Peer Review File

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Comments

Reviewer A

The authors performed a nice review on four meta-analyses of stereotactic body radiation therapy versus external beam radiotherapy for painful bone metastases. The paper is valuable because the four meta-analyses reached different conclusions and a guide to interpret the current evidence of stereotactic body radiation therapy for bone metastases is necessary. The work is useful as such a guide for physicians involved in treatment for bone metastases. Some points, however, may be considered before its acceptance.

- On the following sentence, I recommend specifying which studies reported so.
"Some studies even showed that patients who received cEBRT had a better QOL."

- In the Introduction section, I suggest citing the following recent meta-analysis that reported pain response rates based on the International Consensus Endpoint.

Pain response rates after conventional radiation therapy for bone metastases assessed using International Consensus Pain Response Endpoints: a systematic review and meta-analysis of initial radiation therapy and reirradiation. Nobuki Imano, Tetsuo Saito, Peter Hoskin, et al. Int J Radiat Oncol, in press (doi: 10.1016/j.ijrobp.2023.01.050.).

- I strongly agree with the authors that the durability of pain relief after initial pain response is an important and clinically meaningful endpoint. The following paper may be worth citing in the context of the importance of standardizing the statistical methods in the assessment of the duration of pain response.

Bias due to statistical handling of death and reirradiation in the assessment of duration of response after palliative radiotherapy: a scoping review and analysis of clinical data. Tetsuo Saito, Kenta Murotani, Kei Ito, et al. Br J Radiol 2023;96(1141):20220398 (doi: 10.1259/bjr.20220398.).

- I think that the paper #18 may be that "Crit Rev Oncol Hematol. 2022 Oct;178:103775" (doi: 10.1016/j.critrevonc.2022.103775), and not a paper on J Med Imaging Radiat Oncol.

- "Another unsettled issue is WHETHER SBRT…" may be the authors' intent instead of "Another unsettled issue isSBRT improves outcome for patients with…".

Thank you for your comments.

Comment 1: On the following sentence, I recommend specifying which studies reported so. “Some studies even showed that patients who received cEBRT had a better QOL.”

Reply 1:
This is amended. Please see Page 7, Line 15.

Comment 2: In the Introduction section, I suggest citing the following recent meta-analysis that reported pain response rates based on the International Consensus Endpoint.

Pain response rates after conventional radiation therapy for bone metastases assessed using International Consensus Pain Response Endpoints: a systematic review and meta-analysis of initial radiation therapy and reirradiation. Nobuki Imano, Tetsuo Saito, Peter Hoskin, et al. Int J Radiat Oncol, in press (doi: 10.1016/j.ijrobp.2023.01.050.).

Reply 2:
This citation is added. Please see Page 3, Line 11.

Comment 3: I strongly agree with the authors that the durability of pain relief after initial pain response is an important and clinically meaningful endpoint. The following paper may be worth citing in the context of the importance of standardizing the statistical methods in the assessment of the duration of pain response.

Bias due to statistical handling of death and reirradiation in the assessment of duration of response after palliative radiotherapy: a scoping review and analysis of clinical data. Tetsuo Saito, Kenta Murotani, Kei Ito, et al. Br J Radiol 2023;96(1141):20220398 (doi: 10.1259/bjr.20220398.).

Reply 3:
This citation is added. Please see Page 5, Lines 31-34

Comment 4: I think that the paper #18 may be that “Crit Rev Oncol Hematol. 2022 Oct;178:103775” (doi: 10.1016/j.critrevonc.2022.103775), and not a paper on J Med Imaging Radiat Oncol.

Reply 4:
This is amended. Please see the new renumbered reference 21.

Comment 5: “Another unsettled issue is WHETHER SBRT…” may be the authors’ intent instead of “Another unsettled issue is SBRT improves outcome for patients with…”.

Reply 5:
This has been clarified. Please see Page 10, Line 8.

Reviewer B

This is a very high-quality review paper in terms of its methods, results, interpretation, and discussion. This paper provides one answer to a very important question for radiation oncologists worldwide.

I have only one comment. This study focuses on the pain relief effect; hence it would be better to remove the description regarding oligometastases in the Discussion to avoid blurring the focus. However, whether to remove the description or not is up to the author's judgment.

Thank you for your comments.

Comment 1: I have only one comment. This study focuses on the pain relief effect; hence it would be better to remove the description regarding oligometastases in the Discussion to avoid blurring the focus. However, whether to remove the description or not is up to the author's judgment.

Reply 1:
We wish to discuss oligometastases in our paper because the current evidence suggests that SBRT may provide more durable local control compared to cEBRT, and patients with oligometastases may be most justified to receive SBRT in the case of resource limitations. We believe including this topic in our discussion would make the clinical practice review more comprehensive. We have significantly shortened the paragraph on oligometastases to avoid blurring the focus. Please see page 11, lines 7-11.

Reviewer C

The authors should be commended for highlighting an important discrepancy regarding a series of recently published systematic reviews.

However, I find the content of the manuscript does not support the conclusions laid out in the abstract and seems to be combination of an editorial or commentary and a review. If the former, then the manuscript should be significantly shortened and focus on highlighting a key point, which is that the Ryu study is the one that did not show a benefit to SBRT and given large sample size, meta-analyses that include it do not show a benefit to SBRT as far as pain control. Is it valid to exclude the Ryu study because has not yet been published? Table 2 should include all primary studies used in all reviews, primary endpoint, how pain was measured, if purpose is to analyze why there is discordance in methodology and conclusions.

The rest of the manuscript comments significantly on cost effectiveness and other reasons why certain reviews many have drawn some conclusions but not others when in looking at primary data, it seems clearly driven by the Ryu study.

