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ORIGINAL ARTICLE

The risk of radiation-induced neurocognitive impairment and the impact of sparing the hippocampus during pediatric proton cranial irradiation

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ABSTRACT

Background and purpose: Hippocampus is a central component for neurocognitive function and memory. We investigated the predicted risk of neurocognitive impairment of craniospinal irradiation (CSI) and the deliverability and effects of hippocampal sparing. The risk estimates were derived from published NTCP models. Specifically, we leveraged the estimated benefit of reduced neurocognitive impairment with the risk of reduced tumor control.

Material and methods: For this dose planning study, a total of 504 hippocampal sparing intensity modulated proton therapy (HS-IMPT) plans were generated for 24 pediatric patients whom had previously received CSI. Plans were evaluated with respect to target coverage and homogeneity index to target volumes, maximum and mean dose to OARs. Paired t-tests were used to compare hippocampal mean doses and normal tissue complication probability estimates.

Results: The median mean dose to the hippocampus could be reduced from 31.3 Gy_{RBE} to 7.3 Gy_{RBE} ($p < .001$), though 20% of these plans were not considered clinically acceptable as they failed one or more acceptance criterion. Reducing the median mean hippocampus dose to 10.6 Gy_{RBE} was possible with all plans considered as clinically acceptable treatment plans. By sparing the hippocampus to the lowest dose level, the risk estimation of neurocognitive impairment could be reduced from 89.6%, 62.1% and 51.1% to 41.0% ($p < .001$), 20.1% ($p < .001$) and 29.9% ($p < .001$) for task efficiency, organization and memory, respectively. Estimated tumor control probability was not adversely affected by HS-IMPT, ranging from 78.5 to 80.5% for all plans.

Conclusions: We present estimates of potential clinical benefit in terms of neurocognitive impairment and demonstrate the possibility of considerably reducing neurocognitive adverse effects, minimally compromising target coverage locally using HS-IMPT.

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Neurocognitive impairment; normal tissue complication probability; tumor control probability; craniospinal irradiation; hippocampal avoidance; pediatric hippocampus

Introduction

Primary central nervous system (CNS) tumors are the second most common type of cancer in children [1]. The most frequent malignant CNS tumor in children is medulloblastoma. In children above three to five years of age, most medulloblastomas are treated with a combination of surgery, chemotherapy and craniospinal irradiation (CSI). The treatment depends on age and tumor-related risk factors, such as residual tumor volume, M-stage, histology, molecular subgroups including various genetic mutations [2]. Treatment has become more stratified over the last decade, however, with only minor changes and no new therapeutic modalities. Most long-term survivors of malignant pediatric CNS tumors treated with CSI have significant neurocognitive late effects, and patients irradiated at a younger age tend to have worse outcomes [3,4]. Recently, in order to reduce the common, treatment related, neurocognitive side effects, several studies have investigated hippocampal-sparing (HS) irradiation modalities [5–10].

Long term childhood cancer survivors constitute a rapidly growing group of young adults [11]. Since the frequency and severity of late side effects, such as cognitive dysfunction, hearing loss, endocrine deficiencies, radio-necrosis and secondary tumors generally increase with time, they are especially debilitating for pediatric cancer survivors as they mature into adulthood [12–15]. Certain parts of the brain (e.g., the hippocampus) are believed to be more sensitive to radiation [8,16,17] and neurogenesis occurs within the

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dentate gyrus of the hippocampus [18]. Radiation further damages hippocampal stem cell differentiation [19] and it is associated with reduced memory preservation. Consequently, avoiding high-dose irradiation of the hippocampus should be a priority [7,20].

No clinical trials of hippocampal sparing in children with CNS tumors have yet been published. The most compelling evidence to date comes from the randomized phase III trial NRG Oncology CC001 that showed significantly lower risk of cognitive failure in adults with brain metastases in the arm receiving hippocampal-sparing whole-brain irradiation [21].

