Peer Review File

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Reviewer A

Very well written. I would recommend taking the word "highly" out of "highly effective". I think it's hard to say anything is "highly effective" when at the end of the follow up period 41.6% of patients died. But I do commend the authors for their work. It is cleanly written and compelling.

Reply 1: The word “highly” has been removed as requested.

Changes in the text: The modification has been made in the highlight box(see Page 3, line102).

Reviewer B

1) I suggest the authors to indicate the clinical research design of this study in the title such as a retrospective cohort study.

   Reply 1: The title has been revised based on the suggestions: What is the Optimal SBRT Dose with Immunotherapy for Pulmonary Oligometastases: A Retrospective Cohort Study.

   Changes in the text: The modification has been made in the title (see Page 1, line2-3).

2) In the abstract, the authors need to clarify the novelty of the research question on the dose of the SBRT in the background, describe the inclusion of subject, follow up procedures, and how the best dose was ascertained in the methods, and describe the characteristics of the patient sample and the OS and PFS in the whole sample in the results.

   Reply 2: Revisions have been made to the background, methods, and results based on the suggestions.

   Changes in the text: Refer to the revised sections in the abstract(see Page 1, line35-42, Page 2, line49-54, Page 3, line67-80).

3) In the introduction, please review what has been known on the dose of SBRT, how the dose was determined in clinical practice, and influencing factors of dose. The authors need to clarify the current knowledge gap.

   Reply 3: Revisions have been made to the introduction.

   Changes in the text: Refer to the revised sections in the introduction(see Page5, line145-155 , Page 6, line162-183, Page 6, line189).

4) In the methodology, please describe the sample size estimation, details of follow up, and how the prognosis outcomes were collected. In statistics, it seems that the authors did not attempt to analyze the best dose. I do not think analyzing the

prognosis of different dose groups is equivalent to the identification of the best dose.

Reply 4: The sample size has been described in the Patient and tumor profile section of the Results; for details, refer to (Page 10, line305-333). The follow-up details and evaluation criteria are specifically explained in the Data Collection and Follow-up section (Page 8, line255-264). In our study, the selection of the optimal dose is based on a comprehensive analysis of multiple clinical outcomes, not merely a simple comparison of prognosis across different groups. We compared various SBRT dose regimens (50 Gy/5 fractions, 50 Gy/10 fractions, 70 Gy/10 fractions, and 60 Gy/10 fractions), and the conclusion indicated that the 60 Gy/10 fractions regimen achieved the best balance across several key clinical indicators.First, in terms of **overall survival (OS)**, the 60 Gy/10 fractions regimen showed a median OS of 39 months, significantly better than the other regimens. As OS is considered the gold standard for assessing treatment benefit, it is one of the core reasons for identifying 60 Gy/10 fractions as the optimal dose.Second, **local control (LC)** is also crucial for evaluating the effectiveness of local therapies. In our study, the 60 Gy/10 fractions regimen achieved the highest LC rate (92.4%), demonstrating its strong efficacy in controlling local lesions.Moreover, **toxicity** is another key factor we considered. Although higher doses are generally associated with increased toxicity, in this study, the 60 Gy/10 fractions regimen had lower toxicity than the 50 Gy/5 fractions regimen, while being comparable to the toxicity levels of the 50 Gy/10 fractions and 70 Gy/10 fractions regimens. Therefore, the toxicity of the 60 Gy/10 fractions regimen is relatively manageable, making it the regimen that strikes the best balance between efficacy and safety.In summary, we identified 60 Gy/10 fractions as the optimal dose not only because of its superior performance in OS and LC, but also due to its manageable toxicity profile. This regimen provides the best survival benefit and toxicity control for patients with pulmonary oligometastases, which is why we recommend it as the optimal choice for clinical practice.

Changes in the text: In subsequent studies, our goal is to conduct a prospective study to accurately determine the optimal dosing regimen, and we look forward to sharing our findings in the future.

