Peer Review File

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Reviewer A:

The authors asked the question of whether the 30day mortality metric is appropriate in the palliative radiotherapy setting. At initial glance, I find the topic to be interesting and relevant to our daily work as radiation oncologists.

In essence they have reviewed the literature which showed that radiotherapy works well and rapidly for the purpose of poor performing patients. They have also discussed how the efficacy of radiotherapy in this group of patients might be augmented by rapid access palliative radiotherapy clinics. Their efforts are commendable.

Comment 1: However, with respect to the research question of "appropriateness" in the title, I do humbly feel that the literature covered is lacking.

As a reader, I wonder what is the current literature on the "real world scenario" of using 30 day mortality as a predictor for deciding palliative radiotherapy? As the authors have rightly pointed out, the prediction models available out there are just a guide at best. These models do not specifically address the end point of 30day mortality per se and I believe it is not the intention of the authors of the respective models to preclude patients from radiotherapy just on the strength of the models alone. I personally would also not base my treatment decision on one metric alone.

Reply 1: We thank the reviewer for the comment. We agree with the reviewer that in "a real world scenario" we do not base the clinical management on just one predictor metric. In order to provide a better understanding of this point, we have modified this in the objective and conclusion of our review (see page 2, line 56; and page 9, lines 273-280).

Comment 2: The authors sought to discuss the dangers of using the 30 day mortality metric in making treatment decisions. However, I do not see the evidence presented in the paper addressing the purported dangers. I am interested to see the actual "harm" from the literature on withholding radiotherapy in patients expected to die within 30day. One would argue that even with the most rapid administration of RT, if the patient is to die within a few days to a couple of weeks of RT, it would not have been a good use of the resource. It must be pointed out that the literature on rapid access clinics comes from mainly western advanced economies. There are centers where resources are limited and radical intent radiotherapy needs to be prioritized.

In summary, the authors have addressed the "inappropriateness" of 30 day mortality, but I think it would have been a more balanced review if there was a discussion on the "appropriateness" of 30 day mortality.

Reply 2: We thank the reviewer for highlighting this. We have reviewed the literature and changes have been addressed (see page 8, lines 254-258; and page 3, lines 110-112).

Reviewer B:

This is a literature review that seeks to rebut the idea that palliative radiation in the final month of life is futile. It is worthy of publication and does not require major revisions.

Comments to the authors:
Overall this is an important rebuttal to the claim that patients with a life expectancy under 30 days will not benefit from palliative RT. As radiation oncologists, we need to educate other physicians about the short-term benefits of RT, and not allow policies such as a 30-day rule lead to increased patient suffering.

Comment 1: Grammatical issues:
Line 49: "barriers exist which…" should be "barriers exist that…"
Line 80: "A literature research…" should be "A literature search…"
Line 162: "and develop of…" should be "and development of…"

Reply 1: We thank the reviewer of taking care of these grammatical issues that have been corrected. Please, see lines 86, 119 and 216.

Comment 2: The authors state that the outcome of interest from the literature review is response time to single fraction palliative RT. However, the conclusion could more strongly state their findings (i.e. palliative radiation does help with symptoms, in that 30 day window specifically). In other words, even if we were always correct about life expectancy predictions, patients who would die in 3-4 weeks could still benefit from palliative RT, based on this report.

Reply 2: We thank the reviewer for the suggestion to emphasize the conclusion of our review. Please, see page 9, lines 286-287.

Comment 3: In the discussion of cord compression, the claim is made that the efficacy of SFRT is non-inferior to MFRT. It should be noted that the general concern with SFRT is durability of response, which is less of a concern in the population discussed in the manuscript (short life expectancy).

Reply 3: We thank the reviewer to for highlighting this. It has been addressed in page 6, lines 177-180, and 184-188.

Comment 4: Regarding the discussion of RAPRT clinics, particularly in the United States, the barriers to widespread implementation are not discussed. The authors' recommendation to increase the number of RAPRT clinics is tempered by concerns with billing/reimbursement for same day E&M/sim/treatment, the limited number of academic centers within a reasonable travel distance to the rural population, and the fact that many patients in need of palliative RT do not have a tissue diagnosis of cancer at the time of presentation. It would be worth mentioning the barriers to RAPRT implementation since the authors recommend it so strongly.

