Peer Review File

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Reviewer A

The manuscript describes a retrospective cohort of patients performed in a single center with brainmetastases receiving upfront SRS or start with ICI/TKI in the first line. The goal is to find out whether it is more effective to start with systemic treatment with ICI or TKI or to treat with upfront SRS and to identify potential correlation between timing of these treatments and e.g. OS.

General comments

Comment 1: I would advise to use initially treated with instead of upfront TKI/ICI throughout the whole manuscript. Also, to use SRS and not RT.

Reply 1: We thank the reviewer for this advice! "upfront TKI/ICI" and "RT" was changed accordingly.

Comment 2: In my opinion it is necessary to organize the results better – for example by adding headings for the different subgroups. However, the presentation of the results is not clear.

Reply 2: We followed this excellent advice and added subheadings to the results section.

Changes in the text:

"Patient characteristics" (Page 9, Lines 217)

"Upfront SRS/SRT versus initial ICI/TKI treatment" (Page 10, Line 232)

"Subgroup ICI: Upfront SRS/SRT vs. initial ICI treatment" (Page 10, Line 244)

"Subgroup TKI: Upfront SRS/SRT vs. initial TKI treatment" (Page 11, Line 251)

"Subgroup upfront SRS/SRT: concurrent vs. sequential ICI/TKI treatment" (Page 11, Line 258)

Abstract

Comment 3: Sentence 36 – leave out first

Reply 3: "First" was left out in this sentence.

Comment 4: S41 upfront SRS/SRT and instead of upfront TKI/ICI initially treated with…. Please continue this naming method for the whole manuscript

Reply 4: We followed the naming method suggested by the reviewer for the whole manuscript.

Comment 5: S43-44: Both OS and iPFS were defined as the time from SRS/SRT to either death or disease progression, respectively – why not from start of treatment? Defining OS and PFS as time from start of treatment is preferred

Reply 5: As suggested by the reviewer we recalculated the Kaplan-Meier survival analysis and revised the text and the figures accordingly. The significance of the results did not change with the different definition of survival.

Changes in the text:

"The survival times considered for analysis were overall survival (OS) since start of treatment (SRS/SRT or ICI/TKI, respectively) and intracranial progression-free survival (iPFS) since start of treatment (SRS/SRT or ICI/TKI, respectively). Radiation necrosis free-survival was calculated from start of SRS/SRT." (Page 9, Lines 211-214)

Comment 6: S142 what is sec?

Reply 6: This was a typo. We meant "sex".

Comment 7: S187 why survival since study RT?

Reply 7: As answered above we redid the survival calculation following the suggested definition of survival since start of treatment. Radiation necrosis-free survival is still defined from start of RF.

Changes in the text:

"The survival times considered for analysis were overall survival (OS) since start of treatment (SRS/SRT or ICI/TKI, respectively) and intracranial progression-free survival (iPFS) since start of treatment (SRS/SRT or ICI/TKI, respectively). Radiation necrosis free-survival was calculated from start of SRS/SRT." (Page 9, Lines 211-214)

Comment 8: S00-201 explain this sentence: "But, upon closer examination of the disparity between scores of 0–2 and 2.5–4, the p-value was 0.032"

Reply 8: Thank you for pointing out this misleading sentence. It describes a closer examination of the score when separated into groups. Reviewer B made a good suggestion to change the sentence, which we integrated.

Changes in the text:

"However, when analyzed as a binary variable of the scores 0–2 and 2.5–4, the p-value was 0.032." (Page 10, Lines 227-228)

Comment 9: S219 replace 'substance'

Reply 9: We rephrased the sentence avoiding "substance" following a suggestion by reviewer B.

Changes in the text:

“With respect to specific ICI regimens 22 (91.7%) patients received pembrolizumab, the other two nivolumab and ipilimumab/nivolumab.” (Page 11, Lines 246-248)

Comment 10: S229-230 “The analysis unveiled significantly improved OS and iPFS in the concurrent cohort compared to the sequential cohort (P=0.009 and P=0.030, respectively) (Figure 2)” – Figure 2 D1 and 2 show the opposite.

Reply 10: The figure displays the correct results; the sentence was changed accordingly. We excuse this mistake.

