Peer Review File

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Reviewer A (Comments to the Author):

Mo Chen et al provide a comprehensive review of therapies for brain metastases in NSCLC.

Major points:

1.lines 152-159: the icORR results by treatment type are among the most valuable data reported in this study. I suggest to create a bar plot similar to FIgure 8 to visualize them (x-axis: type of treatment, y-axis: icORR). I suggest that for this and for the bar plot of Figure 8 error bars (e.g. 95% CI or SE) are also shown, and the results of formal statistical testing are added (NB in lines 201-208 "significant differences" are mentioned, but there are no details on the statistical results).

Rely: Thank you for pointing this out. According to the revised content, we have added Figure 2B to clearly show the differences among the icORR results by different treatment types, and 95% CI was added in Figure 8. Furthermore, a detailed description of the statistical method for median intracranial PFS was also added in the Method (see Page 7, lines 143-144) and Result (see Pages 11-12, lines 236-245) of the entire study. We hope that the changes in the revised version of the manuscript and our explanations above to answer this question.

Changes in the text: Page 7, lines 143-144; Pages 11-12, lines 236-245.

2.Results lines 189-196: the text describes differences among "prospective vs. retrospective trials" iwth reference to Figure 6, while Figure 6 itself shows results according to "WBRT vs. SRT"

Rely: We are very sorry for the mistakes in this manuscript and the inconvenience they caused in your reading. After checking, the differences among "prospective vs. retrospective trials" were shown in Figure 7， the error was corrected in the revised manuscript (see Page 11, lines 222-223).

Changes in the text: Page 11, lines 222-223

3.Discussion lines 267-269: the finding of this study that there was no difference between WBRT and SRT (FIgure 6) should be highlighted as such with acknowledgement of course of the limitation due to the small sample size. The fact that the observation

"SRT=WBRT" does not agree with the findings of Ref. 29 (line 268-269) is not "regrettable", but in good accordance to the data in EGFR/ALK-NSCLC, where WBRT does not offer better intracranial control than SRT (e.g. https://pubmed.ncbi.nlm.nih.gov/34090172/), and this is probably related to the better systemic tumor control with TKI and ICI compared with pure chemotherapy (which could also be a smooth transition to the next paragraph starting in line 270).

Rely: Thanks for your helpful suggestions. As suggested by the reviewer, we have highlighted no differences were observed between WBRT and SRS, and added essential discussion for the perspective of different types of brain radiation. Supplementary literature reported the intracranial results of EGFR/ALK-NSCLC patients with BM (1), which are in good accordance with our data, and proposed possible reason to explain this phenomenon (see Page 16, lines 339-349).

Changes in the text: Page 16, lines 339-349

4.One important point that could be added is the increased incidence of radionecrosis after combination of ICI with RT (e.g. https://pubmed.ncbi.nlm.nih.gov/29327059/).

Rely: Thank you for pointing out this problem in the manuscript. We have added essential discussions about the increased incidence of radionecrosis after the combination of ICI with RT (see Pages 15, lines 311-323). Firstly, we suggested the higher incidence was affected by synergy. Secondly, several relevant literature was cited to confirm the strong association between radionecrosis and the use of combined ICI in patients with BM from different perspectives (2-4).

Changes in the text: Page 15, lines 311-323

5.The Results in the Abstract could be improved, e.g. it is not clear what the p=0.000 in line 38 refers to (which statistical test was applied), and why "the iPFS is highly favoring nivolumab plus ipilimumab plus chemotherapy: 13.5 month" (line 39) -> what was the iPFS of other options. For each of the parameters which you want to present (e.g. icORR, iPFS, +- OS), I suggest to present results for at least two patient subgroups.

Rely: Thank you for your comments. We have revised the Result of Abstract (see Pages 2-3, lines 40-49) and made supplementary explanations for some confusing descriptions.

Firstly, the p=0.000 in line 38 refers to the significance differences by Z-test, in the revised manuscript, we have deleted the description of the P-value of the Result of Abstract (see Page 2, lines 38-42) to avoid confusion for the reviewer and added more detailed description of the Z-test in Method (see Page 6, line 126) of the entire study.

Secondly, we have added the intracranial PFS of different treatment groups in the Result

of Abstract (see Pages 2-3, lines 40-49) to illustrate the differences between these groups, including ICI plus RT, chemotherapy plus RT and ICI plus chemotherapy.
Change in the text: Pages 2-3, lines 40-49; Page 7, lines 143-144.

6.Also, I suggest to adopt a more conservative formulation in the Conclusions of the Abstract (lines 44-49) and the entire study (lines 288-293), because the results of this study cannot dictate what "would be preferable" (line 290) or "would be a good choice" (line 47) in a specific clinical situation. Instead, you could just stick with the data and for example state that benefit from "treatment X is better than that from treatment Y".

Rely: Thank you for pointing this out. We have rewritten the Conclusion of the Abstract (see Page 3, lines 51-56) and the entire study (see Page 17, lines 367-374) to describe the conclusions obtained from our data more precisely.
Change in the text: Page 3, lines 51-56; Page 17, lines 367-374

Minor points:

1.some linguistic polishing, e.g. "fatal death factors", "wild-gene"， "targeted drugs resistance patients" (Introduction of the abstract), "chemotherapy monopoly" (line 77) etc; and correction of typos, e.g. "For" (line 68).

