Peer Review File
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Reviewer A

Thank you very much for an interesting article regarding the combination of SBRT and immunotherapy and NLR as a predictive and prognostic biomarker.
The study investigated the synergistic effects of stereotactic body radiotherapy (SBRT) and immunotherapy on patients with lung oligometastases, particularly focusing on prognostic factors of OS and the potential role of NLR as a prognostic indicator.
Combining SBRT with immunotherapy is timely and relevant, considering synergistic effects and enhancing the immune system for improved tumor response Additionally, identifying NLR as a significant prognostic factor could provide a simple and accessible biomarker for predicting patient outcomes post-treatment.
However, the study is limited by its small sample size of 43 patients, which might not provide a robust statistical power to generalize the findings broadly. Being a retrospective analysis, the study is prone to selection bias and lacks the controlled conditions of a prospective trial, which can affect the validity of the conclusions drawn. Furthermore, the inclusion of patients with mixed histological types of tumors introduces variability that could confound the results and make it difficult to attribute outcomes specifically to the combination of SBRT and immunotherapy. The use of different systemic therapies (TKI and immunotherapy) among patients adds another layer of complexity, as varying responses to these treatments could influence the results independently of the SBRT. Variations in the interval between radiotherapy and immunotherapy among patients could also impact (bias) outcomes, as suggested by the study itself, where a shorter interval was associated with better OS and the impact of previously treatment on NLR.
While the study presents intriguing data on the potential benefits of combining SBRT with immunotherapy for lung oligometastases, the limitations warrant cautious interpretation of the results. These factors collectively suggest that the study might not provide sufficiently robust evidence to be accepted without further validation through larger, prospective studies with more homogeneous patient populations and standardized treatment protocols.

Reply:

First of all, thank you for your valuable comments and suggestions on this paper. Indeed, our paper was a retrospective clinical study with a small sample size. Due to the short time since SBRT technology was introduced in our center and the limited inclusion and exclusion criteria, the sample size was only 43 patients. However, these are only preliminary findings, and our center will continue to follow up the current patients and include more patients. If the number of cases is large enough, the next step may be to conduct separate studies for each cancer disease. If similar positive results are obtained from these retrospective clinical studies, prospective studies will be planned to further clarify the efficacy of immunotherapy combined with SBRT in patients with lung oligometastatic tumors. For the bias caused by different primary tumors in the patients included

in the study, just as in Figure1, when screening patients with pulmonary oligometastases who had received SBRT (n=114), only signs of stable or inactive control of the primary tumor and extrapulmonary metastases were included. The number of lung metastases was 1-5 and could be measured, and all metastases were in the lung. For all cases whose metastases have been examined by chest enhanced CT or PET-CT for several times and were jointly confirmed by clinicians and radiologists. The inclusion and exclusion criteria were not clearly written. The inclusion and exclusion criteria have been clearly written in the article, which can preliminary exclude errors caused by the progression of primary tumors or poor control of extrapulmonary metastases.
We will continue to conduct relevant research and analysis to make up for the current deficiencies.
Change: Page 5 line190-197

Reviewer B

This is an interesting and timely manuscript suggesting that the concurrent treatment with SBRT and immunotherapy is associated with longer overall survival and a higher rate of local control among patients presenting with pulmonary oligometastases. Furthermore, increased post-SBRT NLR levels were indicative of a poor prognosis. Overall the manuscript is well written and my comments are mostly minor.

