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Article information: https://dx.doi.org/10.21037/tlcr-23-756

Reviewer A

Novelty in looking at pneumonitis rates with chemoradiation vs chemo+checkpoint inhibitors plus or followed by radiation. Exclusion of SBRT enriched the included patients for those with significant thoracic radiation. Lot of data looking at pneumonitis from chemoradiation followed by checkpoint inhibitors but not many in this order.

Reply: Thank you. Yes, in this study we mainly focused on pneumonitis in patients received ICIs combined with chemotherapy before radiation, which was rarely reported before.

Changes in the text: None.

Reviewer B

The topic is about NSCLC patients but 22/152 patients were SCLC type (14.5%). This should be excluded and analyze data again.

Reply: Thank you for carefully finding this mistake. In this article, we mainly focused on the risk of pneumonitis occurring in chest radiation when combined with chemotherapy and immunotherapy concurrently or sequentially, rather than efficacy. So, the type of lung cancer was not an important impactor factor and small cell lung cancer patients that meet our inclusion criteria were still enrolled. I apologized for the typo in the naming.

Changes in the text: We modified “non-small cell lung cancer” into “lung cancer” in the title.

Reviewer C

1) First, the title needs to indicate that this is a retrospective cohort study.
   Reply: Thanks for your advice and we had modified the title.
   Changes in the text: We added “retrospective” in the title.
2) Second, the abstract is not adequate. The background did not describe the knowledge gap on the incidence of pneumonitis in chemoradiation plus immune checkpoint inhibitors compared with chemoradiation alone and why the current data deserved to be studied. The methods did not describe the inclusion criteria, follow up procedures, and data collection of baseline factors. The results need to summarize the clinical characteristic of the study sample, and the OR and accurate P values for the identified factors. The conclusion should not repeat the main findings, and please have comments for the clinical implications of the findings.
   Reply： Thanks for your advice. We had modified the abstract. In background, we pointed out that because of the increased efficacy, which was specifically described in discussion

part, physicians were tend to initiate ICIs at the beginning of chemoradiation, but whether ICIs combined with chemoradiation would increase the incidence of treatment-related pneumonitis was lack of real-world data. In the method part of abstract, we added some details about the inclusion criteria, follow up procedures, and data collection of baseline factors, but because of word limits, the details were descripted in "method" part. In the results, we added clinical characteristic of the study sample, and the OR and accurate P values for the identified factors. In conclusion, we deleted the repeat of main findings and give our comments to the results.

Changes in the text: We rewrite our abstract as advised (see page2 and 3, Abstract)

3) Third, the authors need to explain why "whether chemoradiation combined with ICI would increase the risk of pneumonitis requires further investigation" and why there is a need for the real-wold data. If it is true that chemoradiation combined with ICI increases the risk of pneumonitis, why the authors re-examined this research question.

Reply: At first, the exploration of combination therapy is necessary, which might increase the treatment efficacy. It was explained in paragraph 1 of discussion. Secondly, as ICIs or chemoradiation alone was possible to induce treatment-related pneumonitis (paragraph 2 of discussion), whether the combination therapy would increase the rate of pneumonitis should be take into account as well. Thirdly, already published papers were not adequate. some clinical trials had reported pneumonitis in combination therapy, but they were small-scale sing-arm study without comparison with chemoradiation alone. Other retrospective papers were more about recalled RP in patients receiving ICI after cCRT (detailed in paragraph 2 of discussion). At last, why there is a need for the real-world data. As explained in paragraph 2 of discussion, many former studies demonstrated the different results between clinical trials and real-world application. Clinical trials usually selected a specific population through a series of inclusion and exclusion criteria that could not determine the generalizability in real clinical practice. While real-world subjects were generally selected without special restrictions.

In this study, we confirmed that combination therapy induced the risks of pneumonitis, but we also pointed out that the history of chronic lung disease was the only independent risk factor of grage≥3 pneumonitis. So, we demonstrated that combination therapy was generally safety, but not for patients with history of chronic lung disease.

Changes in the text: We modified "conclusion" to declare our point of view.

4) Fourth, in the methodology of the main text, please describe the sample size estimation of this comparative study. In statistics, it is wrong to test the difference between incidence rates by using t-test. Please describe the details of the multiple logistic regression analysis. The development of a prediction model is not the focus of this study, the authors need to explain why.

Reply: Thank you. The sample size calculation was based on previous reports estimating the probability of severe pneumonia to be 7% in the concurrent chemoradiation group and

15% in the ICIs plus chemoradiation group, 1-β=0.8 and α=0.05. A total sample size of at least 60 patients was required, with at least 30 patients in each group. We retrospectively collected patients during January 2020 and December 2021 at West China Hospital and 152 patients meet inclusion criteria, in which 58 received chemoradiation combined with ICIs and 94 received chemoradiation alone.

The incidence rate of pneumonitis in the 2 groups were evaluated by Chi-squared tests, but not t-test. It was a mistake and modified.

The details of the multivariate logistic regression analysis were described in "statistical analysis" of "method" part and "Risk factors of pneumonitis" of "Result" part.

The development of a prediction model is not the focus of this study and we had deleted this part.

Changes in the text: We added sample size calculation at page 5 in "Method-patient" part. We changed "independent-sample t-test" to "Chi-squared tests" in "Method-statistical analysis" part.

We added details of multivariate logistic regression analysis in "statistical analysis" of "method" part and "Risk factors of pneumonitis" of "Result" part.

We deleted the last paragraph in "Risk factors of pneumonitis" part and Figure 3 about the ROC curve.

5) Finally, please cite several related papers: 1. Tao H, Li F, Wu D, Ji S, Liu Q, Wang L, Liu B, Facchinetti F, Leong TL, Passiglia F, Hu Y. Rate and risk factors of recurrent immune checkpoint inhibitor-related pneumonitis in patients with lung cancer. Transl Lung Cancer Res 2022;11(3):381-392. doi: 10.21037/tlcr-22-168. 2. Chao Y, Zhou J, Hsu S, Ding N, Li J, Zhang Y, Xu X, Tang X, Wei T, Zhu Z, Chu Q, Neal JW, Wu JTY, Song Y, Hu J. Risk factors for immune checkpoint inhibitor-related pneumonitis in non-small cell lung cancer. Transl Lung Cancer Res 2022;11(2):295-306. doi: 10.21037/tlcr-22-72. 3. Shi Y, Ji M, Jiang Y, Yin R, Wang Z, Li H, Wang S, He K, Ma Y, Wang Z, Lu J, Shi M, Shen B, Zhou G, Leong TL, Wang X, Chen C, Feng J. A cohort study of the efficacy and safety of immune checkpoint inhibitors plus anlotinib versus immune checkpoint inhibitors alone as the treatment of advanced non-small cell lung cancer in the real world. Transl Lung Cancer Res 2022;11(6):1051-1068. doi: 10.21037/tlcr-22-350.

Reply: Thank you. These related papers were useful. We had cited them in our paper.

Changes in the text: We added references (1)(16)(28).