Changes in the text:

“The analysis unveiled significantly improved OS and iPFS in the sequential cohort compared to the concurrent cohort (P=0.009 and P=0.030, respectively) (Figure 2, C1 and C2).” (Page 11, Lines 261-263)

Comment 11: Figure 2 – please add number of patients at risk to time-points at the horizontal bar

Reply 11: The numbers of patients at risk was added to the Kaplan-Maier curves (Figure 2 and figure S1), as requested.

Comment 12: Table 4-6 to supplementary data

Reply 12: As suggested, Table 4-6 were added as tables S1-S3 to the supplementary data.

Discussion

Comment 13: S239 “Due to the high efficacy of EGFR-targeted TKI, the role of RT in patients with EGFR-mutated NSCLC remains uncertain” I do not agree with this statement – the role of SRS was clear – the question is whether EGFR-targeted TKI should replace SRS or that it should be combined.

Reply 13: The statement was adjusted accordingly.

Changes in the text:

“Due to the high efficacy of EGFR-targeted TKI, the question remains, whether TKI can replace SRS/SRT in patients with EGFR-mutated NSCLC or if patients benefit more from the combination of SRS/SRT and TKI.” (Page 12, Lines 272-274)

Comment 14: S241-245 “Moreover, a recently published trial by Wang et al. involving 133 patients with oligometastatic EGFR-mutated NSCLC (without brain metastases) receiving first-line TKI found that those who received upfront focal RT to all tumor sites exhibited significantly enhanced OS (25.5 vs. 17.4 months, P<0.001) and PFS (20.2 vs. 12.5 months, P=0.001)”. Comparison with extracranial mets is confusing in this discussion.

Reply 14: With all due respect, we believe that creating analogies such as this may enhance the perspective on this topic by providing a broader view. However, we agree that the

sudden reference to a paper about extracranial metastases can be confusing. We attempted to guide the reader more effectively by adding a subsentence.

Changes in the text:

“When looking at extracranial metastases, a recently published trial by Wang et al. involving 133 patients with oligometastatic EGFR-mutated NSCLC (without brain metastases) receiving first-line TKI found that those who received upfront focal SRS/SRT to all tumor sites exhibited significantly enhanced OS (25.5 vs. 17.4 months, P<0.001) and PFS (20.2 vs. 12.5 months, P=0.001)34.” (Page 12, Lines 275-280)

Comment 15: The two week timeframe between concurrent and sequential is not logic since the T1/2 is > 3 weeks of eg. ICI agents. Can you discuss more the possible mechanism behind the difference that is observed between concurrent and sequential?

Reply 15: Reviewer D also pointed out that the section discussing the difference between concurrent and sequential treatment is unclear. This section was therefore revised accordingly. Additionally, we explained our decision more precisely in the methods section.

Changes in the text:

“Regarding the comparison between concurrent and sequential application of systemic treatment with RT, patients appeared to benefit more from sequential application, as concurrent treatment of systemic treatment may have a certain impact on toxicity, as it was recently suggested in a study regarding SRS and ipilimumab/nivolumab in melanoma brain metastases30, a reason here fore may the higher treatment morbidity. However, due to the minimal incidence of radiation necrosis in our study (only one patient in this subgroup), this aspect couldn't be thoroughly analyzed.” (Page 13, Line 307-313)

“The decision to use this two-week timeframe was defined analogous to a comparable analysis conducted in the context of melanoma brain metastases, in which a difference between sequential and concomitant treatment was first seen when reducing the usual time frame of four weeks to two weeks, or even only one week30.” (Page 8, Lines 190-194)

Comment 16: Conclusion: “In patients treated with ICI (mainly pembrolizumab) and SRS/SRT as first-line treatment for brain metastases of NSCLC, upfront SRS/SRT followed by ICI lead to significantly prolonged OS than upfront ICI followed by SRS/SRT”- this cannot be the conclusion – because of the retrospective design and the very low number of patients. So at least temper this statement.

Reply 16: The conclusion was toned down by referring to the small cohort of the study and its retrospective design.

Changes in the text:

“In this small retrospective cohort, patients treated with ICI (mainly pembrolizumab) and SRS/SRT as first-line treatment for brain metastases of NSCLC, upfront SRS/SRT followed by ICI lead to significantly prolonged OS than initial ICI treatment followed by SRS/SRT.” (Page 14, Lines 332-334)

Reviewer B

Overall, this is a well-written retrospective study of timing of SRS relative to targeted therapy or immunotherapy.