Reply: Thank you. We are very sorry for the mistakes in this manuscript. We have carefully checked and corrected the grammatical errors and typos in our original manuscript. We hope the revised manuscript can meet the journal's standards.

2.what is "KAKS mutation" in line 143? Do you mean KRAS mutations? KRAS mutations are frequent with 30-35% in all other "wild studies" as well, even if this is not explicitely mentioned.

Reply: We feel ashamed of the simple error. In line 145, what we wanted to express was that KRAS mutation， these typos have been corrected(see Page 8, line 167).
Changes in the text: Page 8, line 167

Reviewer B (Comments to the Author):

I have read with interest the manuscript entitled "Efficacy of different therapies in Brain Metastases of Non-small-cell Lung Cancer: A Systematic Review and Meta-Analysis". It adds additional knowledge to the management of NSCLC BM in patients not eligible to

receive targeted therapy in terms of efficacy of the different systemic agents combined with RT. The materials and discussion are well written, and the limitation well recognized. Such studies in BM patients population are challenging, due to the presence of heterogeneity between each study and it requires an effort to synthethise the data and draw meaningful conclusions.

My only concern is that it should be recognized that the type of RT in combination with systemic therapy is crucial when reporting the results on icORR and iPFS. Receiving WBRT vs SRS might represent completely different clinical scenarios, regardless of what type of systemic agent is added, and actually have a bigger impact on the endpoints of the study. The local control and distant brain control, as well as intracranial progression free survival with WBRT and SRS differ. Authors should comment on that.

The study adds additional knowledge to the field of NSCLC-BM, but more insight from the perspective of different types of brain radiation (WBRT vs SRS) should be given.
Reply: Thank you for reading our paper carefully and giving the above positive comments. We have added essential discussions about the differences between WBRT and SRS according to the comments (see Pages 15-16, lines 327-349). We hope the reviewer will be satisfied with what we have written.
Firstly, we have added the description of the applicable population of WBRT and SRS, and highlighted their own advantages and disadvantages.
Secondly, several recent literature was added to further illustrate the differences in the efficacy of WBRT and SRS from a different perspective (5, 6).
Lastly, we proposed that too small data volume may be the major reason of the no significant difference in icORR or iPFS between WBRT and SRS subgroups in our results. We also follow the advice from reviewer A, who suggests adding literature supporting our results. The above supplementary content discussed the different types of RT in combination with ICI and present future studies should explore this mechanism further.
Change in the text: Pages 15-16, lines 327-349

Also, some minor grammar misspellings should be corrected in the manuscript.
Reply: Thank you for your comments. In the revised manuscript, we carefully corrected the grammatical errors in the entire study.

Reviewer C (Comments to the Author):

The mix of patients with different backgrounds and receiving different treatments makes it difficult to understand what this study examined. I think that the authors should first clarify the purpose of this study. The purpose of this study will change which studies should be included and analyzed in the meta-analysis.

Moreover, I think that it is necessary for the author to explain in detail what criteria were used to determine which papers to include in the meta-analysis.

I believe the authors should reconsider their research objectives and methods.

Reply: Thank you for your very meaningful suggestions, which are also the concerns of us. We have rethinked and described in detail crucial content.

The complexities of real-world studies were undeniable, which related to characteristics of the population included and various therapeutic regimens. Therefore, systematic review and meta-analysis were required to perform pooled analysis.

The shortcomings of previous studies consist of the number of studies they included was limited and their analyses lacked efficacy comparison between various therapeutic regimens. Therefore, to make a comprehensive assessment, we have compared six therapeutic regimens in the study, then subgroup analyses were performed to obtain reliable and consistent results. In order to ensure sufficient numbers of events in subgroups, the included patients with different backgrounds would be inevitable. As compensation, we conducted more detailed sub-analysis in the study, such as the first-line treatment subgroups and PD-L1 expression subgroups, which were also the innovation of our study.

After careful consideration, we gave explanations for some confusing descriptions by the reviewer.

Firstly, the aim of our present study was to assess the most active strategies for intracranial lesions comprehensively in NSCLC patients, especially those whose driver genes mutations are negative or TKI resistant by comparing different therapeutic regimens.

Secondly, the inclusion criteria were determined as:

(1)the participants are NSCLC patients with BM;

(2)the type of studies is randomized controlled trial, non-randomized clinical trial, prospective or retrospective observational studies or abstracts

(3)outcomes included one or more of the following: intracranial ORR, and intracranial PFS.

(4)patients treated with non-targeted therapy.

The corresponding revised text in the Page 5, lines 96-105

Thirdly, as it has been described above, the disadvantage of confounding background of research objectives was to ensure the number of subgroups based on different treatments, and we have done a lot of work to ensure the rigor of the study. And the innovation of this study is the comparison between diversified therapeutic regimens. Therefore, the target population was defined as NSCLC patients with BM treated with different therapeutic regimens, especially those whose driver genes mutations are negative or TKI resistant. Furthermore, we make improvements in the statistical method for median intracranial PFS, which are reanalyzed by using R to ensure the credibility of the results. the modified results are recorded in the Results of the Abstract (see Page 2, line 38-42) and the entire study (see Page 10, line 202-207).

Lastly, we seek for the reviewer's tolerance and understanding. Many thanks for your kind help!

Change in the text: Pages 2-3, lines 40-48; Pages 11-12, lines 236-245.