We previously studied the feasibility of reducing the dose to the hippocampi and found IMPT to be remarkably promising [5]. However, the study was based on generic proton data and without consideration to clinically accepted proton therapy protocol for planning and delivery.

In the current work we studied the risk of neurocognitive impairment from intensity-modulated proton therapy (IMPT) craniospinal treatment. Specifically, we investigated the possibility of lowering the hippocampal dose significantly without compromising dose to the whole-brain target, regarding clinically acceptable (defined as plans acceptable for treatment at our institution) objectives. The deliverability of the HS IMPT plans was evaluated based on different plan uncertainty and robustness criteria.

Materials and methods

Patients and delineation

We identified 24 eligible patients treated at our institution between 2005 and 2015. The patients in this study had all undergone photon CSI treatment. All patients were re-planned and a total of 504 HS IMPT plans were generated for the 24 patients (Table 1), with 432 plans evaluating different levels of HS and robustness for the elective whole-brain treatment and 72 plans evaluating the dose contribution from the boost treatment. The elective target volume was defined as the whole brain (clinical target volume, CTV) denoted as $CTV_{elective}$, disregarding the spinal part of the target in this study. The hippocampi and the postoperative resection volume, including residual tumor if any, (denoted GTV) were contoured on MRI co-registered with CT images (Figure 1) by an experienced senior radiologist using the contouring protocol from Radiation Therapy Oncology Group 0933. The boost target volume (denoted CTV_{boost}) was defined as the GTV plus a 5 mm margin. Two patients treated in earlier years had no GTV contoured; their boost volumes consisted of the entire posterior fossa.

Table 1. Characteristics of the 24 pediatric patients included in the study.

	n	%
Sex		
Male	12	50
Female	12	50
	Median	Range
Age (y)	9	4–18
Distance[a] (cm)		
CTV - Hippocampus	1.4	1.0–4.3
Target and OAR volumes (cm^3)		
$CTV_{elective}$	1427.2	1137.7–1770.7
CTV_{boost}	44.7	11.5–228.3
Hippocampus	3.4	0.8–10.6

[a]Defined as the distance between the center of the hippocampus to the closest point of CTV_{boost}.

Treatment planning

The total prescribed dose was 54 Gy_{RBE} in 1.8 Gy_{RBE} per fraction, 23.4 Gy_{RBE} from the elective whole-brain plan and 30.6 Gy_{RBE} from the boost plan. All plans were normalized so the mean target volume dose was 100% of the prescribed dose and robustly optimized using 2%/2 mm and 3.5%/3 mm uncertainty criteria in all directions. Treatment plans were generated using the Eclipse™ treatment planning system v.13.7 (Varian medical systems, Palo Alto, CA, USA). Robust optimization was carried out on both $CTV_{elective}$ and hippocampi using nonlinear universal proton optimizer (NUPO) v.13.7.15. Three incident fields (90°, 180° and 270° with the patients positioned head first supine) with field specific targets, with no range shifter, 3 mm spot size and multi-field optimization were used. For each plan, target, normal tissue and organs-at-risk (OARs, with the exception of the hippocampus for different dose levels) objectives were kept constant to minimize planner bias. Multiple plans were generated for each hippocampal dose before choosing the superior plan in terms of hippocampal dose and target coverage. Minimum dose or coverage of the target area has been set as a constraint to exclude treatment planning system specific effects and there was no difference in plan quality between using and not using a range shifter despite the superficial target.

The hippocampal dose objectives were defined in relation to five different levels of avoidance; 5, 7, 9 (Figure 1), 12 and 15 Gy_{RBE} with the intent of studying how the target coverage and plan quality was affected by the different levels of hippocampal sparing. These levels were chosen as representative levels of what can be accomplished using higher or lower priorities on target and hippocampus as well as other OARs. Treatment plans with no priority or dose restriction to the hippocampus (denoted standard CSI plan), were generated for comparison.