Minor edits are as follows.

Comment 1: Line 142 change sec to sex

Reply 1: Thank you for pointing out this typo. It was corrected accordingly.

Comment 2: Line 178 change data was to data were.

Reply 2: This grammatical error was changed.

Comment 3: Line 200 – consider changing "But upon close examination of the disparity between scores … " to "However, when analyzed as a binary variable of scores …"

Reply 3: The sentence was changed accordingly.

Changes in the text:

"However, when analyzed as a binary variable of the scores 0–2 and 2.5–4, the p-value was 0.032." (Page 10, Lines 227-228)

Comment 4: Line 219 change "Concerning the substance" to "With respect to specific ICI regimens …"

Reply 4: Thank you for this suggestion.

Changes in the text:

"With respect to specific ICI regimens 22 (91.7%) patients received pembrolizumab, the other two nivolumab and ipilimumab/nivolumab." (Page 11, Lines 248-250)

Comment 5: The major limitation of this study is the small numbers. This is particularly an issue with the TKI cohort in which there are only 10 patients. It may be more appropriate to simply state that while the differences between upfront TKI (n=7) and upfront TKI (n=3) were not statistically different, the numbers of patients were too small to make any meaningful conclusions.

Reply 5: We already addressed this limitation in the discussion. Additionally, we added the following statement in the conclusions to further clarify this fact.

Changes in the text:

"Specifically, for the analysis of the TKI cohort, a larger patient cohort would be necessary to draw more definitive conclusions". (Page 14, Lines 322-323)

“While the difference between patients treated upfront SRS/SRT and patients initially treated with TKI was not significant, the number of patients in this subcohort was too small to make any meaningful conclusions.” (Page 14, Lines 334-337)

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“While the difference between patients treated upfront SRS/SRT and patients initially treated with TKI was not significant, the number of patients in this subcohort was too small to make any meaningful conclusions.” (Page 14, Lines 334-337)

Comment 11: I would consider omitting Table 5 and Figure 2C1-2.

Reply 11: Following the suggestion of reviewer A tables 4-6 were moved to supplementary material. Therefore table 5 is as table S2 now in the supplementary data. We did the same with figure 2 (now figure S1).

Reviewer C

1) Abstract:

Comment 1: The description of the patients provided in the abstract is confusing, particularly providing someone does not read the whole manuscript. Why do you refer here to 34 patients and not to the whole group of 54 patients ? I suggest to follow the way of description provided in the first paragraph of this review.

Reply 1: Of the 54 patients, only 34 received the examined treatments as first-line treatment for brain metastases and were therefore the ones actually analyzed. We did not want to mislead the reader of the abstract into thinking all 54 were included in the analysis. However, we agree with the reviewer that the current way the cohorts are presented is somewhat confusing. Following the reviewer's suggestion, we changed the way how the cohorts are presented in the abstract.

Changes in the text:

"The analysis encompassed 54 patients of which 34 (63.0%) patients received SRS/SRT and TKI/ICI as their first-line therapy. Of the latter, 17 (50.0%) patients received upfront SRS/SRT and 17 (50.0%) were initially treated with TKI/ICI; 24 (70.6%) received SRS/SRT and ICI ,and 10 (29.4) received SRS/SRT and TKI." (Page 3, Lines 76-79)

Comment 2: Please describe here the whole group of 54 patients that you analyse. While you partially describe this group in results sections this should be moved to Material/methods, otherwise it is confusing.

Reply 2: We moved the description of the cohort to the material and methods creating a separate paragraph of section under the subheading "Patient cohort and its subgroups" an went into more detail here:

Changes in the text:

"Following the database evaluation, a total of 54 patients were identified who received SRS/SRT in combination with ICI or TKI. Among them, 34 patients received ICI/TKI as their initial treatment as their first-line therapy for a total of 99 brain metastases. The latter cohort consisted of seventeen (50.0%) patients for both upfront SRS/SRT and upfront TKI/ICI, each; 24 (70.6%) received SRS/SRT and ICI, and ten (29.4) received SRS/SRT and TKI. From the patients who received TKI (n=10), seven (70.0%) received upfront SRS/SRT and three (30.0%) initial TKI treatment. Conversely, among the patients who received ICI (n=24), ten (41.7%) patients underwent upfront SRS/SRT and 14 (58.4%) patients were initially treated with ICI. The distribution of the cohort and its subgroups is depicted in figure 1." (Pages 8-9, Lines 196-204)

Comment 3: A brief summary of description of the whole group of 54 patient in the table seems mandatory for me. Description of the subset of upfront RT and upfront ICI/TKI is of importance, but several outcomes referring to the other patients are presented in the manuscript, hence complete description of patients is needed.

