

Peer Review File

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Reviewer A

Comment 1: The authors aim to provide a review on current radiation treatment techniques for both primary and secondary brain tumors. The review is structured and overall well-written.

As detailed as the presentations of glioma and meningioma trials are, are the BM statements lacking depth. Possibly, the article would have benefited from concentrating on either one of these two entities. A major revision is necessary before a publication can be considered.

Reply 1: Thank you for your comment. The authors agree and have limited the paper to a discussion regarding glioblastoma.

Comment 2: Brain metastases: While not giving wrong information, this section is missing the wider view that was suggested in the abstract. There is no mentioning of fractionated stereotactic RT (and their differential dose prescription and fractionation concepts) and intraoperative RT at all. The first is SOC for many European centers, the second is a new and innovative technique that may prove useful in certain situations. Please provide information and references for said techniques and discuss pros and cons for each of the methodologies including clinical outcome, but also patient-centered aspects.

Reply 2: The authors agree and are no longer discussing brain metastases in this manuscript.

GBM/Glioma

Comment 3: Line 147 please correct sentence, reads oddly.

Reply 3: This has been fixed.

The sentence initially read like this:

- This was a randomized trial testing different chemotherapy regimens, in which the first cohort of patients were treated to a dose of 60.2 Gy to the whole brain, though patients were subsequently treated to 43 Gy to the whole brain followed by a cone down to the tumor volume to 17.2 Gy.

The sentence now reads like this:

- However, two different radiation volumes were used, allowing a comparison between whole brain radiation and more focal radiation as adjuvant treatment for glioblastoma. In the first cohort of patients, treatment was delivered with a dose of 60.2 Gy to the whole brain, while in a second cohort, patients were treated initially to 43 Gy to the whole brain followed by a cone down to the tumor volume to 17.2 Gy.

Comment 4: Line 213 correct sentence

Reply 4: This sentence was described anaplastic glioma and is no longer in the manuscript since we are now focusing on glioblastoma.

Comment 5: Line 241 same

Reply 5: This sentence is no longer in the manuscript.

Comment 6: 325 missing word

Reply 6: This sentence is no longer in the manuscript

Comment 7: A table would probably increase readability and informativity of this review. I could imagine a table for every entity, with comparison of relevant endpoints in the various techniques and relevant trials.

Reply 7: The table has been created .

Comment 8: Fig. 1: Please provide details on dose prescription and organ at risk constraints for the hippocampus.

Reply 8: The details for the dose prescription have been added.

Comment 9: Fig. 2: Please provide details with a reference of how the dose prescription and contouring was performed.

Reply 9: This figure is no longer included as part of the manuscript.

Comment 10: Please provide a legend for the dose for both figures.

Reply 10: There is now a legend for the figures.

Comment 11: Overall, I'm struggling with the term personalized RT because it is not reflected by the content of the review. I would expect more in-depth analyses of individual prognostic or predictive factors that influence either the RT prescription or concomitant therapies. Please overthink this wording or add more of said content.

Reply 11: This is a fair comment. The authors have now included more in- depth analyses of individual prognostic factors such as MGMT methylation and therapeutic measures that may potentially overcome this.

Reviewer B

Comment: The authors should be congratulated on putting together an ambitious review on the personalized radiation for CNS cancers. However, this is clearly too big a topic to cover in one review, as a result, this discussion is superficial and main dated information.

Reply: This is a fair comment. The authors have made significant revisions to the manuscript and now limited the manuscript to management of glioblastoma.

Specific recommendations

Comment 1: Too broad a topic to cover, as a result there is no insightful discussion, may consider limiting to brain metastasis or GBM only.

Reply 1: This is a fair comment; as a result the authors have limited the discussion to management of glioblastoma.

Comment 2: The topic is "cancers", as a result, discussion on meningioma is not well suited.

Reply 2: This is a fair point. As a result the manuscript no longer discusses meningiomas and is now limited to glioblastoma.

Comment 3: The authors claim the "personalized radiation by optimizing patient selection molecular markers". Unfortunately, this is not achieved.

Reply 3: This is a fair critique of the initial version of the manuscript. The authors have now discussed personalized medicine for management of glioblastoma in great detail.

Comment 4: For the brain met discussion, the authors need to discuss radiation selection decision based on histology, molecular mutation (such as BRAF mutation in melanoma, EGFR, KRAS, ALK mutation in NSCLC, HER2 in breast etc.). The authors should have in depth discussion on these factors impact the personalized radiation selection.

Reply 4: This is a fair comment. The manuscript no longer discussed brain metastasis.

Comment 5: For GBM, this authors only discussed old evaluation of WBRT to partial brain, such approach is not "personalized". The authors should discuss the impact on EGFR, BRAF on selection of radiation, sequencing of radiation and systemic therapy, etc

Reply 5: This is a good point and the authors have now included a discussion of EGFR, sequencing of radiation therapy and systemic therapy included Temozolomide and interferon alpha, and tumor treating fields.