Analysis and evaluation metrics

Treatment plans were exported to the Computational Environment for Radiotherapy Research (CERR) [22] and subsequently analyzed in MATLAB release 2019a (The MathWorks Inc., Natick, MA, USA). Plans were evaluated with respect to target coverage, homogeneity index, maximum dose to target and mean and maximum doses to OARs.

Target coverage was evaluated by calculating the percentage of the target volume receiving $\geq$95% ($V_{95\%}$) and $\leq$107% ($V_{107\%}$) of the prescribed dose. The homogeneity index was calculated according to a definition proposed by Spruijt et al. [23]. The dose to 0.03 cm^3 of the target volume and brainstem was used to represent clinically relevant maximum dose received by these structures.

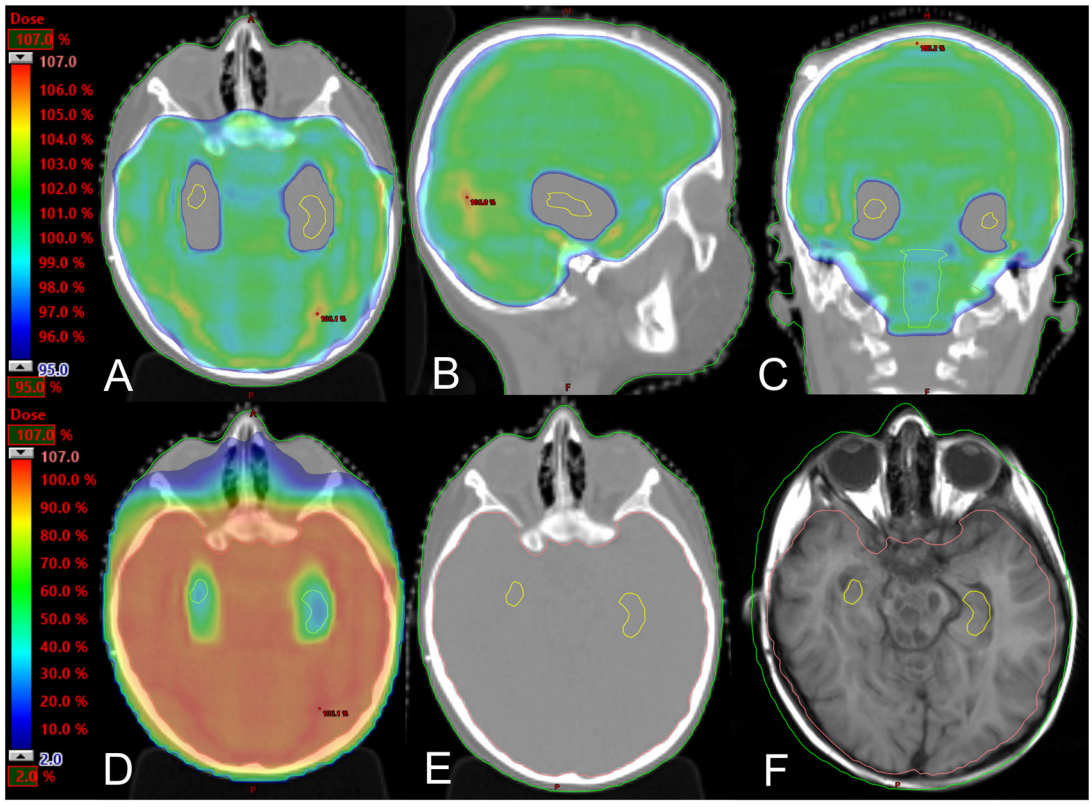

Figure 1. Absorbed dose in color-wash 95–107% for (a) transversal, (b) sagittal and (c) frontal view and absorbed dose in color-wash 2–107% for (d) transversal. A transversal slice of the (e) CT image and (f) T1-weighted MRI. All images show the contoured hippocampus (yellow contour). The hippocampal dose constraint was set to 9 Gy_{RBE} for the elective target.

