Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-24-17

Reviewer A

Major changes

- Graphical abstract: as previously indicated it is not included. Authors beyond the description on page 3 should do this correctly.

Reply: Thanks very much for your reminder! We have added it.

Changes in the text: We have added it (see Page 4).

- Results, section 3.2: safety normally goes at the end of the results and separate from efficacy. If the authors do not want to include efficacy as a separate item so as not to increase the space, they can join it with survival, which is more correct.

Reply: Thanks for your comment! We have rearranged the paragraphs as advised. A new section "3.4 Safety and surgical complications" was added to the end of the Result. While "efficacy" and "survival" were combined into one item (3.3 Efficacy).

Changes in the text: We have modified our text as advised (see Results, section 3.3 & 3.4)

- Results, lines 250-251: was EGFR and ALK analysis not performed prior to the decision to initiate neoadjuvant chemo-immunotherapy? This should be stated in the inclusion criteria of the material and methods.

Reply: Thanks for the critical question. EGFR mutations and ALK rearrangements status analysis were not recommended routinely before treatment, while they were performed in some patients based on individual surgeon recommendations and patient wishes. Patients with EGFR mutations and ALK rearrangements were not excluded from neoadjuvant chemo-immunotherapy and our analysis.

Changes in the text: We have added the above statement in the inclusion criteria of the material and methods (see Patients and methods, lines 152-156,158).

- Results: What subsequent adjuvant treatment did patients receive after surgery?

Reply: Thanks for the critical question. Adjuvant treatment was received by 22.8% of the patients. We have summarized the details in Table S2.

Changes in the text: We added the details about adjuvant treatment in Results (lines 244-249) and Table S2.

Minor changes

- Introduction, lines 121-125: the aim of the study should be stated at the end of the introduction, not part of the material and methods.

Reply: Thanks for your comment! The aim of the study is stated at the end of the introduction.

Changes in the text: We have put the aim of the study at the end of the introduction (see

Introduction, lines 131-135).

- *Human genes should be indicated in italics.*
Reply: Thanks for pointing out this problem! We have corrected them in this essay.
Changes in the text: We have corrected this problem throughout the article as advised.

- *Patients and methods: permitted chemo-immunotherapy schedules should be indicated in the inclusion criteria.*
Reply: Thanks for pointing out this point. All PD-1/PD-L1 immune checkpoint inhibitors combined with platinum-based chemotherapy were permitted. Because our study was conducted in a real-world setting, we did not limit the choice of specific drugs. We present the specific drug names and the number of patients who used them in Table S1.
Changes in the text: We have modified our text as advised (see Patients and methods, lines 161-162; Table S1)

- *Patients and methods: PET-CT was performed on all patients? Specify, prior to a neoadjuvant schedule should be mandatory in all patients.*
Reply: Thanks for your question. In our study, prior to a neoadjuvant schedule, patients could choose to undergo PET-CT or a combination of chest CT+ abdominal CT + brain MRI + radionuclide bone scanning according to their wishes and economic conditions. But they must choose one or the other to exclude distant metastasis.
Changes in the text: We have changed our expression in the text (see Patients and methods, lines 170-173)

- *Patients and methods: as above, re-evaluation after chemo-immunotherapy and prior to surgery was performed with PET-CT?*
Reply: Thanks again! As above, not all patients relied on PET-CT for comprehensive preoperative radiological evaluation. Some patients relied on a combination of hest CT+ abdominal CT + brain MRI + radionuclide bone scanning.
Changes in the text: We have changed our expression in the text (see Patients and methods, lines 181-182).

- *Results: everything related to surgery should be reported in a separate section.*
Reply: Thanks for your practical advice! We have rearranged the paragraphs. A new section “3.2 Surgery summary” was added in the results.
Changes in the text: We have modified our text as advised (see Results, section 3.2)

- *Results: were there any subsequent relapses among patients with pCR? This is a fundamental fact that the authors should highlight in order to know the subsequent adjuvant treatment.*
Reply: Thanks for your critical advice! One patient who achieved pCR was found to have intracranial metastasis at 13 months after surgery.
Changes in the text: We have added the data in the results (see Results, lines 301-303).

Reviewer B

1. As one of inclusion criteria, the authors described that "(4) received radical resection and systemic lymph node dissection". On the other hand, in the Abstract and in the Main text, the authors described that "No treatment-related death was observed during neoadjuvant treatment". Because patients who died during neoadjuvant treatment cannot receive radical resection, such description sounds strange. The reviewer considers that the authors should analyze all patients who received neoadjuvant immunotherapy including those who could not receive pulmonary resection.