1) Were the percentages of irAEs, especially pneumonitis, comparable between comparison groups?
Reply:Thank you for your valuable suggestion. However, unfortunately, this study has not yet analyzed immune-related adverse reactions for the following two reasons: 1. This study was retrospective and included several different cancer types, and there were differences in the ICIs involved and the number of courses of treatment. 2. In this study, patients with serious adverse reactions and treatment interruption were excluded, which seemed to cause selection bias in the incidence statistics of irAEs, so no further statistical analysis was conducted on immune-related adverse reactions. However, no serious radiological and immune-related adverse reactions (grade 3 or greater) occurred in 43 patients by the end of follow-up.
Change: No change

2) It would be informative to also consider systemic immune inflammation index in your analysis.
Reply: Thank you for your valuable comments, many relevant studies have shown; Inflammatory indicators such as SII, PNI, PLR, and NLR can all be prognostic indicators of various solid tumors. However, this study was a preliminary study with a small sample size, and platelet counts were not collected when patient information was collected. However, we plan to include all inflammatory

indicators in our analysis in further studies and expand the sample size to produce more confident results. However, the systemic immunoinflammatory index is of great significance for the prognosis of solid tumors, so the relevant research analysis results are added in the discussion section.
Change: page 11 line446-456

3) Please also analyze NLR as a continuous variable versus a binary cutoff-value of 4.12.
Reply: In this paper, OS-related COX univariate and multifactor regression analysis was performed. Because the sample size in this study was too small, only two independent variables that were significant in the univariate analysis were included in the multivariate analysis. Results showed that NLR after SBRT was an independent prognostic factor for OS, HR=1.10 (95%CI: 1.01-1.9), indicating that the higher the NLR after SBRT, the shorter the OS. Since NLR after SBRT is a continuous variable, it is not convenient to compare the survival process. Therefore, the ROC curve will be used to take the truncation value, and the NLR after SBRT will be changed into a binary classification variable, and the survival difference between the two groups will be compared by Log-rank test. As far as we know, continuous variables cannot be directly used to compare survival processes. Maybe we don't understand your suggestion very well.
Change: No change

4) A covariate analysis with Charlson comorbidity index and performance status could be informative.
Reply: The Chalson Comorbidities Index is used to assess the impact of comorbidities other than the underlying disease that is currently the primary treatment on a patient's survival over the next 10 years. Including myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, diabetes, etc., the higher the score, the worse the prognosis and the lower the survival rate. However, when we formulated the inclusion and exclusion criteria, patients with serious medical diseases or contraindications to radiotherapy were excluded, so there was no significant difference in the charlson comorbidities index between patients. We will consider including the Charlson comorbidity index as a variable in the next large sample study.
Change: No change

5) If available, please provide PET SuVMax and Bronchus maximum dose.
Reply: Thank you for your reminding. However, most patients did not undergo PET-CT examination due to objective factors such as economic reasons, so PET-CT data were not included.
Change: No change

6) As the sample size is very small, I would suggest referencing the study as pilot or preliminary in the title.

Reply: Thank you for your reminding. The sample size of our study was small, and the title of the preliminary study was more rigorous. Therefore, we revised the title to: Efficacy and prognostic factors of stereotactic body radiotherapy combined with immunotherapy for pulmonary oligometastases: a preliminary retrospective cohort study.

Change: Page 1 Line3-4

Reviewer C

This manuscript is focused on clinical outcomes following SBRT + immunotherapy in treating oligo-lung metastasis, and authors achieved more or less favorable outcomes. There are s few weak points in supporting authors' speculations.

1. Characteristics of 43 patients are quite heterogenous in terms of primary cancer sites, and the reason of applying the same treatment policy seems not logical.

Reply: Among the 43 patients included in our study, there were lung cancer, rectal cancer, esophageal cancer, head and neck malignancies, etc., and immunotherapy had a relatively stable position in the metastasis stage of these tumors. At the same time, for patients with pulmonary oligometastatic tumors, SBRT as a local treatment, its effectiveness has been proved successively. SBRT initially acts on stage I lung cancer, and its effectiveness has been proved to be similar to that of surgery, so it has become the first choice of treatment for stage I lung cancer patients who cannot or refuse surgery for objective reasons. Although the 43 patients had great heterogeneity in the site and pathological type of the primary tumor, the treatment strategy happened to be similar, and some previous studies have analyzed these patients with great heterogeneity together, such as[Sharma, A. et al. Factors affecting local control of pulmonary oligometastases treated with stereotactic body radiotherapy. Acta Oncologica 57, 1031–1037 (2018). Yamamoto, T. et al. Analyses of the local control of pulmonary Oligometastases after stereotactic body radiotherapy and the impact of local control on survival. BMC Cancer 20, 997 (2020).]