Plans were deemed clinically acceptable if the following conditions were met: $V_{95\%} \geq 95\%$ and $V_{107\%} \leq 107\%$ of prescribed dose, $D_{0.03\,cc} \leq 110\%$ of prescribed dose, $D_{0.03\,cc} \leq 107\%$ of the prescribed dose to the brainstem, dose to the chiasm $\leq 50\,Gy_{RBE}$ and a homogeneity index for $CTV_{elective}$ of ≥ 95 where 100 constitutes a completely homogenous dose to the region of interest.

The association between hippocampal dose and patient characteristics such as GTV size, hippocampal size and the distance between CTV_{boost} and the hippocampus (defined as the center of the hippocampus to the closest point of CTV_{boost}) was evaluated using scatter plots and regression models.

Tumor control probability (TCP) and neurocognitive impairment normal tissue complication probability (NTCP) was estimated using previously published models [5,24,25]. The assumption for using these models is that the dose to the temporal lobe represents the dose to the hippocampus as the critical OAR for cognitive function. The TCP dose-response model has been evaluated against recently published data [26] to test their applicability and updated (Supplementary Table S1) for use in this study.

Statistical analysis

Shapiro–Wilk test and visual histogram inspection were used to assess normality and equal variance. Paired t-tests were used to compare hippocampal mean doses and NTCP estimates, where $p < .05$ was considered statistically significant. Stepwise comparison between each of the hippocampal dose objectives was performed; Standard CSI plan vs. 15 Gy_{RBE} vs. 12 Gy_{RBE} vs. 9 Gy_{RBE} vs. 7 Gy_{RBE} vs. 5 Gy_{RBE}, respectively.

Results

It was possible to reduce the dose to the hippocampus considerably with minimal compromise to the whole-brain target coverage. However, the lowest dose constraint to the hippocampus was related to a higher risk of one or multiple target objectives failing clinically acceptable criteria (Figure 2). The different robust optimization parameters used resulted in similar plan quality with some minor differences.

The median mean dose (range) to the hippocampus from whole-brain and boost plans was 7.1 Gy_{RBE} (5.0 to 11.7 Gy_{RBE}, $p < .001$), 9.0 Gy_{RBE} (6.8 to 13.7 Gy_{RBE}, $p < .001$), 10.4 Gy_{RBE} (8.4 to 15.4 Gy_{RBE}, $p < .001$), 13.0 Gy_{RBE} (11.0 to 17.8 Gy_{RBE}, $p < .001$), 15.9 Gy_{RBE} (13.9 to 20.5 Gy_{RBE}, $p < .001$) and 31.4 Gy_{RBE} (23.3 to 39.5 Gy_{RBE}, $p < .001$) for 5, 7, 9, 12, 15 Gy_{RBE} and standard CSI plans, respectively (Figure 2).

There was a clear correlation between hippocampus dose and distance between the hippocampus and CTV_{boost} (Supplementary Figure S1). Trends were seen for the correlation between GTV and hippocampal size with mean hippocampal dose (Figure 3(b,c)). The strongest correlation was seen for standard CSI plans where HS was not applied. The hippocampus dose was reduced with approximately 4.7 Gy_{RBE} and 1.3 Gy_{RBE} per cm distance between the

