Peer Review File

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Reviewer #A:

In this retrospective study the authors compare unresectable NSCLC patients who received concomitant immunotherapy compared to sequential immunotherapy treated with chemoradiotherapy. The topic as such is very relevant and therefore of high interest for the thoraco-oncological community. Although the results in this very small cohort are promising a few issues remain to be addressed.

1. PFS: The patient number is very small with 36 versus 42 patients in each group. If one finds statistically significant differences ($p < 0.01$ for PFS) in cohorts that are so small, the real difference and clinical impact must be huge (if it is not a statistical artefact). I believe that the authors should include more patients to verify their results.
Response: Thank you for your valuable feedback. We have been working hard to collect samples of stage III unresectabe non-small cell lung cancer, but due to the limited number of such samples and the COVID-19 epidemic, we have not been able to collect enough samples, and we apologize for any inconvenience this may have caused.

2. Lines 159 – 160: Patients received a bone scan and abdominal ultrasound as follow-up imaging. I think that this is not the optimal procedure to determine whether a patient has distant metastases or not. The standard should be whole body CT. Why was it not done? Please comment.
Response: Thank you for your valuable comments. Your expertise and thoughtful comments certainly help to improve the quality of our work. When we reconfirmed our case, we found that our patients did have brain lesions assessed by MRI or CT of the brain, whereas extracranial lesions were assessed by bone scan, CT of the chest, and abdominal ultrasound. Retrospective studies do have such limitations, and we regret the confusion caused to readers!

3. Toxicity was not assessed at all. This is – to my mind – a major weakness of this paper since concomitant immunotherapy is not yet standard of care. It would be of special interest to the reader to see how concomitant IO goes together with high dose radiation therapy with total doses >60Gy. Please provide these data.
Response: Thank you for this valuable feedback. Your expertise and thoughtful comments have undoubtedly helped to strengthen the quality of our work. However, this retrospective study had a small sample size, with two patients (2/36, 5.5%) receiving both IO and high-dose radiotherapy at a total dose of more than 60 Gy, which prevented us from counting the efficacy of the high dose. Some patients were reviewed at other hospitals, and physicians assessed toxicity on-site, which has not yet been shown in the case system. Therefore, we did not reflect toxicity assessments in the article. Retrospective studies do have such limitations, and we regret the confusion caused to readers!

4. Local control (defined as tumour re-growth within the PTV) was also not mentioned: Do patients who received more than 60 Gy have better local control?

Response: Thank you for this valuable feedback. Your expertise and thoughtful comments have undoubtedly helped to strengthen the quality of our work. Five patients (5/78, 6.4%) receiving high-dose radiotherapy at a total dose of more than 60 Gy, which prevented us from counting the efficacy of the high dose. Retrospective studies do have such limitations, and we regret the confusion caused to readers!

5. Line 64: Concurrent immunotherapy instead of Immunotherapy concurrent
Response: Thank you for this valuable feedback. We apologize for overlooking the language quality of the manuscript, and we have made revisions to the language in this manuscript. The relevant changes are in line 65 (Concurrent immunotherapy with chemoradiotherapy may be associated with delayed disease progression as compared to consolidative immunotherapy following chemoradiotherapy.).

6. Lines 67 – 68: Leave out.
Response: Thank you for your valuable feedback. We apologize for neglecting the linguistic quality of the manuscript and have removed Lines 67 - 68.

7. Lines 82: What is meant by more limited outcome?
Response: Thank you for this valuable feedback. We apologize for overlooking the language quality of the manuscript, and we have made revisions to the language in this manuscript. The relevant changes are in line 73-75 (Our findings indicated that for unresectable stage III NSCLC without sensitizing EGFR/ALK alterations, consolidative immunotherapy following chemoradiotherapy may be less effective than than immunotherapy concurrent with chemoradiotherapy.).

8. Line 87: What is meant by sensitized EGFR/ALK alterations? Does it mean EGFR/ALK mutations?
Response: Thank you for your valuable feedback. Your understanding is very accurate and we apologize for neglecting the quality of the language in the manuscript, which we have revised to reduce the disturbance to the reader. The relevant change is on line 77-79 (Based on the results of this study, we suggest that immunotherapy concurrent with chemoradiotherapy might improve outcomes as compared to sequential approach in patients with unresectable stage III NSCLC without EGFR/ALK mutations.).

Reviewer #B:

Overall, this analysis is well-written, with clear aims and an excellent introductory section. The supporting motivation for the manuscript is clearly outlined. The subject discussed is highly topical and covers an essential subject for the radiation oncology community. Nonetheless, the manuscript suffers from minor flaws that the authors must address prior to the publication that related to the discussion section. Below are my specific comments:

Discussion:
I have few concerns about the discussion:

1. It currently reads as a review of what other studies have reported, which is interesting and

important, but they are not clearly linked back to the results. Can you emphasis your results compare to other studies?

