Peer Review File

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Reviewer A

This article could be interesting, but it needs significant improvements. The authors should address the points listed below and reorganize the different parts of the article (see comments). Once these points are corrected, the manuscript could be suitable for publication.

Thank you for taking the time to review our article and for providing thoughtful feedback and suggestions.

Authors should number the page to facilitate the reviewer's report:

Paragraph: "To achieve the above goals, this review report is organized into sections dedicated to covering important background, history, available treatment techniques, and current recommendations. Section 2 provides an educational background on the hippocampus, its response to radiation, and widely used dose constraints. Section 3 describes the available hippocampal-sparing RT techniques, common treatment planning methods, and dosimetric parameters. Section 4 addresses other steps in the workflow, including patient simulation, quality assurance, 59 and treatment delivery for hippocampal-sparing RT. Section 5 summarizes the current state-of-the-art techniques with recommendations from the authors. »
Comment: This section is written in a scholarly style, which is not very scientific, and should be made more fluid for the reader

Reply: Thank you for the comment. We decided to remove that section entirely to improve the fluidity of the paper.

Line 79-80: "Preclinical studies have demonstrated that radiation doses as low as 20 cGy
can result in histologic changes in hippocampi neuronal cells, which indicates that the hippocampi are particularly sensitive to radiation"
Comment: This data remains disputable, as this difference of 20 cGy could only be observed when using a different planning system.

Reply: We agree with this comment and have removed this sentence from the manuscript.

Line 89:
Comment: Change "Fevre" by "Le Fevre"\

Reply: Done (line 97).

Line 110:
Comment: The authors can refer to the article on the French recommendation "RECORAD," which

proposes certain dose constraints based on the literature (DOI: 10.1016/j.canrad.2021.11.001)

Reply: Thank you for the reference. It has been added to the dose constraint discussion (lines 126-128)

The following text was added:
"Similar constraints based on the results of the RTOG 0933 study as well as Birer et al (24) (discussed in Section 4.2.2) are recommended in French clinical practice guidelines (27)."

Comment: Before addressing the section on dosage, we recommend that the authors include a segment discussing the delineation of the hippocampus. This should cover topics such as the use of planning target volumes (PTVs) or margins to effectively shield them, as well as the benefits of distinguishing between the right and left hippocampus. In a similar vein, the authors could also explore the concept of automatic delineation, as this method represents the future of current delineation practices.

Reply: Thank you for your comment, we agree that discussing the delineation of the hippocampus would be useful for readers. This has been added (lines 75-90).

The following text was added:
"The hippocampus is best delineated on a T1-weighted MRI axial sequence. An MRI of 1.25 mm slice thickness is preferred to contour the hippocampus accurately. To begin contouring the hippocampus, locate the caudal most extent of the temporal horn and contour the gray matter inside the curve of the temporal horn. Continue contouring postero-cranially until the top-most extent of the hippocampus which stops at the lateral edges of the quadrigeminal cisterns. At this level, the crux of the fornix can be visualized anteriorly and the splenium of the corpus callosum emerges posteriorly. Hippocampal avoidance zones are generated using a 5 mm volumetric expansion on the hippocampus contours and the PTV is generated by subtracting the hippocampal avoidance region from the existing brain contour (12, 13). The increasing availability of high-quality automated contouring tools also has the potential to increase the efficiency and reproducibility of hippocampal contouring.

Additionally, it is important to distinguish between left and right hippocampus and to document dose to each hippocampus respectively. Studies of temporal lobectomy patients suggest that the left hippocampus is crucial for verbal memory whereas the right hippocampus correlates with visuo-spatial memory (14). Correspondingly, radiation injury to the left, usually dominant, hippocampus may have increased effects on verbal memory formation (15)."

Comment: Part 2: The authors should discuss the dose in terms of both total dose and dose distribution for the right and left hippocampus. They should debate whether it is relevant to prioritize shielding one hippocampus over the other. Additionally, they should consider the merits of distributing the dose equally between both hippocampi versus favoring one side.

Reply: Thank you for the comment. We agree that a discussion of unilateral hippocampal dose

constraints is important and has been added to this section (lines 118-125).

The following text has been added:

"In addition to these bilateral constraints, studies found that dosimetric parameters (e.g., Dmean, Dmin) specific to the left sided hippocampus exerted an influence on immediate recall of verbal memory (15, 26). Tsai et al. reported that Dmax ≥ 12.4 Gyα/β=2 to the left hippocampus was significantly associated with functional preservation in preservative errors of Wisconsin Card Sorting test (15). Le Fevre et al. stated that, if Dmean to the left hippocampus is increased by 1 Gy, there may be four-fold increase in the risk of neurocognitive decline in immediate recall of verbal memory (18). These studies suggest that in cases where bilateral hippocampal sparing may not be feasible, sparing of the left hippocampus should be prioritized."

Paragraph 3.4 Head-Tilting Baseplate
Comment: This paragraph should be placed before the discussions on dose and planning system calculations. In this section, the authors can explore the utilization of more stringent plastic immobilization masks

Reply: This paragraph has been moved to the CT simulation section (lines 144-149). We have also added a few references comparing mask and frame-based immobilization systems (lines 155-157).