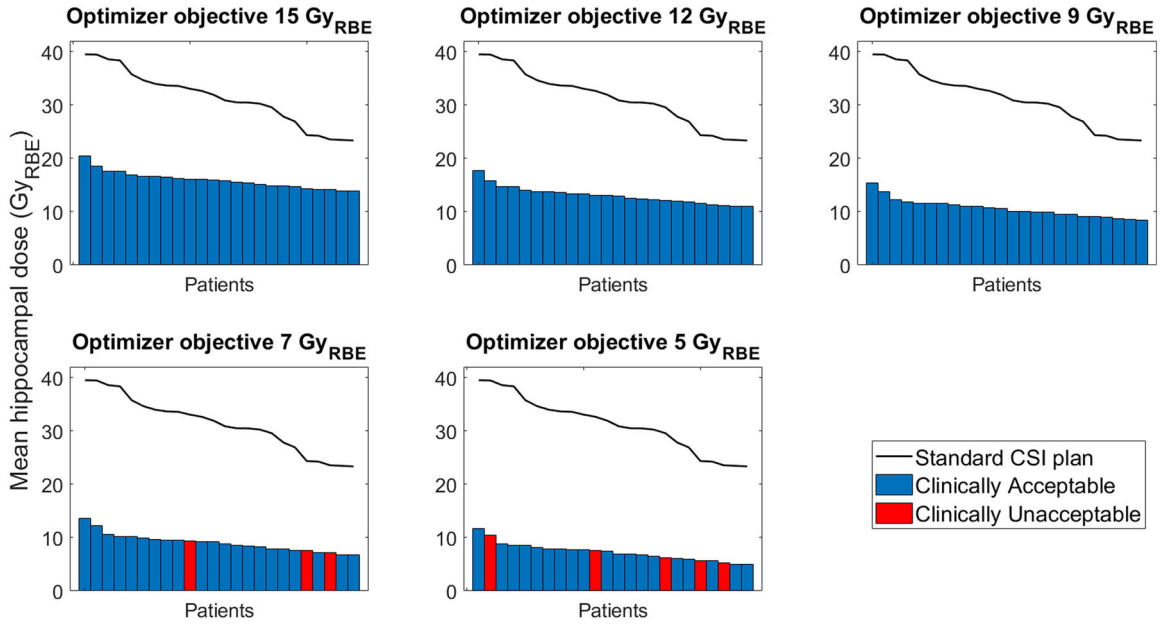

Figure 2. Mean hippocampus dose (Gy_{RBE}) for all patients optimized with 2%/2 mm where blue bars indicate a clinically acceptable plan and red bars a plan deemed unacceptable regarding target coverage ($V_{95\%}$ ≥95% of prescribed dose), homogeneity (≥95), maximum target dose ($D_{0.03\,cc}$ ≤110% of prescribed dose) and doses to the OARs ($D_{0.03\,cc}$ ≤107% of the prescribed dose to the brainstem, dose to the chiasm ≤50 Gy_{RBE}). The black line corresponds to each of the patients showing mean hippocampus dose (Gy_{RBE}) for the plans optimized without any priority or dose restriction (standard CSI plan).

hippocampi and CTV_{boost} for standard CSI plan and 9 Gy_{RBE} for HS plans, respectively.

The TCP remained relatively consistent with an estimated 78.5–80.5% event free survival (EFS) for all evaluated plans and patients. The NTCP was calculated for cognitive impairment (Table 2) which was divided into three major domains; Task efficiency (Figure 3(a)), Organization (Figure 3(b)) and Memory (Figure 3(c)). These domains are derived from Armstrong et al. [24] as they are reported upon being parts of the quality-of-life questioners in that study.

Discussion

This study shows that it is possible to reduce the dose to the hippocampus considerably with minimal impact on whole-brain target coverage with IMPT, in particular when inspecting dose-volume histograms. Even with acceptable target coverage, there might, however, be hot- and cold-spots throughout that would affect clinical acceptability, which is why this was explicitly evaluated. The high HI can be explained by the fact that the hippocampus only constitutes roughly 1% of the total irradiated volume. Gondi et al. [27] found that the HS volume with added planning-risk expansion accounted for about 2.1% of the whole-brain in adults. The lowest HS dose constraints tested in this study (5 Gy_{RBE}) might be difficult to achieve for some patients, especially depending on tumor location and GTV size. This is in agreement with results from a previous study [6] where plans were not based on a clinical protocol for treatment planning as well as on robust plan optimization. For the 9 Gy_{RBE} HS constraint, all plans were deemed clinically acceptable, demonstrating the possibility to lower the mean dose to the hippocampus by 20 Gy_{RBE} and still achieve acceptable plans.

