Peer Review File

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Reviewer A

generally a well written and comprehensive summary.
may be useful for busy clinicians
1) Will be good to qualify that, in general, re-irradiation data in this paper refers to the 2nd course of RT, and may not be applicable to the 3rd course onwards.
2) for table 2, reference 18 (Miker Zabel paper) - only median dose is presented. please include fractionation. if details not available, may be good to state that most patients were treated with conventionally fractionated or hypofractionated
3) table 2 and 3 : RE rate of neurotoxicity. severity or grade should be mentioned in the text. I would presume this refers to severe neurotoxicity (Grade 2 or more?)

Response:

1. Introduction: It is now stated that this review summarizes the outcomes after a second course of radiotherapy (first reirradiation) [page 3, lines 72-73].
2. Table 2: Dose range and median dose per fraction have been added.
3. Tables 2 and 3: The corresponding toxicities have been added as footnote, plus the fact that grading of toxicity was not reported. “Neurotoxicity” has been replaced by “myelopathy / radiculopathy”, which is more precise. This modification has also been made in the text [pages 8+9, lines 236, 237, 240, and 249].

Reviewer B

In the mini-review ’Reirradiation of the central nervous system: Part 2 – Metastatic epidural spinal cord compression” by D. Rades et al. review a number of articles reporting re-irradiation of metastasis to the spinal cord. They address re-irradiation with conventional radiotherapy, highly conformal radiotherapy and, stereotactic body irradiation therapy (SBRT). They report different outcomes including cumulative dose, clinical outcomes, and toxicity.

The manuscript is very relevant and interesting, and the tables are easy to understand.

Major comments:
The authors examine a very relevant clinical question; what is the status quo in the literature for reirradiation of metastasis in the spinal cord? What is the cumulative dose and tolerance of the tissue? What toxicities pre-dominate the treated patients?

The manuscript, however, lack a designated method section for the literature included in the review as well as small paragraph discussing background literature for cumulative doses and issues when linear-quadratic model is applied on the clinical cases with large doses on one or very few fractions (see below comment in the "Reirradiation of MESCC with using highly-conformal radiotherapy" section).

For the method section:
The authors should include an explanation for inclusion/exclusion criteria of papers and the search strategy. How far back in time do the authors include paper, language etc.
A suggestion is to follow PubMed key steps for the narrative review:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9380643/

The manuscript lacks an overall strength and limitation paragraph. It should be included in the manuscript to address the risk of bias, e.g. selection bias.

Minor comments:
Paragraph "Abstract:
P2, line 42: *"…. other studies (n=?)…"*, please include number of studies referred to.

Paragraph "Introduction":
The introduction has a good length.
P3, line 73: '"outcomes" – the manuscript would benefit from a more elaborated definition of what outcomes the manuscript is assessing.

Paragraph "Tolerance doses of the spinal cord to radiotherapy":
Question: Ref. 2 and 3 uses an alpha/beta ratio for the cervical spine = 0.87. I believe this is quite unusual. The authors should comment/discuss this value in the context of the reported articles. What point do the authors wish to make with the first 2 sentences in the paragraph?

Paragraph "Reirradiation of MESCC using conventional radiotherapy"
Questions:
The section regarding reference 11, P5, line 126-136: You write that 85% have an overall response. Suggestion to add "defined as" →: *"Overall response (defined as: improvement or at least…)…"*
P3, line 88: how should the 1-5% be understood? Which percentages relates to what dose and fractionation?
P6, line 170-171, related to reference number 15: What was the follow up time?

The following are suggestions to make the text clearer and reader friendly:
P3, line 91: please include number of studies → *"A few studies (n=?)…"*
P3, line 92: is the re-calculated dose BED or EQD2?
P4, line 98-99: is the cumulative dose BED or EQD2?
P4, line 118-119: Please consider rephrasing "without these risk factors.."? What are the risk

factors? The time between courses? Or dose in one course? Could the sentences have more clarity?
P5, line 144: range reported with different format than the rest of the text. "… 9 months (range: 2-52 months" → *".. 9 (2-52) months.."*
P6, line 163-164: Consider to rephrase to → *"Hence, elderly patients do benefit…"*
P6, line 176: EQD2 misspelled

Paragraph: "Reirradiation of MESCC using highly-conformal radiotherapy":
What are your reflections on the follow up time for the papers in this section? The ranges are quite wide. Please discuss this a bit more.
What are your reflections for calculation of cumulative doses after SBRT? (P8, line 242-246). Is the linear-quadratic model applicable for high single doses? Do we have a better alternative? A discussion of this is encouraged – either with more background to this or a discussion in the section.

P7, line 192: please specify, normo-, hypo- or hyperfractionated?

Paragraph: Conclusions
Questions: See previous regarding cumulative dose after SBRT.

Tables:
Table 1: References are written with full bio, should be re-formatted to a more abbreviated reference per journal standards. Do the two scoring tools have names?
Table 2+3:
Consider to report year of the publications in the "Reference" column.
Consider to report dose and fractionation as Gy/number of fractions e.g. 30Gy/10F (nicer for the eye).
Consider to report radiation modality (photon/proton).
Consider to include time between first and second course.

Response:

1. A new methods section has been added [page 3]. The limitation of the LQ model is discussed in the new Limitations Paragraph [page 9].
2. A new methods section has been added [page 3].
3. A new Limitations Paragraph has been added including new references 29+30 [page 9].
4. Abstract: Number of studies has been added [page 2, line 41].
5. Introduction: Outcomes are defined [page 3, lines 73-74].

6. Tolerance doses: The paper of Schultheiss has been removed, references have been adjusted [page 3, lines 86-88]. Moreover, a subsequent text passage has been modified [page 4, lines 93-95].
7. Tolerance dose: Sentence has been re-written [page 4, lines 97-99].
8. Conventional RT: The sentence has been modified accordingly [page 5, line 145].
9. Conventional RT: Follow-up has been added [page 6, lines 182-183].
10. Conventional RT: The eight suggestions have been considered [pages 4-7, lines 103-192].
11. Highly-conformal RT: The wide range of follow-up periods and the limited usability of the LQ model for SBRT have been added to the new Limitations Paragraph [page 9].
12. Highly-conformal RT: The dose per fraction has been added [page 7, line 209].
13. Conclusions: The aspect of alternative models for calculation of the biologically effective dose for higher doses per fraction has been added to the conclusions [page 10, lines 291-293].
14. Table 1: References have been shortened.
15. Tables 2 + 3: The year has been added. Dose-fractionations have been modified. Protons do not apply. Interval has not been added to not overload the tables.