5) Finally, please cite several related papers: 1. Begum H, Swaminath A, Lee Y, Fahim C, Bramson J, Naqvi A, Shargall Y, Finley C, Hanna W, Agzarian J. The histologic effects of neoadjuvant stereotactic body radiation therapy (SBRT) followed by pulmonary metastasectomy—rationale and protocol design for the Post SBRT Pulmonary Metastasectomy (PSPM) trial. Transl Cancer Res 2022;11(4):918-927. doi: 10.21037/tcr-22-232. 2. Piao MN, Xie J, Jin MM, Ma XT, Dou Z, Wang JP, Li JL. Efficacy and prognostic factors of stereotactic body radiotherapy combined with immunotherapy for pulmonary oligometastases: a preliminary retrospective cohort study. Transl Lung Cancer Res 2024;13(8):1950-1963. doi: 10.21037/tlcr-24-588. 3. Capone L, Antonia Allegretta S, Bianciardi F,

Tolu B, Rea F, Giraffa M, Confaloni V, Raza GH, D'Ambrosio C, Cavallo F, Marchesano D, Grimaldi G, El Gahwary R, Cinelli E, Minniti G, Gentile P. The impact of a mono-institutional experience in lung metastases treated with stereotactic body radiation therapy (SBRT): a retrospective analysis. Ther Radiol Oncol 2023;7:13.

Reply 5: The newly added references have been included in the introduction section, revisions have been made to reference 8/9/12/.

Changes in the text: Refer to the revised sections in the introduction (see Page 5, line155/166, Page 6, line 176/181).

Reviewer C

This is a retrospective single-institution analysis of 101 patients treated with SBRT for oligometastases to the lung from various histologies.

Major comments are as follows:

The authors associated survival and cancer control outcomes with different dose-fractionation schedules, implying that certain schedules yield better outcomes. Yet they describe that the dose schedule was "tailored " based on lesion size and anatomic location. And that the dosing was based on the tumor's radiobiology and patient's overall treatment plan. Clearly there are inherent selection biases in the dose selection and yet throughout the paper the authors misleadingly +attribute better outcomes with specific dose schedules even though the "better" treatment is neither the least or most dose-intense which is lot logical (particularly for local control). This is a major limitation that is not adequately addressed in the text.

Reply: We appreciate the reviewer's insightful comments regarding the potential selection bias in our study and the implications of associating survival and cancer control outcomes with specific dose-fractionation schedules. As noted, the SBRT dose schedules in this study were indeed tailored based on individual tumor characteristics, such as lesion size, anatomical location, radiobiological factors, and the patient's overall treatment plan. This personalized approach inevitably introduces selection bias, which could influence the observed correlations between specific dose schedules and improved outcomes.We acknowledge that this is a limitation of our study and have now addressed this concern more explicitly in both the **Discussion** and **Conclusion** sections of the manuscript. Specifically, we clarify that while the 60 Gy in 10 fractions regimen was associated with improved overall survival (OS) and local control (LC), this should be interpreted cautiously due to the inherent selection bias. The association of better outcomes with this regimen may reflect the characteristics of the patient group rather than the dose regimen itself.To mitigate this bias, we employed multivariable Cox regression models to adjust for confounding variables such as tumor size, location, and patient demographics, which could influence treatment outcomes. However, we agree that prospective, randomized trials are necessary to rigorously evaluate the optimal

SBRT dose without the influence of selection bias. These trials would provide more definitive conclusions on the dose-response relationship, particularly concerning local control.In summary, we have revised the manuscript to reflect the limitations more clearly, emphasizing that the results should be interpreted in light of the individualized dose selection and the need for future prospective studies to confirm the optimal dosing strategy.Thank you again for your valuable feedback, which has helped us improve the clarity and transparency of our study.
Changes in the text: Revisions can be seen in the conclusion of the abstract(see Page 3, line 81-88), the last paragraph of the discussion(see Page 16, line 531-545), and parts of the conclusion(see Page 17, line 562-587).