However, this is a retrospective study, and the ICIs selected for different primary tumors. are also very different, and the segmentation scheme of SBRT is also very different, which has certain defects. If possible, we want to further determine the treatment effectiveness of SBRT and immunotherapy for patients with lung oligometastatic tumors through a larger sample size study. Moreover, the reliability of the conclusion is enhanced through prospective studies with strict experimental design such as standardized split dose scheme.

Change: no change

2. There existed nonnegligible selection biases: patients who suffered severe acute side effects were excluded; those who received less than 2 rounds of immunotherapy were excluded; and those who had myelosuppressed state were excluded.

Reply: Thank you for your advice, but there was a significant selection bias in this study. In this study, patients who received immunotherapy less than twice were excluded (n=4), because it was difficult to judge the efficacy related to immunotherapy if they received immunotherapy less than twice. None of the four patients had immune or radiotherapy-related adverse reactions, one stopped immunotherapy due to sudden myocardial infarction, one was terminally ill due to uremia, and two gave up further immunotherapy due to economic reasons. Patients with myelosuppression and those receiving chemotherapy were excluded mainly because myelosuppression during chemotherapy was transient and reversible, and was not associated with disease prognosis. Therefore, in studies on inflammatory indicators such as NLR, ALC, PLR, and SII, Blood system diseases, acute and chronic infections, kidney diseases, chemotherapy, white injection and other diseases or factors affecting blood indicators are usually excluded;

Change: no change

3. Quite heterogenous SBRT dose schemes, without information on target sizes and location (central vs. peripheral), were utilized and it seems impossible that all patients underwent the same (or at least similar) dose schedules.

Reply: Thank you for your valuable suggestion. Unfortunately, our study is a retrospective study, and there are great controversies on SBRT dose segmentation schemes for pulmonary oligometastatic tumors at home and abroad. There are indeed great differences in our SBRT dose segmentation schemes, which is not conducive to comparison between groups. The physical dose is uniformly converted into bioequivalent dose (BED) in various dose segmentation modes. The volume of the target area and the size of the tumor have been included in the research analysis, as shown in Table1. However, the location of the target area (center or around) was not included in the study, because our total sample size was too small, so we could only reduce the independent variables. Moreover, 39 of the 43 patients were those with the target area around them, with extremely uneven distribution. Therefore, after discussion and analysis, the researchers decided not to include the location of the target area as an independent variable.

Change: no change

4. Clinical outcomes are in 1- or 2- year rates only, and it is impossible to speculate that these figures are good or bad, without comparable data drwan by authors. How good is good? What dose "better" mean without comparable values?

Reply: Thank you for your valuable comments. Because our study is a preliminary study, only 1-year and 2-year survival indicators were analyzed at present. In the survival analysis of 43 patients, we did not set up a control group, so there was no comparison data between groups. In the relevant studies in recent years, there is a lack of literature on the treatment of stage IV tumors by SBRT combined with

ICI. There are several literatures on the treatment of lung oligometastatic tumors by SBRT alone, and the results are close to the survival analysis results of this study. I have added these data to the discussion section for better comparison.
Change: Page 10 line 418-422

5. Authors' speculations on neutrolphil counts are not easily understood and supported by audinary readers. No comparable information is provided bu authors.
Reply: NLR is the ratio of neutrophils to lymphocytes. In the initial part of this study, Wilcoxon paired rank sum test was used to compare the changes of ALC, NE and NLR before and after SBRT. The results showed that the changes of ALC and NLR were statistically significant, while the changes of NE were not. Therefore, it was considered that the changes of NLR were mainly related to the changes of ALC. It can be assumed that the increase of NLR is the result of lymphocyte depletion. Additional explanations on this have been added to the discussion section.
Change: page 12 line 477-480

