

Peer Review File

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Review Comments

Subject : Reirradiation of metastases of the central nervous system: Part 1 - Brain metastasis

In the mini-review 'Reirradiation of the central nervous system: Part 1 – Brain metastasis' by D. Rades et al. selected literature (17 papers, counted from the tables) is assessed and outcomes after irradiation to the brain is reported with regards to different re-irradiation modalities: whole-brain radiotherapy (WBRT) after WBRT, single fraction stereotactic radiosurgery (SF-SRS) after WBRT and SF-SRS or fractionated stereotactic radiation therapy (FSRT) after SF-SRS or FSRT, and tolerance doses to the brain including risk of radionecrosis is evaluated (2 papers).

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

Major comments:

The authors examine a very relevant clinical question i.e., what is the status quo in the literature for reirradiation of brain metastasis? What is the prevalence of radionecrosis after reirradiation?

The manuscript would, however, benefit from a clearer research question regarding what outcomes are of main interest? I.e., clinical effect on patients, side effects, survival time or presence of radionecrosis? Reirradiation after what type of primary radiotherapy? Etc. This will help the reader for better orientation in the paragraphs throughout the manuscript.

The length of the paragraphs is good and the manuscript should not be longer overall. The tables support the text well, however there is quite some overlap in reported numbers in the text and tables.

In general, the following paragraphs ("Reirradiation with SF-SRS following WBRT", "Reirradiation with SF-SRS or FSRT following primary SRS or FSRT", "Tolerance doses of reirradiation to the brain and potential risk factors for radiation necrosis") lack a discussion of the reported results and the authors' interpretation of the patterns seen across the included studies.

The manuscript lacks an overall strength and limitation paragraph. This could be sub-divide to the single paragraphs or be one main paragraph. It should be included in the manuscript including the risk of bias.

The approach a narrative review is understandable, the relevant papers will most likely be few and heterogenous in design, however the manuscript lack a 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, etc.

A suggestion is to follow PubMed's key steps for the narrative review: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9380643/>

Consequently, the broad research question, lack of method paragraph and not addressing strengths

and limitations leaves the reader puzzled and maybe more confused: Is this an opinion or the actual status quo of reirradiation of brain metastasis? Transparency for the risk of selection bias etc. should be addressed.

Minor comments:

General comments:

-In the beginning of each paragraph the actual number of papers referred to should be specified instead of “several studies”, “few papers”.

-When reporting data from the included papers there should be a consistency across all paragraphs to the same format, e.g., p4 line 113/115: Symptoms improved for 68% (n=??) of the patients is different from p4 line 115/116: Ten patients (32%)...

It is preferred that both number and percentage is reported.

-Range should be reported the same way throughout the manuscript; either “xx (range xx-xx)” or “xx (xx-xx)”.

-Dose and fractionation: to make the text in paragraphs and tables more reader-friendly, the suggestion is to report dose and fractionation like: 30Gy/10F instead of 10 x 30Gy.

-“Respectively” is used a lot throughout the manuscript – this can maybe be weed out here and there.

-How the primary and secondary radiotherapy course are named and referred to throughout the text should be the same in all sections.

Paragraph “Abstract”

P2: Include (n=?) after “Several studies...” (line 36), “Very few studies...” (line 43) and “Several studies...” (line 46).

P2, line 53: include course after first ...receiving 12 Gy at the first course and the second course...

P2, line 56, question: “in general, cumulative...” this is based on two studies. Suggesting rephrasing to avoid “in general”.. soften the expression.

Paragraph “Introduction”

The introduction has a good length.

Suggestion to rephrase sentence number 2 (p 3 line 68/69) and number 3 (p3 line 70/71). The direction of the sentences is not clear, and they both lack references for the statements made.

Suggestion for the re-phrasing:

... Novel systemic therapies have prolonged survival time/improved prognoses for cancer patients (ref), thus patients needing reirradiation of e.g., brain metastasis, have increased (ref). ...

P3, line 68/69: please include a reference for the statement for longer survival time after targeted therapy.

P3, line 72-74: please include a reference for statement regarding tolerated doses to the brain etc.

P3, line 74/75: please include a reference for statement regarding development of radionecrosis and neuropathy after reirradiation of the brain.

Paragraph “Tolerance doses of the brain in general, brain stem, and optic nerve”:

Question: is this a background section or a part of the review? What is the sub-conclusion to the

paragraph?

The following are suggestions to make the text clearer and reader friendly:

□P3, line 83: "... <55, 55-60, and >60 Gy..." the numbers should all have the unit "...<55 Gy, 55-60 Gy, and >60 Gy..."

□P3, line 89/90: ... were identified, including... replace "... include..."

□P3, line 90/94: the two sentences could be fused to: "... treated with one or more courses of SF-SRS, and found lesions >1,0 cm, location... (ref)."