Reply 1: Thanks for your comment, our description was indeed misleading. Although the description of treatment-related deaths during neoadjuvant therapy was true in all 257 neoadjuvant chemo-immunotherapy patients, it conflicted with the inclusion criteria of this study. So we deleted it and analyzed patients who did not undergo surgery after neoadjuvant therapy in the results as advised.

Changes in the text: We deleted the description of treatment-related deaths during neoadjuvant therapy and analyzed patients who did not undergo surgery after neoadjuvant therapy in the results as advised (Results, lines 316-324 & Figure S1).

2. Furthermore, the rate of patients who could not receive surgery (15-20% in previous clinical trials) is also important to report.

Reply 2: Thanks again for your comment, we have analyzed patients who did not undergo surgery after neoadjuvant therapy in the as advised.

Changes in the text: We have analyzed patients who did not undergo surgery after neoadjuvant therapy in the results as advised (Results, lines 316-324 & Figure S1).

3. *As the authors emphasize "the real-world setting" in this manuscript, it would be important to know how many patients, among their cohort, were not ineligible for the inclusion criteria of clinical trials such as CheckMate 816 study (and what was the reasons for the ineligibility).*

Reply 3: Thanks for your comment! In RCTs, the researchers set strict standards to meet different requirements. However, in the real clinical setting, things might not be the same. Patients' age, gene mutational landscape, and general conditions might all contribute to various clinical outcomes. Such as, in our study, 85 (53.8%) of patients with no PD-L1 status available; and 8 (5.1%) patients with EGFR mutation, were not ineligible for the inclusion criteria of CheckMate 816. Compared with clinical trials, the demographics of patients are also more closely aligned with clinical practice in our study (e.g., more men, smokers and stage III tumors).

4. What was the cause of the excessive hemorrhage that was observed in more than 10% of patients? Was that associated with neoadjuvant immunotherapy?

Reply 4: Thanks for your comment! The excessive hemorrhage might not necessarily

correlate with neoadjuvant immunotherapy, since this study has enrolled a relatively large proportion of patients at stage III, indicating a higher surgery difficulty. Moreover, a larger proportion of calcification of lymph nodes across patients from Northern China might also bring difficulties to the lymph node dissection process, thereby increasing hemorrhage during the surgery.

5. The details of patients who died due to irAE should be described. The authors described that at least one patient died from severe side effects of postoperative immunotherapy.

Reply 5: Thanks for your comment! The details of patients who died due to irAE have been added to the text (Results, lines 306-309).

Changes in the text: The details of patients who died due to irAE have been added to the text (Results, lines 309-311).

Reviewer C

1. The patients were treated between 2019 and 2022, at that time there were only studies such as checkmate 816 or the AGEAN study in which immunochemotherapy was tested. At that time, there was no approval for preoperative immunochemotherapy. I am surprised that so many patients were treated in this way and wonder where the approval for this procedure came from.

Reply 1: Thanks very much for your question, please allow me to explain from the following aspects.

Firstly, as is well-known, CheckMate-159 study which was published in 2018 demonstrated impressive efficacy and safety of neoadjuvant immunotherapy in NSCLC. And then NADIM trial showed unprecedented preliminary efficacy with controllable safety of neoadjuvant chemo-immunotherapy at the 2018 ASCO Meeting. Furthermore, at that time, the combination of immunotherapy and chemotherapy had shown good safety and effectiveness in neoadjuvant therapy of other cancers and advanced treatment of lung cancer.

Secondly, early on, our patients were enrolled in neoadjuvant chemo-immunotherapy very cautiously. Of the 158 patients included in the study, the proportion of patients in 2019 was small (11/158, 7.0%). The 11 patients were mostly at stage III (7 patients at stage IIIB and 2 at stage IIIA) and we want to fight for the opportunity of surgery by active neoadjuvant therapy, which was expected to shrink the tumor and reduce the stage. We explained the principle and purpose of neoadjuvant chemo-immunotherapy to the patient in detail and obtained the patient's informed consent. This procedure has also been approved by the hospital and relevant administrators.

Thirdly, this study was conducted in two large-scale centers in northern China, with a total number of 465 beds, so we have a relatively large number of cases.

I hope my explanation can relieve your doubts to a certain extent and thank you again for your question!