In determining why there would be different conclusions drawn from the 4 published, papers, the authors should focus more on the primary data and the methodology used in each review and justify why or why not that was a rational criteria or if one approach was better than another (use of PROSPERO and PRISMA methodology etc). I find a review of reviews to be problematic in methodology and seems to be not a statistically sound methodology, given lack of weight or disproportionate weight given to individual studies that may or may not have been included in the 4 systematic reviews, which are also not clearly laid out in the manuscript.

Perhaps this should be laid out more clearly as far as what constitutes a "critical appraisal" and framed more clearly as a commentary.

I think in order to warrant publication, selecting any of the suggested action items described in abstract (the individual patient-level meta-analysis, delphi consensus panel to address open or unanswered questions or highlight level of consensus on any of points raised in Table 5) but otherwise I think manuscript reads much like a commentary and would probably benefit from being more focused and streamlined such that conclusions are more limited in scope.

Table 5 in particularly is also not evidence based based on data within paper.

Thank you for your comments.

Comment 1: However, I find the content of the manuscript does not support the conclusions laid out in the abstract and seems to be combination of an editorial or commentary and a review. If the former, then the manuscript should be significantly shortened and focus on highlighting a key point, which is that the Ryu study is the one that did not show a benefit to SBRT and given large sample size, meta-analyses that include it do not show a benefit to SBRT as far as pain control. Is it valid to exclude the Ryu study because has not yet been published? Table 2 should include all primary studies used in all reviews, primary endpoint, how pain was measured, if purpose is to analyze why there is discordance in methodology and conclusions.

The rest of the manuscript comments significantly on cost effectiveness and other reasons why certain reviews many have drawn some conclusions but not others when in looking at primary data, it seems clearly driven by the Ryu study.

Reply 1: We position our paper as a clinical practice review based on the four systematic reviews and meta-analyses recently published. Therefore, apart from commenting on the results of the four reviews and the included primary studies, we provided a comprehensive review on the pros and cons of routine use of SBRT in clinical practice, and how to perform more research to better characterize the use of this technique in the future.

Table 2 is amended to include all primary endpoints of the included studies and how pain was measured.

Comment 2: In determining why there would be different conclusions drawn from the 4 published, papers, the authors should focus more on the primary data and the methodology used in each review and justify why or why not that was a rational criteria or if one approach was better than another (use of PROSPERO and PRISMA methodology etc). I find a review of reviews to be problematic in methodology and seems to be not a statistically sound methodology, given lack of weight or disproportionate weight given to individual studies that may or may not have been included in the 4 systematic reviews, which are also not clearly laid out in the manuscript.

Reply 2:
We agree that there is no statistical method to compare systematic reviews. One could only examine the results of the reviews and derive reasons for their differences based on the studies included and how the data was analyzed. We have added a on the study designs of the systematic reviews in the second section of the manuscript (Page 4, Lines 14-17). We added a comment on the limitation of including other study designs apart from randomized controlled trials in this section in the systematic review by Song et al. Please see Page 4, Lines 3-8.

We have highlighted that the inclusion of Ryu's study, which is the largest randomized controlled trial published to date on this topic, could have driven the results of the meta-analyses (Page 4, Lines 21-23). We also described reasons why Ryu's study was negative (Page 4, Lines 29-37; Page 5, Lines 1-17), and how performing an exploratory sensitivity analysis in the systematic review by Lee et al. helped assess whether Ryu's study drove the results of the meta-analysis (Page 4, Lines 26-28).

Comment 3: Perhaps this should be laid out more clearly as far as what constitutes a "critical appraisal" and framed more clearly as a commentary.

I think in order to warrant publication, selecting any of the suggested action items described in abstract (the individual patient-level meta-analysis, delphi consensus panel to address open or unanswered questions or highlight level of consensus on any of points raised in Table 5) but otherwise I think manuscript reads much like a commentary and would probably benefit from being more focused and streamlined such that conclusions are more limited in scope.

Reply 3: As mentioned above and as was requested of us for this Editorial Office-invited critical appraisal, we position our paper as a clinical practice review and, therefore, included all aspects that could affect the clinical decision on whether to offer SBRT to patients and how future studies should be done to better address the existing controversies reflected in the systematic reviews and in the literature. We have amended in the introduction that our paper is a clinical practice review instead of a critical appraisal. Please see page 3, line 29.

Comment 4: Table 5 in particularly is also not evidence based based on data within paper.

Reply 4: We acknowledge that some points in Table 5 are not based solely on conclusions derived from the systematic reviews. We wish to provide a one-table summary on practical considerations of SBRT and areas of future research on top of what we learnt about pain response from the systematic reviews.

Reviewer D

It is quite difficult to analyze the selective use of SBRT and conventional radiotherapy in bone metastases. This is because the treatment methods and clinical situations of the patients are very diverse. Nevertheless, this review provides a good brief scope to understand the esoteric literature.

I have no objection to the contents of this review. However, the number of authors is too large, and review papers generally have 2-3 authors (because manuscript is difficult to be written divided by more than 20 people). It is recommended to specify the role of the authors. Authors who did not play a major role should be included in the acknowledgment. If the authors constitute a particular consortium, it is recommended to state the name of the consortium.

Thank you for your comments.

Comment 1: I have no objection to the contents of this review. However, the number of authors is too large, and review papers generally have 2-3 authors (because manuscript is difficult to be written divided by more than 20 people). It is recommended to specify the role of the authors. Authors who did not play a major role should be included in the acknowledgment. If the authors constitute a particular consortium, it is recommended to state the name of the consortium.

Reply 1: We invited a large group of international radiation oncologists as co-authors with the aim to present our shared position on when and how SBRT should be employed in clinical practice for painful bone metastases based on the latest evidence, and what we think are the areas of future research. All co-authors have reviewed and approved the content of the article and meet the definition for authorship.