Since tumor control remains the primary goal of HS-CSI, it might be inappropriate to spare the hippocampus for patients with high-risk medulloblastoma (MB), as their risk of recurrence may be higher [28]. Recently, it was also shown that lowering the dose to the entire craniospinal volume to 18 Gy for patients with standard-risk MB resulted in lower EFS and is currently not recommended [26]. Lately, laudable efforts have been made toward HS and the comprehensive phase III NRG Oncology CC001 trial demonstrated that for adults with CNS metastases, it is possible to significantly spare short-term cognitive function without deterioration of either progression-free survival and overall survival in a randomized setting [21].

Most modern radiotherapy techniques are able to spare the hippocampus to some extent [5,8–10,27] although the data suggests that IMPT would be the preferred alternative [5,10], especially for novel proton radiotherapy techniques [29]. In this study, we show that it is possible to considerably spare the hippocampus using IMPT. Doses to the hippocampus found in this study are comparable to previously published research [5,6,10]. Blomstrand et al. [5] determined that it was possible to spare the hippocampus to approximately 10 Gy_{RBE} using IMPT without compromising the $V_{95\%}$ $CTV_{elective}$ coverage. An important addition from this study is the use of robust optimization instead of using approaches mainly used for photon treatments, ensuring that IMPT plans will be deliverable.

The general consensus is that proton therapy is safe, effective and recommended for many types of pediatric cancers [30] and pediatric patients are, furthermore, expected to benefit from IMPT considerably even though the assumption is that radiation-induced adverse effects

