Peer Review File
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Reviewer A

1. Line 136: is there a reference to SSV? Has that be done previously in other studies or is this the first study to examine this approach? As seen in Ref 24/37. scalp sparing is not new. Please clarify that and state what is new within this study!

   Reply 1: Point well taken. Added a reference to a trial evaluating SSV (page 8, lines 149-150) and commented on the need for a direct dosimetric comparison between SSV and non-SSV techniques (page 8, lines 150-152)

   Changes in the text: *A single arm pilot study (clinicaltrials.gov Identifier: NCT03477110) investigated the safety of delivering SSV in conjunction with TTFields and reported favorable findings (14). To our knowledge, a head-to-head dosimetric comparison between SSV and traditional non-SSV approaches has not been reported in the literature.*

2. Line 146: Please add the number of Patients already here, not only in the results part.

   Reply 2: Added (page 9, line 173)

   Changes in the text: *We retrospectively queried patient databases from TJUH and identified 19 patients with newly diagnosed GBMs.*

3. Line 164 - 182: Why these two guidelines? As I understand for some patients EORTC and for other RTOG was used. Please state why and add a number how many patients followed which protocol.

   Reply 3: Added rationale for choosing the EORTC and RTOG guidelines and treating them as equivalent for the purposes of treatment delivery (page 11, lines 211-213). Number of patients treated with EORTC guidelines (page 14, line 292) and RTOG guidelines (page 14, line 303) are mentioned in our paper.

   Changes in the text: *A prospective randomized trial revealed no difference in outcomes in patients treated with either the RTOG volumes or the smaller EORTC volumes. Hence, treating physicians were allowed to use the guideline of their choice.*

4. Line 190: please add a note, how the original plans were done. Probably not all with the same TPS-Version over the time of 2015-2018? Or did you recalculate/reoptimise the original plans with the current TPS-version?

Reply 4: Added clarification on how the original plans were done and which TPV version was used for plans and replans (page 11, lines 221-225).

Changes in the text: *Initial treatment plans for all patients from 2015 through 2018 were planned in Eclipse version 11.0. Replanning with scalp sparing constraints for this study were done in Eclipse version 15.6.*

5. Line 198: I think for the original plans the same constraints were used? How was the normalization of the PTV dose made? Please state that!

Reply 5: Clarified which constraints were used for the plans and replans (page 12, lines 237-238), and how plans and replans were normalized (page 11, lines 233-236)

Changes in the text:

TJUH institutional dose constraints, derived from various protocols (28), were used for the initial plans and replans:

Plans and replans were optimized to ensure that 95% of the PTV was covered by 100% of the dose. If the treatment consisted of initial and sequential boosts, each plan was normalized separately to cover 95% of the PTV with 100% of the dose, and then combined into a composite plan.

6. Line 221: as mentioned before: I'd rather see these numbers of patients in the method part than in the results part.

Reply 6: Included number of patients in both the methods (page 9, lines 172-173) and results (page 13, line 262). For changes in the text, see response to comment #2.

7. Figure 3 and 4: Instead of one example, I'd rather see a mean DVH over all patients,

Reply 7: Both figures 3 and 4 have been updated to depict both individual DVHs and mean DVHs over all patients.

Changes in the text:

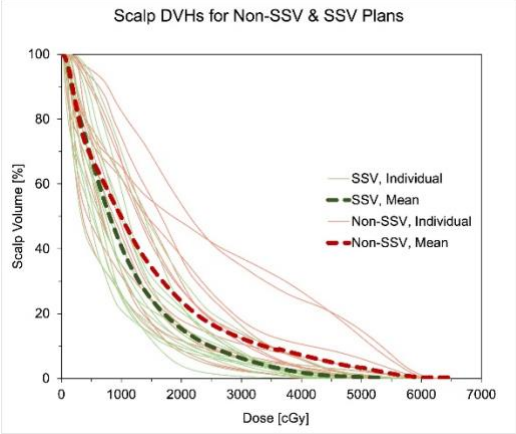

Figure 3: DVHs showing a reduction in scalp dose across all patients when planned using an SSV (green) versus a non-SSV approach (red). The thinner solid red lines represent individual non-SSV scalp DVHs, while the thicker dashed red line depicts the mean non-SSV scalp DVH. The thinner solid green lines represent individual SSV scalp DVHs and the thicker dashed green line depicts the mean SSV scalp DVH.