The authors describe BED10 conversions, and report that in a table, yet don't seem to analyze it as a factor. While this would similarly be affected by selection biases, it would not yield a nonsensical result of 60 Gy in 10 fractions being superior to 50 Gy or 70 Gy in 10 fractions.
Reply: Thank you for your valuable feedback regarding the use of BED10 conversions and their impact on the dose-fractionation analysis. We would like to clarify that BED10 was analyzed in our study and was included as a factor in the multivariable Cox regression analysis, as shown in Tables 3 and 4. A cutoff of 100 Gy was used based on its clinical relevance and prior SBRT studies. However, in our analysis, BED10 using this cutoff did not yield statistically significant results.Regarding the finding that the 60 Gy in 10 fractions regimen appeared superior to 50 Gy or 70 Gy in 10 fractions, we believe this reflects a balance between efficacy and toxicity. The mid-range dose of 60 Gy offered optimal tumor control while minimizing the side effects often associated with higher doses (e.g., 70 Gy), which is consistent with the biological effects described by the BED10 model. We acknowledge that selection bias may have influenced these results, and we will address this limitation in the discussion.Thank you again for your insightful comments, which have helped to clarify the interpretation of our analysis.
Changes in the text: Revisions can be seen in the conclusion of the abstract(see Page 3, line 81-88), the last paragraph of the discussion(see Page 16, line 531-545), and parts of the conclusion(see Page 17, line 562-587).

In the methods (first paragraph) the authors summarize the patient cohort (which is really results and not methods). They describe 27 patients as having no metastases. This is either an error in writing or a major issue with this analysis that is specific to patients with oligometastases (i.e. were patients with Stage I NSCLC included here??).
Reply: This means that these 27 patients had only pulmonary metastases. The content has been moved to the Results section.
Changes in the text: Revisions have been made in the Results section based on the suggestions(see Page 10, line 313-317).

Along those same lines, for PFS the authors analyze "presence of lung metastases" as a prognostic factor. Yet the entire cohort was treated for lung metastases. So it is unclear

what is being analyzed or what patients are truly included in this study.
Reply: Thank you for your thoughtful feedback. We appreciate your interest in the analysis of "presence of lung metastases" as a prognostic factor. To clarify, the study cohort includes two distinct groups: one group with only intrapulmonary (lung-only) metastases and another group with both pulmonary (intrapulmonary) and extrapulmonary metastases. This distinction is crucial for our analysis, as we aimed to evaluate how the presence of metastases outside the lungs affected progression-free survival (PFS).As shown in Table 2, the cohort was divided accordingly, and our analysis compared these two groups. The Kaplan-Meier survival curves highlight that patients with both intrapulmonary and extrapulmonary metastases had relatively worse outcomes in terms of PFS compared to those with only lung metastases.
Changes in the text: none.

The most likely factor affecting outcome is indolent disease. Over half had a prior history of lung metastases “exceeding 2 years”. This should be analyzed as a factor.
Reply: Thank you for your valuable comment. To clarify, the "history of lung metastasis diagnosis exceeding two years" refers to the time between the initial diagnosis of the primary tumor and the development of lung metastases. We agree that time from diagnosis to lung metastasis could be an important factor influencing outcomes, and we included this variable (time from diagnosis to lung metastasis) in our Cox proportional hazards analysis for both progression-free survival (PFS) and overall survival (OS).However, after conducting the multivariable Cox analysis, we found that this factor did not have a significant impact on either PFS or OS in our cohort. While we initially hypothesized that a longer history of lung metastasis might reflect a more indolent disease course, our analysis did not support this association in the statistical results.
Changes in the text: none.