Reply 4: We thank the reviewer for this comment and we agree with adding information about the barriers of the RAPRT clinics (see page 8, lines 256-263).

Reviewer C:

This is a very well-written narrative review of the appropriateness of applying 30-day mortality as the major criterion for palliative RT. The hypothesis (that it is NOT appropriate) is very interesting and clinically relevant and the case well-argued in my opinion. I like the succinctness of the text, balanced against the detail in the Tables (although I have not checked the latter in detail).

Comment 1: A criticism would be that there is minimal acknowledgement of well-known counter arguments e.g. reported re-treatment rates with SFRT (of limited relevance in this population) and patient reluctance to wait around for many hours on one day with the RAPRT model. This criticism could be addressed in a single extra paragraph.

Reply 1: We thank the reviewer for the suggestion; however, we have not addressed them in an extra paragraph. Please, see the revised comments in page 5, lines 171-173.

Comment 2: Minor suggestions:
1. P2, line 58: …has been examined…
2. P4, line 109: A single randomized trial…
3. P5, line127: …sphincter function…
4. P6, line 162: …time interval…and development…

Reply 2: We thank the reviewer of taking care of these minor suggestions, which have been addressed in lines 91, 154, 177 and 215-216.

Reviewer D:

This paper questions and argues for the value of palliative RT in patients approaching end of life. Their arguments appear to be valid overall, but could be stated more clearly throughout the paper with a more robust thesis.

Comments to the authors:

The authors tackle on an interesting and controversial topic regarding the use of palliative RT in patients at the end of life. The main arguments are that palliative RT should be strongly considered even in patients who are thought to die within 30 days because 1) 30-day mortality predictions are often incorrect, 2) even with short life expectancy, RT can effectively provide relief for pain, bleeding, neurological deficits, 3) these reliefs come fairly rapidly that could be meaningful even at the last weeks of a patient's life, 4) the burden of RT can be reduced with single fraction treatment and access to rapid access clinics. These arguments are presented in the paper, however, they could be more clearly stated in an organized way to deliver their message to the readers.

Comment 1: Title/Introduction

Hypothesis is stated well in the introduction, but I suggest a title that is less (mis)leading and something that encompasses the full scope of the paper (the validity of 30-day mortality as a metric, time to response after palliative RT, effect of palliation at the end of life, decreased time burden with single fraction or rapid access clinics, etc.).

Reply 1: We thank the reviewer for the suggestion. It was not our intention to use a (mis)leading title and we have decided to make a change. Please, see page 1, lines 3-4.

Comment 2: Methods
Please state the three indications for palliative RT that were examined in this study.

Reply 2: We thank to the reviewer for this comment. We have address this change in page 4, lines 121-122 and 129-130.

Comment 3: Results
Other than complete/partial response, it would be helpful to discuss data on the decreased reliance of opioids after palliative RT, PRO metrics other than pain response only. Even if the pain response rates are good, one could possibly argue that such pain can be managed medically optimally enough without having to involve RT simulation and treatment, and the financial costs on the healthcare system.
Financial toxicity is likely beyond the scope of this paper, but proponents of limiting palliative RT at end of life often mention burden on the healthcare system and costs as arguments against end of life RT. Has this been looked at?
Can pain response occur even earlier than 2-4 weeks (which is the time point for which most of the cited studies report on the pain response rate)? Did the studies look at response within the first week of RT? If available, it would be helpful for the tables should present response rates at an earlier time (1-2 weeks). This would be particularly convincing for RT done for bleeding, since response times can be much earlier than 4 weeks.
In general, original studies should be cited instead of or in addition to reviews.