□P4, line 100/101: "Volumes of 5, 10, and >15cm3...", the numbers should all have the unit change to "Volumes of 5 cm3, 10 cm3, and >15cm3..."

Paragraph "Reirradiation with WBRT following WBRT":

Questions:

P4, line 120/124: The paper Sharp et al include a subpopulation of patient treated prophylactic with WBRT as their first course – please comment your reflections on this. Should this study be included? Can the subpopulation be taken out from their data? Are those patients comparable to all the other patients? If yes, how?

P5, line 135/136: Why do you think those four studies saw different prognoses/outcomes for lung cancer patients?

P5, line 139/140: is this a mistake? Should it be absence or presence of extracranial metastases? If presence of extracranial metastases is a good prognostic factor with brain metastasis, please help clarify why.

The following are suggestions to make the text clearer and reader friendly:

□P4, line 107: Several studies... please include number of studies (n=?)

□P4, line 110, 111, 114: percentage patients are reported, should also include the number of patients: xx% (n=xx)

□P4, line 116: range reported, should be the same format as the rest of the manuscript.

□P4, line 121: range is missing after "13,4 months".

□P5, line 126: range and median are here reported different than in the rest of the manuscript

□P5, line 127/128: "... following repeat WBRT." Is this = second WBRT course? Consistent wording for the courses is suggested throughout the manuscript.

Paragraph: "Reirradiation with SF-SRS following WBRT":

Questions:

Reference 14-17 from the literature list is reported in this paragraph, however reference number 16 is not mentioned in the manuscript. Where should the paper be referenced in the text? Should it be included in table 2 as well?

The following are suggestions to make the text clearer and more reader friendly:

□P5, line 149: Very few studies... please include number of studies (n=?)

□P5, line 156: range reported differently, please report the same way throughout the manuscript.

□P5, line 162/163: "...5, 5, 8 and 14 months..." 5 is mentioned twice.

Paragraph “Reirradiation with SF-SRS or FSRS following primary SRS or FSRT”:

Questions:

The first study in the paragraph included 17 patients (=40%) having had WBRT as their primary course of RT. Is the data further reported from this study for the subpopulation having SRS/FSRT as primary or how should this be understood? The same for reference number 22 (p7 line 199/202). Table 3 report local control rate but it is not specified in the header of the column, if this is the One-year or two-year local control or some other. For some studies they have both reported in the text but only one in the table. Please specify in the header of the table what local control rate is reported.

What is the sub-conclusion to this paragraph? Any patterns seen across studies/primary cancer diagnosis/photon or protons etc.?

Radionecrosis in table 3: was this clinical significant in the studies? How was radionecrosis diagnosed across the studies? What are the issues with diagnosing radionecrosis? The authors could consider reporting the fraction of asymptomatic radionecrosis in table 3 for transparency.

Consider reading the paper by Søren Møller et al: <https://pubmed.ncbi.nlm.nih.gov/29054380/>.

The following are suggestions to make the text clearer and more reader friendly:

- ☐ P6, line 174: Several studies... please include number of studies (n=?)
- ☐ P7, line 191: range reported, make sure to report range consistently
- ☐ P6, line 181/183: delete “respectively” in line 183.
- ☐ P7, line 204/205: delete “respectively” in line 205
- ☐ P8, line 220: delete “respectively”
- ☐ P8, line 222: delete “respectively”
- ☐ P8, line 225: delete “respectively”

Paragraph “Tolerance doses of reirradiation to the brain and potential risk factors for radionecrosis”:

Questions:

Mayer and Sminia paper: did they distinguish between symptomatic and asymptomatic radionecrosis?

See questions for radionecrosis above.

The following are suggestions to make the text clearer and reader friendly:

- ☐ P8, line 240: Several studies... please include number of studies (n=?)
- ☐ P8, line 244/245: please include p-value if available (p=?)

Paragraph: Conclusions

Questions:

What are the guiding points for the clinicians from this review? Is WBRT a no-go? Are there some cancer diagnoses, which are no-go for re-irradiation? Does the shorter survival time for WBRT represent a general lower performance status? What is the survival time for matched cohort who did not get reirradiation with WBRT? Shorter or the same or even longer? Should WBRT vs SF-SRS be tested prospectively in matched cohorts?

Tables:

Consider to report year of publication 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 coursey.