Table 2 (last rows) indicates that all patients had surgery or RFA prior to SBRT. What surgery did these undergo? Why did all patients undergo surgery or RFA? This is not typical of a cohort of patients undergoing SBRT for oligometastases.
Reply: All patients underwent surgery prior to SBRT, referring to surgery on the primary tumor, not the lung oligometastatic lesions. Additionally, RFA was used to treat liver metastases in some colorectal cancer patients, not the lung oligometastatic lesions. None of the lung oligometastatic lesions in the study received local treatment.
Changes in the text: Revisions have been made in the Results section based on the suggestions(see Page 10, line 327-332).

The authors emphasize immunotherapy prior to SBRT but neglect to describe any therapy after SBRT. Did any not receive immunotherapy prior to SBRT but them did so afterwards. I would anticipate not which leads to the next comment.
Reply: Thank you for your comment. To clarify, no patients in our cohort did any not receive immunotherapy prior to SBRT but them did so afterwards.
Changes in the text: none.

Presumably those who did not undergo Immunotherapy were not candidates for immunotherapy which makes their analyses on this factor relatively meaningless given the selection biases associated with receipt of immunotherapy vs not.

Reply: Thank you for your insightful comment regarding the potential selection bias between patients who received immunotherapy and those who did not. We agree that patients who did not undergo immunotherapy likely had contraindications or were not suitable candidates for this treatment, which introduces a selection bias that could impact the interpretation of our results.In our study, the decision to administer immunotherapy was made based on clinical judgment, taking into account individual patient factors such as performance status, comorbidities, and tumor biology. Consequently, patients who did not receive immunotherapy were inherently different from those who did, which could influence the observed outcomes.

We acknowledge this limitation and will revise the manuscript to explicitly address this potential bias. In the revised discussion, we will clarify that the comparison between patients who did and did not receive immunotherapy should be interpreted with caution, as the lack of randomization and the selection bias related to eligibility for immunotherapy affect the robustness of the analysis.We appreciate your observation, and we will ensure that the limitations of the immunotherapy analysis are highlighted in the manuscript.

Changes in the text: Revisions have been made in the Results section based on the suggestions(see Page 10, line 324-325).

Minor comments

The study by Palma et al is not an “observational study but rather a prospective randomized study

Reply: Thank you for your careful reading and helpful feedback. You are correct that the study by Palma et al. (SABR-COMET) is a prospective randomized study, not an observational study as initially described. We have corrected this in the manuscript to accurately reflect the nature of their research. We apologize for the oversight.

Changes in the text: Revisions have been made according to the suggestions. Please refer to the Introduction section for details(see Page 6, line 176-178).

The dose constraints table would be better for supplemental text. It is unclear if the doses that are listed are maximum doses, point doses (0.035 cc) or something else altogether.

Reply: Thank you for your feedback. We would like to clarify that the doses listed in the dose constraints table represent **maximum point doses**. We will move the dose constraints table to the supplementary section for better clarity and ensure that this information is appropriately detailed in the supplemental text.

Changes in the text: It has been revised to Table S1 according to the suggestions.

What grading system was used for toxicity and how was this assessed? retrospectively? or were these data collected systematically.

Reply: Thank you for your insightful question regarding the grading and assessment of toxicity in our study.The evaluation of treatment-related adverse events was conducted using the **Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**. These adverse events were classified based on their severity, following the standard definitions provided by the CTCAE. The data were collected retrospectively, as part of the patient follow-up records, and the toxicity grading was applied systematically based on documented clinical observations and follow-up data.

Changes in the text:none.

Prescribed dose should not in and of itself impact toxicity but rather the organ at risk exposure. This seems to conflated here.

Reply: Thank you for your insightful comment regarding the relationship between prescribed dose and organ-at-risk (OAR) exposure. To clarify, in our study, the OAR dose constraints were adjusted based on the number of fractions for each specific dose-fractionation regimen. As outlined in **Table S1**, the limits for normal tissue exposure were set according to the specific fractionation scheme used for each patient, ensuring that normal organs were protected irrespective of the prescribed total dose. Target volume delineation and treatment planning were conducted in accordance with these limits to minimize the risk of toxicity while maintaining effective tumor control.

Changes in the text: none.