Reviewer D

In general, one study answered one research question, but this study focused on two questions, the efficacy of SBRT and the prognosis prediction role of NLR. I suggest the authors to revise the title as the efficacy and safety of SBRT+ICIs and prognostic factors, and indicate the clinical research design in the title, i.e., a retrospective cohort study.
Reply: Thanks for your reminding, I have revised the title to: Efficacy and prognostic factors of stereotactic body radiotherapy combined with immunotherapy for pulmonary oligometastases: a preliminary retrospective cohort study
Change: Page 1 line3-4

Second, the abstract needs some revisions. The background did not indicate the knowledge gaps on the efficacy of SBRT+ICIs for pulmonary oligometastases and the corresponding prognostic factors in patients receiving SBRT+ICIs. The methods need to describe the inclusion criteria, assessment of potential predictors including NLR, follow up procedures, and measurements of efficacy and safety outcomes. The results need to briefly summarize the characteristics of patient sample. The current conclusion needs to be tone down since this is only a retrospective cohort study.
Reply: We have revised the background and conclusions of the abstract. However, if inclusion criteria, evaluation of potential predictors, follow-up procedures, and measures of efficacy and safety outcomes were included in the method, the number of words in the abstract would be exceeded, so only the highlights of the method were included.
Change: Page 2-3 Line 54-99

Third, in the introduction, a brief review on the efficacy and safety of SBRT+ICIs for pulmonary oligometastases and prognostic factors in pulmonary oligometastases is needed, as well as the analysis on the current knowledge gaps. In the current version, it seems that there is no controversy or knowledge gaps on efficacy and safety of SBRT+ICIs, so I cannot see the necessity of the current study.

Reply: Thank you for your suggestion. We have added the research related to SBRT+ICI treatment in the introduction and analyzed the current knowledge gaps.

Change:page 4 line164-180

Fourth, in the methodology of the main text, please accurately describe the clinical research design, sample size estimation procedures, and follow up procedures. In statistics, please describe the details of the identification of significant factors associated with the prognosis outcomes.

Reply: In the methodological section of the text, the study design, sample size estimation procedures, and follow-up procedures have been described in detail, and the identification of important factors related to prognostic outcomes has been described in detail by statistical methods.

Change: page 5 line 209-211 page 7 line275-292

Finally, please consider to cite several related papers: 1. Oudin V, Salleron J, Marchesi V, Peiffert D, Khadige M, Faivre JC. CyberKnife® stereotactic radiation therapy for stage I lung cancer and pulmonary oligometastases: is fiducial implantation still relevant?—a cohort study. J Thorac Dis 2023;15(9):4636-4647. doi: 10.21037/jtd-22-1245.

2. Xiang Y, Zhang N, Lei H, Wu J, Wang W, Zhang H, Zeng X. Neutrophil-to-lymphocyte ratio is a negative prognostic biomarker for luminal A breast cancer. Gland Surg 2023;12(3):415-425. doi: 10.21037/gs-23-80.

3. Chan KS, Shelat VG. The role of platelet-lymphocyte ratio in hepatocellular carcinoma: a valuable prognostic marker. Transl Cancer Res 2022;11(12):4231-4234. doi: 10.21037/tcr-22-2343.

4. Luo Q, Chen L, Li Z, Cheng L, Zhang S, Zong Y, Li Q, Suda K, Santarpia M, Dalia S, Meng R. Long-term survival after stereotactic body radiotherapy combined with immunotherapy plus anti-angiogenesis therapy in patients with advanced non-small cell lung cancer and EGFR exon 20 insertion mutation: a report of two cases. Transl Lung Cancer Res 2023;12(11):2330-2341. doi: 10.21037/tlcr-23-542.

Reply: Thank you for the references you provided. I have read these four papers and take two of them as references, and have added relevant content in the discussion section accordingly.

Change: page 16 line677-678 page 18 line 694-695