We moved the head-tilting baseplate section and added the following sentence:
"These invasive head frames have been mostly superseded by the frameless approach discussed earlier for LINAC-based SRS and some GK systems, as studies have not shown any negative impacts on patient outcomes with this less invasive, frameless fixation method (36-38)."

Line 197-199: "The lens dose was also significantly lower with the tilted plans, and treatment delivery times were reduced by 8-18%. Similar reductions in hippocampus and lens dose, as well as improved target dose conformity, can be seen with VMAT HA-WBRT planning using a 40° tilted baseplate"
Comment: This sentence falls outside the scope of the manuscript and should be removed.

Reply: The references to lens dose were removed from this section. Another reference to reduced optical dose was removed as well.

Comment: The authors did not address the potential risk of metastasis localization in the hippocampus based on the number of metastases. However, it's important to note that HA-WBRT is primarily employed when the number of metastases is significant. These two aspects stand in contrast, and the authors should provide their own insights and reflections regarding this issue.

Reply: This topic is discussed in Section 6 (Study Limitations). As this is intended to be more of a practical overview of hippocampal-sparing RT workflows, rather than an in-depth analysis of clinical outcomes, we feel that further discussion of this would be outside the scope of the article. However, we did add several references to studies directly investigating this topic (lines 390-391). We have also updated the title of the article to emphasize that it's a practical guide for clinical

implementation, rather than an analysis of clinical outcomes.
The following sentence was added: "Several studies have estimated the potential risks of underdosing metastases to achieve hippocampal sparing (43, 73, 74)."

Comment: Line 269-272: This portion should be included within the delineation section and could serve as the foundation for a discussion on the relevance of hippocampal protection in light of the potential risks such as sub-dosage or protection of metastases…

Reply: Please see previous reply.

Part 5 CT simulation…
Comment: The section discussing the CT scan should be positioned earlier in the manuscript, connecting it to the delineation guidelines, immobilization techniques, and head positioning

Reply: This section has been moved earlier in the manuscript (Section 3, lines 131-157).

5.2 Dosimetric QA
This section contains general statements without specific data regarding hippocampal irradiation. It should either be deleted or entirely reworked.

Reply: This section has been deleted.

Table 1 : The title and information provided are insufficient. It's crucial to clearly define the prescription. Additionally, discussing the dose in relation to the optic nerves and chiasm is beyond the scope of the manuscript and should be removed

Reply: We have updated the table caption to "Target and hippocampus dose specifications for the RTOG 0933 Phase II Trial of Hippocampal Avoidance during Whole Brain Radiotherapy for Brain Metastases", added the prescription constraints, and removed the optic nerves/chiasm constraints.

Overall, this article is a basic review. The authors have not provided a decision tree for selecting when to shield the hippocampus. They also haven't discussed the necessary margin based on the technique employed or delved into the relevance of dose in relation to fractionation. To ensure definitive publication, this manuscript needs to be more informative and pragmatic for readers.
Moreover, the various sections should follow the patient's journey through a radiotherapy department, including the diagnosis (number of metastases), clinical considerations (cognitive tests before HA-WBRT), delineation using CT scans, specific positioning and immobilization, dose distribution, and so forth. This would make the manuscript more comprehensive and practical for readers.

Reply: Thank you for your comments. We agree that a discussion of hippocampal delineation would be beneficial for the readers and has been added to Section 2.1 (lines 75-90). We have also rearranged the sections to mirror the chronological order of a patient's treatment process. However, this article is intended to be an overview of the current treatment techniques and planning

constraints for hippocampal sparing RT (aimed toward physicists and dosimetrists as the target audience), rather than a decision-making guide for physicians. In other words, this article is meant to guide readers on *how* to spare the hippocampus, not *when* to spare it. Although an article delving into this complex decision-making process and clinical implications would certainly be interesting and useful, we feel that including this in the current article would double the scope of the subject matter and result in far too lengthy of a review. We have updated the introduction to clarify the intended audience of the article (lines 53-55).

The following sentence was added: "Thus, the primary target audience of this study is physicists and dosimetrists, while also considering the educational demands of new physicians and radiation oncology residents."

Reviewer B

I found this paper very interesting and comprehensive. The references are recent and various, tables are clear and the figure is relevant.

Thank you for taking the time to review our article and for providing thoughtful feedback and suggestions.

I suggest, if possible, you add a little but clear table with advantages and disadvantages in hippocampal sparing about each technique you have described.

Reply: Thank you for your suggestion. The authors wholeheartedly agree that such a table would be beneficial for the review paper and have tried very hard to create one. However, due to the wide range of published results and differences in clinical and technical specifications (prescription dose, fractionation, beam angles, as well as target size, number, and location for SRS) between different studies, we found it extremely difficult to compare these techniques concisely without over-simplifying and misrepresenting the results. This is why we chose to describe these differences in findings instead and only include tables comparing studies using the same technique (e.g., Tomotherapy, GammaKnife).

I recommend that you include the specific reference in line 130 and also in line 131.

Reply: These references have been added (lines 176-177).

Furthermore, it is recommended that the font of the text in table 3 is conformed to the rest of the text.

Reply: The text has been reformatted to match the rest of the article.