Response: Thank you for this valuable feedback. The PACIFIC trial, the GEMSTONE-301 trial, and the KEYNOTE-799 trial have shown that combining immunotherapy with chemoradiotherapy is effective in improving the survival prognosis of patients with epidermal growth factor receptor (EGFR)/ALK-negative stage III unresectable NSCLC, however, it did not elucidate the efficacy of concurrent immunotherapy and consolidation immunotherapy in the of concurrent immunotherapy and consolidation immunotherapy. This inspired us to explore whether the order of immunotherapy intervention led to the difference in efficacy, and therefore we performed a statistical analysis of relevant cases in our institution. The relevant change is on line 258-261, 281-282 (Our findings suggest that for this population, PFS of the concurrent immunotherapy group was significantly longer than that of the consolidative immunotherapy group, especially among those who had a non-primary initial site of recurrence; Unfortunately these observational studies did not elucidate the differences in efficacy between concurrent and consolidative immunotherapy.).

2. Discuss the results of the pacific scheme with the data published in the real world and the doubts raised such as time from the end of concomitant treatment to the start of immunotherapy, duration of immunotherapy, etc… Please check below papers for an additional clarity in this matter, Locally advanced non-small cell lung cancer: current issues and recent trends. DOI: 10.5603/RPOR.a2023.0019

Response: Thank you for this valuable feedback. We have carefully considered your suggestions and made revisions accordingly. The relevant change is on line 258-264 (Our findings suggest that for this population, PFS of the concurrent immunotherapy group was significantly longer than that of the consolidative immunotherapy group, especially among those who had a non-primary initial site of recurrence. The PACIFIC trial is the most widely recognized radioimmunotherapy combination therapy for NSCLC. The PACIFIC trial found that the use of durvalumab at the end of chemoradiotherapy provided robust and sustained overall survival compared to chemoradiotherapy alone.).

Reviewer #C:

1. First, the title needs to indicate the prognosis outcomes to be compared and the clinical research design of this study such as a retrospective comparative cohort study.

Response: Thank you for your valuable feedback. We apologize and have revised the title to be less intrusive to our readers. The relevant change is on line 2 (A retrospective comparative cohort study: concurrent versus consolidative immunotherapy with chemoradiotherapy in EGFR- or ALK-negative unresectable stage III non-small cell lung cancer)

2. Second, the abstract needs some revisions. The background did not indicate the purpose and potential clinical significance of this study. The methods need to describe the inclusion of subjects, assessment of baseline clinical factors, follow up procedures, and the statistical analysis for the independent prognostic role of the two treatment strategies. The results need to report the baseline clinical characteristics of the two groups and the test for their comparability, as well as multiple regression analysis results on the independent prognostic role of the two treatment strategies. It is misleading to report the findings from univariate analyses only. The conclusion needs to be tone down due to the methodology and analysis limitations of this study.

Response: Thank you for this valuable feedback. We greatly appreciate the time and effort you put into reviewing our manuscripts. Your expertise and thoughtful comments have certainly helped to enhance the quality of our work. The relevant change is on line 34-59 (Background: The purpose of this study was to determine whether concurrent immunotherapy with chemoradiotherapy was associated with improved outcomes compared to consolidative immunotherapy following chemoradiotherapy in patients with unresectable stage III non-small cell lung cancer (NSCLC), which may provide evidence-based medical evidence for the treatment of stage III non-small cell lung cancer.
Methods: A total of 78 EGFR/ALK-negative patients from the clinical database of the shanghai pulmonary hospital with locally advanced unresectable NSCLC and we evaluated them for baseline clinical factors, follow-up. Patients underwent concurrent immunotherapy with chemoradiotherapy or consolidative immunotherapy after chemoradiotherapy. Patients were classified based on initial site of progression (primary versus non-primary site). The study endpoints were progression-free survival (PFS) and time to death or distant metastasis (TDDM). Cox proportional hazards analysis was used to assess the factors affecting PFS and TDDM.
Results: The median follow-up time for both groups was 26 months, and there was no significant difference in baseline clinical characteristics ($P>0.05$). The patients receiving concurrent immunotherapy (n=36) had a longer PFS than those receiving consolidative immunotherapy (n=42) (median 32.4 *vs.* 15.5 months; $P<0.01$). The TDDM was also longer in patients with concurrent immunotherapy than those with consolidative immunotherapy (median 57.3 *vs.* 31.0 months; $P=0.01$). Furthermore, in a subset of patients with initial site of progression at a non-primary-site, patients undergoing concurrent immunotherapy had longer PFS than those undergoing consolidative immunotherapy (median 22.7 *vs.* 11.9 months; $P=0.03$).
Conclusions: Concurrent immunotherapy with chemoradiotherapy may be associated with improved disease progression outcomes as compared to consolidative immunotherapy following chemoradiotherapy.)