Reply 3: A new table (now table 1) was added, in which the whole cohort (n=54) is elucidated in comparison to the first-line cohort (n=34).

Comment 4: You also need to better elucidate in this section the proportions of the patients who had driver mutations (EGFR, other?) in a whole group and in the subgroups you analyse.

Reply 4: The driver mutations was added to the respective tables.

3) Results:

Comment 5: line 222, 225, 230 To which panel of Figure 2 (A-D) your statements refer? Please explain it in the text.

Reply 5: We added the referred panels to the brackets referencing to the respective figure

4) Figure 2:

Comment 6: Please describe the number of patients to which each of this figures refer (either in the legend or on the graph)

Reply 6: We added the numbers of the patients at risk to each graph (figure 2, figure S1).

5) Figure 2 D1, D2:

Comment 7: concurrent is a continuous line, sequential is dotted line. I read from this figures that concurrent is worse than continuous, while you say in Result section (line 229, 230) "The analysis unveiled significantly improved OS and iPFS in the concurrent cohort compared to the sequential cohort". Clearly there seems to be an error in the graph or in the text: please double check it and correct.

Reply 7: Thank you very much for pointing out this error! The results presented in the figure is the correct one. We corrected this mistake in the text.

Changes in the text:

"The analysis unveiled significantly improved OS and iPFS in the sequential cohort compared to the concurrent cohort (P=0.009 and P=0.030, respectively) (Figure 2, C1 and C2)." (Page 11, Lines 261-263)

6) Discussion

Comment 8: Line 261: “80% of the patients in this subgroup had EGFR mutations” What were the other mutations? What TKI inhibitors were used?

Reply 8: The other mutations were added to the tables as mentioned in a comment above. The TKI inhibitors are mentioned in table 5 (now table S2), but nevertheless we added this information to the text as well.

Changes in the text:

“Three (30.0%) patients received Afatinib, four (40.0%) Osimertinib, two (20.0%) Crizotinib and one (10.0%) Gefitinib.” (Page 9, Lines 255-257)

7) Discussion:

Comment 9: please better describe limitations of this research: the group you analyse appears not representative for non-small cell lung cancer patients that are diagnosed in Europe or USA. The proportion of the patients with squamous cell lung cancer is very small (only 3 individuals) and the proportion of patients with driver mutations seems high (although the description of this issue is inadequate: you only refer to EGFR mutations in some subgroups.

Reply 9: The description of the limitations was expanded encompassing more aspects.

Changes in the text:

“It is important to note the clear limitations of our study, primarily its retrospective nature and the limited number of patients, which posed challenges in analyzing subgroups comprehensively. Specifically, for the analysis of the TKI cohort, a larger patient cohort would be necessary to draw more definitive conclusions. Besides, the low number of squamous cell carcinoma and relatively high number of EGFR positive patients does not make this cohort representative for all patients. Additionally, a selection bias is very likely due to the fact that patients with a good systemic and intracranial response might not have been treated with SRS/SRT afterwards, and thus were not taken into account in this analysis.” (Page 14, Lines 324-328)

Reviewer D

The authors raise a very important issue for discussion. In light of the evidence suggesting a brain response to systemic treatments such as TKI or ICI, it becomes crucial to discern which patients may defer the addition of local treatment, and in which cases it may even be unnecessary. However, this observation is based on a relatively small and non-random cohort, making it challenging to draw definitive conclusions.

Remarks

Comment 1: In the paragraph beginning at line 252, the writers discuss studies that align with the findings of this research concerning the impact of upfront SRS on patients undergoing ICI treatment. It is advisable to elaborate on the details of this trials.

Reply 1: We thank the reviewer for his input, and provided more details in the discussion section.

