Peer Review File

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Reviewer A

We are pleased that the Reviewer views our article as "a nice proof of concept" and is "happy to report that it has the potential to be one of the first of its kind to be published". Contrary to what the Reviewer states (that "partial hippocampal avoidance radiotherapy is done…in most institutions already"), to our knowledge, this is in fact the first report of partial hippocampal sparing radiotherapy.

Comment 1: Re Line 118: "..does not elaborate on whether the patient died soon thereafter, was lost to follow-up, or not enough time has elapsed to collect such data. I would accept this paper if these data were available".

Reply 1: These data are available: not enough time has elapsed to collect such data. Also see Reply 5 below.

Changes in the text: Nil.

Regarding Reviewer A's recommendations:

Comment 2: "Cognitive baseline".

Reply 2: Unfortunately, baseline cognitive function was not determined and hence cannot be provided retrospectively.

Changes in the text: Nil.

Comment 3: Line 95: "What was the timing of…".

Reply 3: Radiation was 9 weeks after the third cycle of pembrolizumab.

Changes in the text: (Case Presentation, second last paragraph, first sentence): "…and 9 weeks after the third cycle of pembrolizumab, ..".

Comment 4: Line 104-111: Re memantine.

Reply 4: This is now provided.

Changes in the text: (Case Presentation, last sentence before dosimetry). “The patient was not commenced on memantine,…”.

Comment 5: Line 111: “Please provide information on clinical course, to include but not limited to cognitive functions..”. “If available, also include quality of life and progression/survival outcomes”.

Reply 5: This is now provided:

Changes in the text: (Case Presentation, final sentence). “The patient remains fit and well with no gross memory or cognition issues, 14 days after completing partial hippocampal sparing whole brain radiotherapy. No formal quality of life studies were performed”.

Comment 6: Re request to cite CC001 study.

Reply 6: The NRG CC001 study has been cited in the Discussion:

Changes in the text: Discussion, second last paragraph.

Comment 7: Re request to cite CCTG CE.7 study.

Reply 7: The CCTG CE.7 study has been cited in the Discussion:

Changes in the text: Discussion, second last paragraph.

Reviewer B

Comment 1: “The dose of the second radiation treatment is not marked”.

Reply 1: We are unsure what the Reviewer means here. The patient had stereotactic radiation to frontal and posterior fossa metastases prior to partial hippocampal avoidance radiotherapy, as detailed in the report.

Comment 2: “..in Figure 2, the meaning of the colour (radiation dose) is not shown”.

Reply 2: We have now added a dose-colour scale on the right hand side of Figure 2, to clearly indicate the range of doses received in the target and avoidance areas.

Changes in the text: Figure 2 is changed as mentioned above and we have also, as requested, included dosimetry in the Abstract: “For the right hippocampal avoidance structure the D100% was 10Gy, maximum 18.4Gy, while for the left hippocampal avoidance structure, the D100% was 8.45Gy, maximum 18.1Gy. The PTV received 28.9Gy, with <2% receiving >31Gy. We prioritised minimising hot spots in the PTV because of the patient’s previous SRS treatment”.

Comment 3: “There is no mention of whether the dose at the first radiation therapy was reduced”.

Reply 3: We are unsure what the Reviewer means here. We hope our foregoing responses satisfy the Reviewer’s comments about sequencing of radiation and radiation dosimetry and would be pleased to provide any further requested information.

Comment 4: Re Line 100.

Reply 4: We are unsure what the Reviewer means here. Our calculations appear correct in the text. We are unsure what the “>” symbol refers to, but would be pleased to provide any further requested information.

Comment 5: Re Line 107.

Reply 5: The patient had bilateral hippocampal metastases, both in the anterior hippocampi, as shown in Figures 1 and 2 and as addressed in the text.

Reviewer C

Comment 1: “Would be good to know what were the dosimetric targets met”.

Reply 1: We have now supplied further dosimetry, as follows:

Changes in the text: The following has been added to the end of the Case Presentation and the end of the abstract: “For the right hippocampal avoidance structure (blue-green in Figure 2), the D100% was 10Gy, maximum 18.4Gy, while for the left hippocampal avoidance structure (blue-green in Figure 2), the D100% was 8.45Gy, maximum 18.1Gy. The PTV received 28.9Gy, with <2% receiving >31Gy. We prioritised minimising hot spots in the PTV because of the

patient's previous SRS treatment".

Reviewer D

We appreciate that the Reviewer feels our report is "Very interesting" and "useful".

Comment 1: "For the discussion I suggest to add one article explaining that anterior and posterior parts of the hippocampus have likely different function...".

Response 1: This has been added as requested.

Changes in text: The following is added to the second last paragraph of the Discussion: Anterior and posterior parts of the hippocampus have likely different functions: the posterior hippocampus has been ascribed functions of spatial navigation and memory, while the anterior hippocampus mediates anxiety-associated behaviour, although this may be somewhat of an oversimplification (new reference 15, Strange et al). The location of hippocampal metastases and radiation doses across the hippocampi may have implications for the different hippocampal functions.

Comment 2: "...and the article of Le Fevre C et al…".

Response 2: This article has been added.

Changes in text: The following is added to the second last paragraph of the Discussion: Where possible, minimising irradiation to even one hippocampus might prove beneficial. Post-irradiation hippocampal atrophy is associated with degraded neurological function, but after low radiation doses a compensatory hippocampal increase in volume has been observed (new reference 16, Le Fevre et al); these authors suggested that delivering the lowest dose to one

hippocampus might help preserve cognition.

Comment 3: “Can you give the doses…”.

Response 3: This has already been done in response to the other Reviewers. The information has been added to the Abstract and the Case Presentation, third last paragraph.

Changes in text: Nil from previous version.

Comment 4: “Can you discuss the option of WBRT + HA and stereotactic irradiation in the both hippocampi region”.

Response 4: This has been done.

Changes in text: The following is added to the second last paragraph of the Discussion: In the case described here, the hippocampal metastases received the whole brain dose. Conceivably, dose-escalating these metastases using SRS may have further improved local control and outcome.

Comment 5: “If you can, add a picture of DVH of hippocampi”.

Response 5: Picture of DVH of hippocampi is not available.

Changes in text: Nil.

New references

15. Strange BA, Witter MP, Lein ES, Moser EI. Functional organization of the hippocampal longitudinal axis. Nat Rev Neurosci. 2014;15:655-69.

16. Le Fèvre C, Cheng X, Loit MP et al. Role of hippocampal location and radiation dose in glioblastoma patients with hippocampal atrophy. Radiat Oncol. 2021;16:112-16.