Responses to the reviewers' comments:

1. The research questions have been added to the Introduction [page 3, lines 80-82].
2. Some overlap between text and tables is intentional. The tables may help the readers to identify important data at a glance.
3. Since this is a mini-review with a limited word count, the more extended discussion and interpretation of the reported results have been added to the Conclusions paragraph [pages 10-11, lines 305-321].
4. The limitations of this review are now more explicitly stated. To draw particular attention to these limitations, they are stated at the end of the article [page 10, lines 305-311]. Moreover, an extra paragraph would mean more words (see 3.). The reference by J. Sukhera has been added.
5. The search strategy has been added to the Introduction section [page 3, lines 82-85]. Moreover, an extra section would mean more words (see 3.).
6. "Several studies" and "few papers" etc. have been replaced by the corresponding numbers, e.g. lines 134, 182, and 209.
7. The format regarding N patients and % is now consistent in the **entire article**. Both numbers and percentages are reported.
8. Ranges are now uniformly given as "xx (xx-xx)" in the **entire article**.
9. Presentation of the dose-fractionation regimens (e.g. 30Gy/F) has been modified as suggested by the reviewer in the **entire article, including tables**. The "blanks" between dose and Gy have been removed.
10. "Respectively" has been removed many times in the **entire article**.

11. “Repeat” radiotherapy has been removed and replaced by “second course” throughout the **entire article**.
12. **Abstract:** “Several studies” and “very few studies” etc. have been replaced by the corresponding numbers.
13. **Abstract:** “Course” has been added after “first.”
14. **Abstract:** “In general” has been removed.
15. **Introduction:** parts of the introduction have been rewritten [page 3, lines 69-85]. Three references (current #3, #4, and #5) have been added.
16. The section “**Tolerance doses of reirradiation to the brain and potential risk factors for radiation necrosis**” has been moved to page 4, since it has a background character.
17. We have followed the reviewers’ suggestions to make the text clearer and reader-friendly throughout, e.g. page 3, lines 89+92 and page 4, line 101.
18. **WBRT following WBRT:** We agree with the reviewer that the study of Scharp et al. may introduce an additional bias and, therefore, is not suitable. The study has been omitted [page 5, lines 149-153]. The list of references has been modified accordingly.
19. **WBRT following WBRT:** The part regarding the results for lung cancer patients has been re-written [page 6, lines 165-169].
20. **WBRT following WBRT:** It should be “absence;” the error has been corrected [page 6, line 172].
21. **WBRT following WBRT:** Ranges are now uniformly given as “xx (xx-xx)”.
22. **WBRT following WBRT:** “Repeat” has been removed and replaced by “second course of WBRT”.
23. **SF-SRS following WBRT:** The reference (former 16, now 24) was already mentioned in the previous version. To make it clearer for the readers, “suggested by the RTOG protocol 90-05” has been added [page 7, line 192].
24. **SF-SRS following WBRT:** “Very few studies” has been replaced by the corresponding number.
25. **SF-SRS following WBRT:** Ranges are now uniformly given as “xx (xx-xx)”.
26. **SF-SRS following WBRT:** Mentioning “5 months” twice is correct (4 patients) [page 7, lines 196-197].

27. **SRS/FSRT following SRS/FSRT:** We agree with the reviewer that both studies (former references 18 and 22) may introduce an additional bias and, therefore, have been omitted [page 7, lines 210-218 and page 8, lines 236-244. The list of references has been modified accordingly.
28. **SRS/FSRT following SRS/FSRT:** Sub-conclusions have been added to the Conclusions paragraph (please, see 3.).
29. **SRS/FSRT following SRS/FSRT:** Regarding RN, the way how RN was diagnosed is added to each study of this paragraph. In table 3, rates of overall RN and SRN are given. Due to limited space, asymptomatic RN is not explicitly listed but can easily be calculated by subtracting SRN from RN. The study of Moller et al. is not considered, since it reports on high grade gliomas, includes only 7 patients evaluable for late toxicity, and follow-up is only 10 weeks.
30. **SRS/FSRT following SRS/FSRT:** We have followed the reviewers' suggestions to make the text clearer and reader-friendly throughout. Ranges are now uniformly given as "xx (xx-xx)". "Several studies" has been replaced by the corresponding number. "Respectively" has been deleted several times.
31. The section "**Tolerance doses of reirradiation to the brain and potential risk factors for radiation necrosis**" has been moved to page 4, since it has a background character.
32. **Tolerance doses of reirradiation:** Meyer and Sminia investigated only SRN, not asymptomatic RN, which is now stated [page 4, line 116].
33. **Tolerance doses of reirradiation:** P-values have been added (page 4, lines 125-126).
34. **Conclusions:** The Conclusions paragraph has been rewritten [pages 10+11, lines 293-321].
35. **Tables:** The year of publication has been added.
36. **Tables:** Presentation of the dose-fractionation regimens (e.g. 30Gy/F) has been modified as suggested. Protons were not used. The interval between both RT courses is already stated in the text and has, therefore, not been added, in order to avoid additional overlaps (see reviewer's suggestion #2).
37. **Table 3:** 1-year local control has been added to the header.