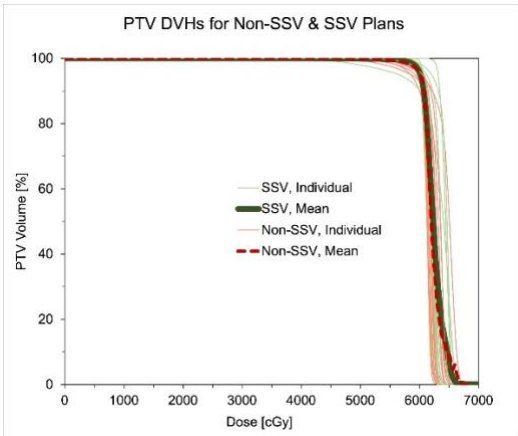

Figure 4: DVHs showing no significant difference in PTV doses across all patients when planned with either an SSV (green) or a non-SSV approach (red). The thinner solid red lines represent individual non-SSV PTV DVHs, while the thicker dashed red line depicts the mean non-SSV PTV DVH for all patients. The thinner solid green lines represent individual SSV PTV DVHs and the thicker solid green line depicts the mean SSV PTV DVH for all patients.

8. Figure 5: I don't think there is need to show this, as it is already mentioned in table 1.

Reply 5: Point well taken. Figure 5 has been eliminated.

Reviewer B

1. First, the title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study.

Reply 1: *Title has been changed (page 1, lines 2-3)*

Changes in the text: *Efficacy of Scalp-Sparing VMAT Approach in Reducing Scalp Radiation Dose for Patients with Glioblastoma: A Retrospective Cohort Study*

2. Second, the abstract needs some revisions. The background did not explain why the SSV approach is effective for reducing the scalp radiation dose and what the knowledge gap is in relation to the effectiveness of the SSV approach. The methods need to describe the inclusion of subjects and how the scalp radiation doses were compared. The results need to briefly summarize the clinical characteristics of the 19 patients. The conclusion needs comments for the clinical implications of the findings.

Reply 2: Abstract updated for improved flow and conciseness (pages 3-4, lines 46-75). Added an explicit statement on why SSV reduces scalp radiation (page 8, lines 136-138). Added a sentence on the knowledge gap (page 8, lines 150-152). Expanded section on patient selection (page 9, lines 171-180), and how radiation doses were compared (page 12, lines 244-250). Summarized clinical characteristics of patients within the text (page 13, lines 262-270) and added a new table (table # 1) to do the same. The conclusion mentions the clinical implications of the findings (page 18, lines 393-394).

Changes in the text:

A novel way to mitigate such toxicities may be to reduce scalp radiation by contouring the scalp as an organ at risk (OAR) and using scalp dose constraints during treatment planning. This techniques is termed scalp-sparing volumetric modulated radiation therapy (SSV) (21).

To our knowledge, a head-to-head dosimetric comparison between SSV and traditional non-SSV approaches has not been reported in the literature.

19 patients treated at TJUH between 2015 and 2018 with SoC including non-SSV radiation plans were selected for our study. Table 1 summarizes baseline patient characteristics. 84% were male while 16% were female. Median age was 65 years (range: 33-78). 37% underwent a gross total resection while 63% received a subtotal resection. 54% were O6-Methylguanine-DNA Methyltransferase (MGMT) methylated and 46% were unmethylated. Isocitrate dehydrogenase (IDH) was mutated in 21% of the patients while 79% were IDH wild type. 47% of the patients received 60 Gy in 30 fractions in a single course, while 53% received split course radiation, with 46 Gy in 23 fractions followed by 14 Gy in 7 fractions delivered to initial and cone-down volumes respectively.

