidence on the benefits of immune-chemotherapy induction in squamous cell carcinoma. According to this, you justify the relevance of your descriptive study on a short series of cases. In your references 14 and 15 (and others in the literature) the authors include good numbers odd squamous lung carcinomas in their analysis, 16 (35% of cases) in reference 14 and 182 cases in reference 15. Thus, there is already some evidence on the topic decreasing the relevance of your report.
Reply 1: Thanks to your comment. Indeed, according to the existing literature, we have deleted the content that was not accurate enough, please see the "Introduction" section.

2. I reviewed your reference 6 to check if those authors conclude that squamous cell lung carcinoma is a particularly aggressive subtype making surgical option challenging. In the whole text I couldn't find such a conclusion. Please consider changing your sentences in lines 72-73.
Reply 2: Thanks to your comment. We have revised the expression and removed incorrectly cited references, please see Page 3, Line 76-78.

3. In your text there is no information on the PD-L1 tumour proportion score in your series. According to other reports in the literature, PD-L1 was significantly higher in

patients who had a complete pathological response. Please include some data on this or, if you have no data, comment as one of the major limitations of your study.
Reply 3: Thank you for your comment, we illustrated the defect as one of the major limitations of our study, please see Page 11, Line 325.

4. Include the occurrence of clinical N3 status as one of the exclusion criteria in your series.
Reply 4: Thanks for your advice. We have added N3 disease as one of the exclusion criteria, please see Page 5, Line 127.

5. You conclude (line 301) that perioperative morbidity and mortality in your series is acceptable. I'm kindly suggesting rewording as: "perioperative morbidity and mortality is comparable".
Reply 5: Thanks for your advice. We accepted your suggestion and revised it, please see Page 11, Line 335.

6. The last conclusion (lines 302-303) should be removed. You have not designed the study to compare parameters of surgical difficulty with other series of cases.
Reply 6: Thanks for your advice. We have deleted the statement, please see the "Conclusions" section.

Reviewer E

Revision of the manuscript entitled "Neoadjuvant immunotherapy combined with chemotherapy in the treatment of stage III lung squamous cell carcinoma: a retrospective cohort study", by Jing Guo et al.

I thank the authors for this manuscript, which is well-written and well-organized.
I would have some comments.
Line 124: might the authors explain what are active and passive methods?
Reply: Thanks to your comment. The active method means that patients go to the outpatient clinic for follow-up regularly, and the passive method means that we follow up patients by telephone, email, etc.
Changes in the text: We have added the meaning of active and passive methods in the "Methods" section, please see Page 5, Line 128-130.

Lines 124-126: did the authors use an informatic or paper-based database to collect patients' information?
Reply: Thanks to your comment. Yes, we have our own informatic database, and the clinical data of patients in the database will be updated every year.
Changes in the text: None.

Line 130: might the authors distinguish between LSCC-related and not-related causes of death?
Reply: Thanks to your comment. Due to the small sample size of this study, the 2 deaths that occurred so far were all LSCC-related deaths.
Changes in the text: None.

Lines 143-144: does this sentence mean that every 6 weeks each patient was subjected to a tissue biopsy of the tumour? How did you measure tumour size? Please explain.
Reply: Thanks to your comment. In fact, all patients accepted radiographic examination to assess the tumor's response based on the RECIST version 1.1, not tissue biopsy. We have a specific description in the Study evaluation section in Methods, please see Page 6, Line 170-171.

Lines 160-161: NR is defined as non-response; would this include all the above-mentioned criteria (i.e. more than 10% viable tumour cells, necrotic/fibrotic tissue etc...)?
Reply: Thanks for your advice, we have made a definition of pathological response (MPR, pCR, pPR, pNR) based on references 21 and 22 to make it more accurate, please see Page 6, Line 175-184.

Line 166: the sentence "were expressed as mean (SD)" should be re-written as mean ± SD" since as it seems that the mean is SD, please revise.
Reply: Thanks to your advice and we have made a revision of it, please see Page 6, Line 189 and Table 1 and Table 3.

Lines 179-182: in the patients' cohort the authors included stages IIIa and IIIb, which were N0 to N2, but some of IIIb might also be N3, what about them? Would the authors please explain?
Reply: Thanks for your comment, N3 disease is not resectable, so we have added N3 disease as one of the exclusion criteria, please see Page 5, Line 127.

Lines 273-276: it is not reasonable to compare stages I to III.
Reply: Thanks to your advice, we have deleted the reference.

Reviewer F

1. PDL1 data needed, very small size, very diverse treatments.
Reply1: We agree that this is the major limitation of our study and illustrated in the Discussion, please see Page 11, Line 324-329. We are expanding the sample size of the study and ensuring the homogeneity of the data as much as possible. Thanks again for your comment.

2. The bibliography should be updated.

Reply 2: Thanks to your advice. We removed some outdated references and added some newer references.