Reply 3: We thank the reviewer for questioning these points. We have added more information about other metrics for pain response in the manuscript, which also we mention in the tables (see page 5, lines 146-148). Unfortunately, we have not included financial data in this review, but this is a good point for future studies.
Regarding the question about earlier response rates, we looked at this information; however, we did not find ant trial which looked for response within the 1-2 weeks. There are some publications that reported earlier response, even it was not the main objective. This is reported in page 4, lines 139-146; page 6, lines 191-193; and also in the table 1.

Reviewer E:

Very well written and clear review about important topic.
I have only few suggestions for authors that may improve their manuscript:

Comment 1:

1) It would be reasonable to put at least slight information about doses and fractionation of palliative radiotherapy in introduction.

2) Authors could consider adding short review of literature about palliative reirradiation and time of pain relief in those cases.

3) Authors conclude that SFRT is effective and linked with minimal toxicity - i fully agree with that, but toxicity of palliative radiotherapy is not discussed in manuscript - please add information about treatment toxicity in review or consider changing the conclusion.

Reply 1: We thank the reviewer for these comments. The first point has been addressed in page 3, lines 100-102. Regarding the second question it is described in page 5, lines 151-156. Finally, we agree that the toxicity is not reported and we removed it from the conclusions (see page 9, line 280).

Editorial Comments:

1. *The title should identify the article as a narrative review. Thus please revise, for example "Is the use of the 30-day expected mortality metric in palliative radiation settings appropriate? A Narrative Review" or others you prefer;*

2. *The Abstract should be structured with the below 4 sections. Thus, please make the revision;*

- *Background and Objective: describe relevant background, reasons for conducting this review and primary objectives of this review.*
- *Methods: briefly describe the search strategy, including databases, time frame, and language considerations.*
- *Key Content and Findings: describe what the literature review will mainly contain and any key findings.*
- *Conclusions: describe the main conclusions and how the review may potentially impact future researches, clinical practice and policy making.*

3. *Attached is the Narrative Review reporting checklist. Please fill in accordingly.*

Reply: We that the comments from the editorial. The title and the abstract have been modified accordingly, and the Narrative Review reporting checklist, is attached with the rest of the revised documents.

4. *Please confirm if the Tables are original and have not been published before. Otherwise, please provide the permission.*

Reply: The tables are original.

5. Please provide the following Authors' contributions:

Authorship Contributions:
(1) Conception and design: Edward Chow MBBS, Srinivas Raman MD MASc and Inmaculada Navarro-Domenech MD.
(2) Administrative support: Srinivas Raman MD MASC, Edward Chow MBBS, Tara Behroozian MD and Inmaculada Navarro-Domenech MD.
(3) Provision of study materials or patients: Srinivas Raman MD MASC, Edward Chow MBBS, Tara Behroozian MD and Inmaculada Navarro-Domenech MD.
(4) Collection and assembly of data: Srinivas Raman MD MASC, Edward Chow MBBS, Tara Behroozian MD and Inmaculada Navarro-Domenech MD.
(5) Data analysis and interpretation: Srinivas Raman MD MASC, Edward Chow MBBS, Tara Behroozian MD and Inmaculada Navarro-Domenech MD.
(6) Manuscript writing: All authors.
(7) Final approval of manuscript: All authors.

Note: 1. With VI and VII, "All authors" is obligatory, while the other credits are case-based (if not applicable, written N/A); 2. The 'Author contributions' section is not required when there is only one author.

6. Please complete the attached Conflict of Interest form and send back all authors' forms.

Reply: There are completed and attached with the rest of the revised documents.

7. For the Reference
a. In the text, references should be cited using numbers in round brackets in which they appear consecutively [e.g., "cancer-related mortality (19)"; "denocarcinoma (29,30)"] instead of superscript (treatment of thoracic conditions1-5).

b. For the Reference format, a Reference should be presented like: XX, XX, XX, et al. Article Title. Journal Abbreviation. Year; Volume; Pages. Please kindly revise according to the journal standard: when there're more than three authors of the article, please add "et al" instead of listing all authors (for example: "Junginger T, Goenner U, Hitzler M, Trinh TT, Heintz A, Wollschlaeger D, Blettner M" should be listed as "Junginger T, Goenner U, Hitzler M, et al").

Reply: Thank you. It is corrected.