	Baseline Characteristics	
1	***Age***	
	Median (range)	*65 years (33-78)*
2	***Gender***	
	Male	*84%*
	Female	*16%*

3	***Resection***	
	GTR	*37%*
	STR	*63%*
4	***MGMT Status***	
	Methylated	*54%*
	Unmethylated	*46%*
5	***IDH Status***	
	Mutated	*21%*
	Wild type	*79%*
6	***Scalp Volume***	
	Median (range)	*423 cm^3 (379-468)*
7	***Treatment Protocol***	
	EORTC	*47%*
	RTOG/NRG	*53%*

Table 1: *Relevant baseline characteristics of patients used for our study. O6-Methylguanine-DNA Methyltransferase, MGMT; Isocitrate dehydrogenase, IDH; European Organization for Research and Treatment EORTC; Radiation Therapy Oncology Group, RTOG/NRG.*

This may lead to reduced acute and late radiation toxicity to the scalp.

3. Third, the introduction of the main text needs to review available treatments for harmful effects of TTFields in scalp, how the SSV was developed and why it is effective for reducing the radiation dose and meanwhile did not reduce the treatment efficacy for GBM. The authors need to review the knowledge gap on the efficacy of SSV.

Reply 3: Added section on the treatments for harmful effects of TTFields (pages 7-8; lines 126-145). Discussed why SSV reduces scalp radiation (page 8, lines 136-138) and added a sentence on the knowledge gap (page 8, lines 150-152) and a reference to a clinical trial demonstrating the efficacy of SSV (page 8, lines 149-150). Please note that text changes for most of these comments have been provided in response to previous comments.

Changes in the text:

1.2.1 Dermatologic Toxicity

Dermatologic toxicity is usually managed either prophylactically or with treatment interventions. Prophylactic measures include educating patients on proper scalp care, hygienic ways to apply and remove the transducer arrays, and to periodically shift the arrays to different parts of the scalp. Treatment interventions can consist of topical corticosteroids if patients develop scalp dermatitis or topical antibiotics if they show signs of scalp infection. For more severe skin side effects, small treatment interruptions can also be considered to give the skin a chance to heal (9,20).

A novel way to mitigate such toxicities may be to reduce scalp radiation by contouring the scalp as an organ at risk (OAR) and using scalp dose constraints during treatment planning. This techniques is termed scalp-sparing volumetric modulated radiation therapy (SSV) (21).

Such scalp avoidance, however, should not trade decreased scalp toxicity for optimal clinical outcomes or expose critical brain structures to unjustifiable risk. These outcomes depend on many factors, including the delivery of a sufficiently lethal radiation dose to the tumor as evidenced by the planning treatment volume (PTV) dose distribution (22). Harm to critical brain structures, including the brainstem, optic nerves, and optic chiasm, is minimized by respecting their radiation tolerances (23).

4. Fourth, in the methodology of the main text, please describe the clinical research design, the sample size estimation, and assessment of clinical factors. The changes in radiation dose is only a short-term outcome, the authors need to further explain why they did not assess the harmful effects on scalp, the prognosis of GBD patients, and the patient-report outcomes such as quality of life and subjective satisfaction. Particularly, patient-report outcomes should also be measured together with changes in radiation dose. In statistics, please describe the statistical software, details of the before-after comparisons by using t test. Please ensure $P<0.05$ is two-sided.

Reply 4: Described the research design (page 9, lines 166) and the clinical features of the patients (page 12, lines 262-270). Assessment of the harmful effects, prognosis, and quality of life is beyond the scope of this paper, but we included reference to research that has done (references 25, 38) so as well as an ongoing trial (page 8, lines 158-159) evaluating just this. Updated statistical analysis section (page 12, lines 252-257) in accordance with the request). Please note that text changes for most of these comments have been provided in response to previous comments.

Changes in the text: *Two-sided student's T-test was used to compare the difference in doses to the parameters listed above between non-SSV and SSV plans. Statistical significance was defined at the 5% level ($p < 0.05$). The analysis was performed using Prism version 10.0.40 for Mac (GraphPad Software Inc, La Jolla, California, USA).*