2. In terms of therapy, patients have received a wide variety of immunotherapeutic agents. Here, too, I wonder where the approval came from. Furthermore, the authors should explain why so many different immunotherapeutics were used. Why didn't they stick with one or two? What is the decision-making process here?

Reply 2: Thanks for your comment! It would be a more promising study if the immunotherapeutic agents could be uniform. In the real-world setting, however, doctors at the two centers have different patterns of immunotherapeutic agent selection based on their preferences, patients' different responses, and patients' financial circumstances. All medications were taken with full consideration of the availability of drugs and the patient's wishes. As a retrospective study, these possible confounding factors are unavoidable limitations.

3. In 53.8% of patients no PD-L1 status was available, why did these patients nevertheless receive immunotherapy?

Reply 3: Thanks again for pointing out this issue! The predictive effect of PD-L1 expression level in neoadjuvant immunotherapy has not been confirmed. Several studies hold views that MPR was not associated with PD-L1 expression, such as the CheckMate-159 study and LCMC3 study, highlighting the limitations of the PD-L1 assay as an effective predictor for neoadjuvant immunotherapy. And large Phase 3 clinical trials like CheckeMate-816 also included people with negative PD-L1 status. Therefore, we do not routinely test for PD-L1 before neoadjuvant immunotherapy.

4. The question is whether chemotherapy alone would have had the same effect in patients without PD-L1 expression. For this reason, the data on pathologic response should be evaluated with caution.

Reply 4: Thanks for your reminder. Our study does have some limitations as a single-arm, real-world, and retrospective study, and we have added relevant explanations at the end of the discussion section.

Changes in the text: We have added relevant explanations at the end of the discussion section. (see Discussion, lines 445-447).

5. Why have some patients received 2, 3 or 4 cycles of immunochemotherapy? What was the decision-making process here?

Reply 5: In the early application stage of neoadjuvant chemo-immunotherapy, the optimal treatment cycle is still being explored. And the drug cycle used in different clinical trials is different (basically 2-4 cycles). Therefore, we decided the number of treatment cycles based on comprehensive consideration of patients' tolerance to drugs and imaging remission of lesions after the second cycle of treatment, according to experience and expert consensus (Liang W, et al. Expert consensus on neoadjuvant immunotherapy for non-small cell lung cancer. *Transl Lung Cancer Res.* 2020;9(6):2696-715.).

Changes in the text: We have added the decision-making process to the text (Patients and methods, lines 183-186).

6. Did the authors find differences in postoperative morbiditiy if patients had 2,3 or 4 cycles of immunochemotherapy?

Reply 6: No significant difference in postoperative morbidity was found between the different neoadjuvant treatment cycles (21.9% for 2 cycles, 20% for 3 cycles and 18.9% for 4 cycles, P = 0.943).

Changes in the text: We have added data to the text. (see Result, lines 329-331).

7. There was a high percentage of patients with IIIa and IIIB stages, How was the adjuvant therapy? Had the patients ungoing immunotherapy, if yes how long? Did they receive again chemotherapy? Did this differ between patients and the number of preoperative immunochemotherapy cycles? This should be described.

Reply 7: Thanks for your question, we have described details about adjuvant treatment in the text and Table S2. Adjuvant treatment was received by 22.8% of the patients (including 18.4% for adjuvant immunotherapy and 11.4% for chemotherapy). Most patients with adjuvant immunotherapy were suggested to take up to 1 year, and partial patients with pCR may be recommended to shorten it to 6 months. The rate of adjuvant therapy was significantly lower in patients who received 4 cycles of neoadjuvant therapy than in those who received 3 cycles of neoadjuvant therapy (0.8% vs. 30.0%, P = 0.042). While there was no significant difference in the proportion of adjuvant therapy in other pairwise comparisons (2 cycles vs. 3 cycles: 17.1% vs. 30.0%, P = 0.186; 2 cycles vs. 4 cycles: 17.1% vs. 10.8%, P = 0.64).

Changes in the text: We have added data to the text (see Result, lines 244-249 and Table S2).

8. How many patients had radiation therapy and if they had radiation what were the reasons?

Reply 8: Thanks for your comments. We have summarized the details of adjuvant treatment in Table S2. Radiation therapy was received by 5 (3.2%) of the patients. Patients with risk factors such as N2 station lymph node metastasis who could not tolerate adjuvant chemotherapy or immunotherapy were advised to undergo adjuvant radiotherapy.

Changes in the text: We added the details about adjuvant radiation in Table S2.