Changes in the text:

“A retrospective trial by Magnuson et al. analyzing 351 patients with EGFR-mutant NSCLC brain metastases treated with TKI demonstrated improved OS when receiving upfront SRS compared to initial TKI treatment and SRS or WBRT at progression (46 vs. 25 months, HR 0.39, p<0.001)15.” (Page 12, Lines 272-275)

“This finding aligns with another retrospective study by Yu et al., indicating that delayed SRS/SRT resulted in poorer OS compared to upfront or concomitant SRS/SRT: within a cohort of 73 NSCLC patients with brain metastases treated with ICI were associated with shorter overall survival when receiving delayed RT (p=0.0029) administration; in a metanalysis with 254 from 4 studies parallelly done in the same article, improved OS was shown for concurrent vs. delayed RT (HR=0.44, p<0.03) and upfront vs. delayed RT (HR=0.32, p<0.01)17. Guo et al. also reported comparable results: while analyzing 461 patients with NSCLC brain metastases receiving ICI, patients with upfront RT showed longer OS (25.4 vs. 14.6 months, HR=0.52, p=0.041)35.” (Pages 12-13, Lines 287-295)

Comment 2: In line 258, it is written: "This suggests that the advantage of ICI alongside upfront RT arises from a complex systemic effect, rather than solely from the prevention of intracranial progression." This conclusion is an extrapolation of the data. I suggest deleting it or writing it in a different paragraph with an explanation and references.

Reply 2: Following the suggestion of the reviewer we deleted the sentence as it opens up a far too complex discussion for satisfyingly exploring it in this article. Furthermore, we explained the cited article by Hess et al. in a more detailed manner:

Changes in the text:

“The fact that in our study OS is significantly different, but iPFS is not, may appear peculiar at first glance, yet it is a common occurrence in trials involving ICI or TKI: Hess et al. specifically analyzed this phenomenon in 192 studies with biological or targeted agents, and concluded that this is not a result of poor study design, but suggested it may be due to still unknown complex mechanisms of action of the biological or targeted agents36.” (Page 13, Lines 297-302)

Comment 3: In line 262, it is not clear which subgroup the authors is referring to.

Reply 3: The referred subgroup was specified.

Changes in the text:

“Given that 80% of the patients in the subgroup receiving TKI had EGFR mutations, it's plausible to assume that the substantial response of EGFR inhibitors on brain metastases might have minimized the impact of SRS in first-line treatment, consequently impacting the timing as well.” (Page 13, Page 303-306)

Comment 4: Between lines 270 and 273, the text lacks clarity. I suggest rephrasing it for better understanding.

Reply 4: This section was rephrased, and is hopefully more understandably now.

Changes in the text:

“Regarding the comparison between concurrent and sequential application of systemic treatment with RT, patients appeared to benefit more from sequential application, as concurrent treatment of systemic treatment may have a certain impact on toxicity, as it was recently suggested in a study regarding SRS and ipilimumab/nivolumab in melanoma brain metastases30, a reason here fore may the higher treatment morbidity. However, due to the minimal incidence of radiation necrosis in our study (only one patient in this subgroup), this aspect couldn't be thoroughly analyzed.” (Page 13, Lines 309-315)

Comment 5: In the conclusion section, I suggest toning down the sentence "Upfront SRS/SRT followed by ICI leads to significantly prolonged OS than upfront ICI followed by SRS/SRT". Given that this is a retrospective non-randomized study with a small sample size, it might be prudent to refrain from drawing definitive conclusions from it.

Reply 5: The sentence was toned down by adding the note that this is a small retrospective cohort.

Changes in the text:

“In this small retrospective cohort, patients treated with ICI (mainly pembrolizumab) and SRS/SRT as first-line treatment for brain metastases of NSCLC, upfront SRS/SRT followed by ICI lead to significantly prolonged OS than initial ICI treatment followed by SRS/SRT.” (Page 14, Lines 332-334)

Comment 6: In the limitations section, the authors should mention the possible selection bias in the group of patients who received upfront systemic treatment. Patients with a good systemic response may also experience a better cranial response, potentially negating the need for SRS, and thus may not be accounted for in the study.

Reply 6: This aspect was added to the description of the study´s limitations.

Changes in the text:

“Additionally, a selection bias is very likely due to the fact that patients with a good systemic and intracranial response might not have been treated with SRS/SRT afterwards, and thus were not taken into account in this analysis.” (Page 14, Lines 325-328)