

Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: Repeatedly, the authors address “unfavorable tumor biology” in elderly patients, but there is essentially no data to support that. On the contrary, there are no molecular signatures specifically associated with old age. This must be restated (section 3). It does not make sense in 2022 to revoke the old stories on IDH mutations, because IDH mutations are no longer related to glioblastoma.

Reply 1: Thank you for your comment. Although we noted the recent WHO classification changes (specifically related to IDH mutations) to provide context, we have removed the discussion entirely. Instead, we have focused on analyses of genomic data that have identified distinct age-related genetic signatures and expression levels (e.g., VEGF).

Comment 2: There is a certain selection of which publications are discussed and which are not. For instance, one of the largest trials in the elderly, NOA-08, is not discussed (PMID: 22578793), although it even has a long-term follow-up analysis (PMID: 32064499), which challenges the role of radiotherapy in elderly patients with methylated tumors. A review article should be balanced and also discuss that may not be so welcome.

Reply 2: Thank you for highlighting these relevant publications. A discussion has been added in Section 3.3.

Comment 3: The discussion on bevacizumab has various aspects that are not directly related to the elderly, but the (probably) only randomized trial in the elderly is not discussed (PMID: 29648580).

Reply 3: Thank you for highlighting this study. A discussion in Section 3.3 has been added.

Comment 4: Section 6, ref. 83, non-randomized trials cannot show that a treatment is effective. This is why we randomize.

Reply 4: We appreciate your comment. The discussion has been edited appropriately.

Comment 5: Of course, the registration trial for TMZ is important, but there is no need to cite it 3 times. Ref. 2, 17, 49 are the same.

Reply 5: Thank you so much for bringing this to our attention. The references have been updated and the duplicates have been deleted.

Reviewer B

Comment 1: We suggest authors add this article’s key findings and conclusions to the abstract. For example, Hypofractionated RT has emerged as a shortened alternative and retrospective studies have suggested survival outcomes are similar for elderly patients with GBM. Prospective studies comparing hypofractionation with conventional treatment regimens are warranted. In addition to evaluating survival outcomes, HRQOL end points should be incorporated into future studies.

Reply 1: We appreciate your suggestion. We have modified the abstract accordingly.

Comment 2: We suggest the authors add 3~5 keywords below the abstract.

Reply 2: Added keywords below the abstract.

Comment 3: We suggest authors add a “Methods” paragraph for describing the literature search process. (eg, years considered, language, publication status, study design, and databases of coverage). Additional inclusion and exclusion criteria for the literature are also recommended.

Reply 3: This was designed as a review article, and pertinent articles for the discussed by the lead authors, and additional suggestions for inclusion of references were suggested by co-authors.

Comment 4: TMZ first appeared in the Radiation Therapy section, please give the full name.

Reply 4: Thank you for pointing this out – the full name has been added.

Comment 5: The following facts need some reference to support them:

(1)“Currently, the literature lacks a clear definition of what is defined as “elderly,” where some studies consider patients that are ≥ 65 yo while others choose 70 yo as the cut-off.”

(2)“The current standard of care for GBM is 60 Gy in 30 fractions for patients < 70 yo, but a hypofractionated regimen (e.g., 40 Gy in 15 fractions) for elderly or frail patients.”

(3)Additionally, the updated analysis demonstrated all prognostic subgroups had improved OS with the addition of TMZ. Notably, a survival benefit was reported in patients 60–70 yo.

Reply 5: Thank you for highlighting these points – they have been addressed.

Comment 6: Please change the format of the citations to the literature in the manuscript. The format refers to the Author Instructions: <https://cco.amegroups.com/pages/view/guidelines-for-authors#content-3-8>.

Reply 6: The references have been changed to Vancouver per manuscript guidelines.