3. Third, the introduction is inadequate. The authors need to review and analyze more on the controversy regarding the prognosis of concurrent versus consolidative immunotherapy with chemoradiotherapy and clearly indicate the limitations and knowledge gaps of prior studies. The further concern needs to be clarified is the retrospective cohort data, which cannot answer the research question: the treatment efficacy of concurrent versus consolidative immunotherapy with chemoradiotherapy.

Response: Thank you for this valuable feedback. We sincerely appreciate your expert evaluation and insightful comments. The relevant change is on line 89, 96, 104 (Standard treatment for unresectable stage III NSCLC that does not involve sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) changes consists of radiotherapy concurrent with platinum-based doublet chemotherapy followed by immunotherapy (4, 5). Despite the survival benefit granted by immunotherapy in this setting, only 1/3 of patients are alive and disease free at 5 years (6). In one study, the 5-year overall survival (OS) was improved by 9% when consolidative immunotherapy following chemoradiotherapy was applied as compared to chemoradiotherapy alone (7).
Previous studies have reported that patients receiving radiotherapy and/or chemotherapy show significant immunogenic patterns, which may improve the response to immunotherapy (8). This inspired us to investigate a better clinical treatment protocol by exploring the sequential order of immunotherapy and radiochemotherapy. Therefore, comparisons of concurrent immunotherapy with chemoradiotherapy or consolidative immunotherapy following chemoradiotherapy warrants further investigation (6, 7, 9).
In our study, we conducted a single-institution retrospective study to investigate whether immunotherapy concurrent with chemoradiotherapy could be associated with disease control outcomes as compared to consolidative immunotherapy following chemoradiotherapy, which may provide evidence-based medical evidence for the treatment of stage III non-small cell lung

cancer.).

4. Fourth, in the methodology of the main text, please describe the clinical research design and sample size estimation procedures of this study. In statistics, please describe the test of the baseline comparability of the two groups and details of multiple analysis to adjust for the potential confounders.

Response: Thank you for this valuable feedback. Regarding the issue with the clinical research design, we made modifications on line 132-144 (***##Study design*** According to the sequence of immunotherapy and chemoradiotherapy, the patients were divided into 2 groups: concurrent immunotherapy (n=36; defined as concurrent chemotherapy, radiotherapy, and immunotherapy followed by consolidative immunotherapy) and consolidative immunotherapy (n=42; defined as concurrent chemotherapy and radiotherapy followed by consolidative immunotherapy). In addition, the patients who experienced disease progression (n=52) were further classified into those with site of initial progression as the primary site (n=21) versus a non-primary site (n=31). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethics Committee of Shanghai Pulmonary Hospital (No. K23-215) and informed consent was taken from all the patients.). Regarding the issue raised in your comment about the statistical analysis, we acknowledge the validity of your concern. We appreciate your attention to detail in this matter. We have not yet used sample size estimation procedures in retrospective studies. We will be sure to pay attention to this issue in future studies

5. Finally, some related papers should be reviewed and cited:

1. Käsmann L, Nieto A, Taugner J, Manapov F. PD-L1 expression on tumor cells as a potential predictive biomarker for patients with unresectable stage III non-small cell lung cancer treated with chemoradiotherapy followed by durvalumab. Transl Cancer Res 2023;12(4):705-708. doi: 10.21037/tcr-23-52.

2. Manapov F, Kenndoff S, Käsmann L. NICOLAS, DETERRED and KEYNOTE 799: focus on escalation of conventionally fractionated chemoradiotherapy by immune checkpoint inhibition in unresectable stage III non-small cell lung cancer. Transl Lung Cancer Res 2022;11(4):702-705. doi: 10.21037/tlcr-21-950.

3. Käsmann L, Taugner J, Eze C, Nieto A, Pelikan C, Flörsch B, Kenndoff S, Hofer TP, Nössner E, Schulz C, Unterrainer M, Tufman A, Klauschen F, Jung A, Neumann J, Kumbrink J, Reinmuth N, Bartenstein P, Belka C, Manapov F. Prospective evaluation of immunological, molecular-genetic, image-based and microbial analyses to characterize tumor response and control in patients with unresectable stage III NSCLC treated with concurrent chemoradiotherapy followed by consolidation therapy with durvalumab (PRECISION): protocol for a prospective longitudinal biomarker study. Transl Lung Cancer Res 2022;11(7):1503-1509. doi: 10.21037/tlcr-21-1010.

4. Baudoux N, Friedlaender A, Addeo A. Management of stage IIIA non-small cell lung cancer

(NSCLC): role of the chemotherapy. Curr Chall Thorac Surg 2022;4:18.

Response: Thank you for this valuable feedback. We appreciate your attention to detail in this matter. We have inserted these reports in the text to make the language more coherent and logical.