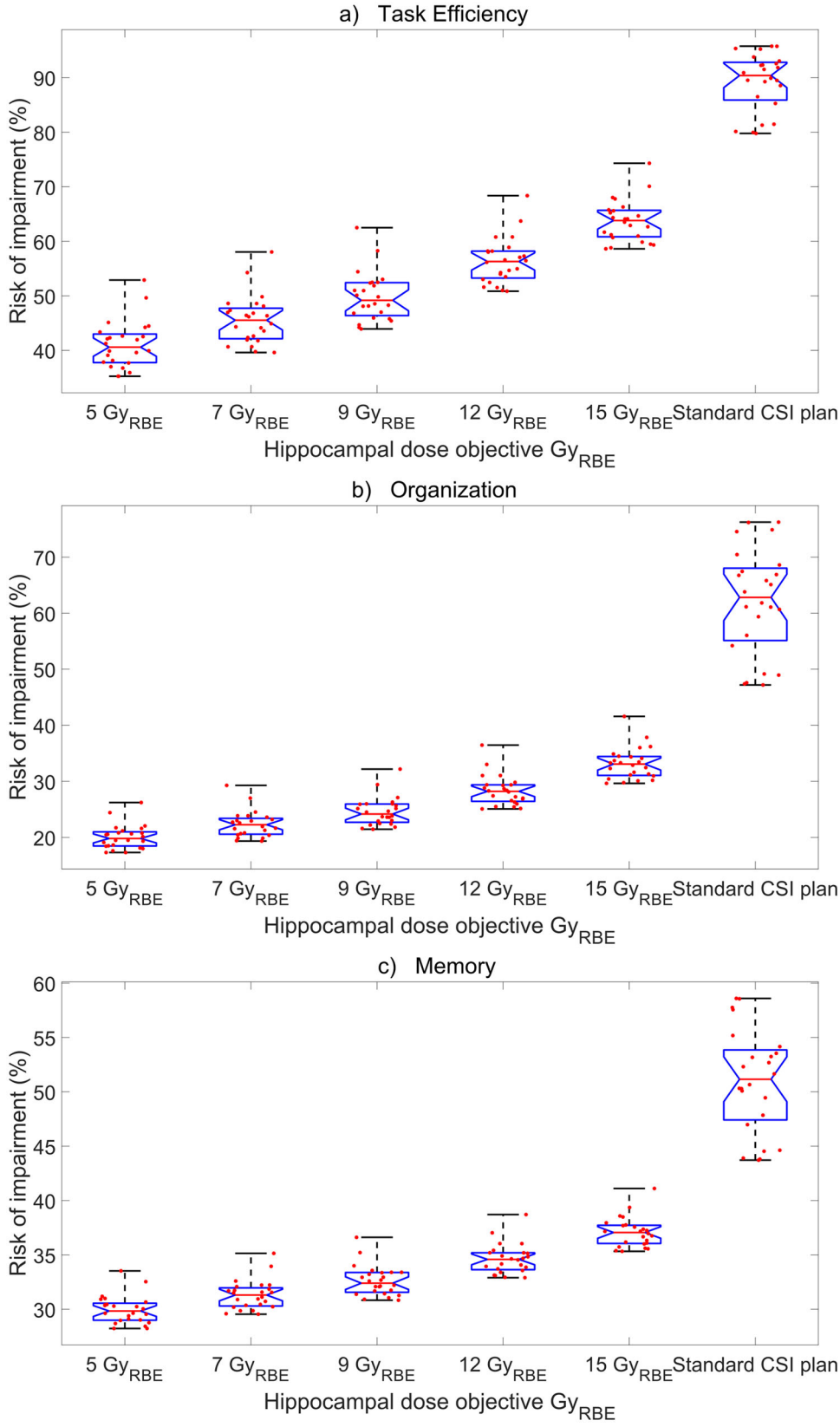

Figure 3. The boxplots represent the distribution of risk of impairment (%) among the 24 patients (red scatter) given as median, 25th–75th percentiles and range for each of the optimizer objectives for (a) task efficiency, (b) organization and (c) memory. For clarification purpose, the y-axes are presented in different ranges, most suitable for each dataset.

might be more substantial for these patients [31,32]. While there are papers that discuss the importance of reducing late side effects as these can increase with time [12–15], this is still very uncertain. Spiegler et al. states that intellectual function declined quickly in the first few years after treatment, and then more gradually [12].

Table 2. Normal tissue complication probability calculations; median mean estimated risk of impairment and average mean reduced estimated risk of impairment for task efficiency, organization and memory, with corresponding 95% confidence intervals or standard deviations.

	Task efficiency	(Range)	Organization	(Range)	Memory	(Range)
Risk of impairment						
5 Gy_{RBE}	40.6%	(35.3–52.9%)	19.8%	(17.3–26.2%)	29.8%	(28.2–33.5%)
7 Gy_{RBE}	45.5%	(39.6–58.0%)	22.3%	(19.3–29.3%)	31.3%	(29.5–35.1%)
9 Gy_{RBE}	49.2%	(43.9–62.5%)	24.2%	(21.4–32.2%)	32.4%	(30.8–36.6%)
12 Gy_{RBE}	56.3%	(50.8–68.4%)	28.2%	(25.1–36.5%)	34.6%	(32.9–38.7%)
15 Gy_{RBE}	63.8%	(58.6–74.3%)	33.1%	(29.6–41.6%)	37.1%	(35.3–41.1%)
Standard CSI plan	90.4%	(79.8–95.8)	62.8%	(47.2–76.3%)	51.2%	(43.7–58.6%)
	Task efficiency	SD	Organization	SD	Memory	SD
Reduced risk of impairment (relative to standard CSI)						
5 Gy_{RBE}	48.2%	3.1	42.1%	7.7	21.1%	3.7
7 Gy_{RBE}	43.7%	3.1	39.8%	7.6	19.7%	3.7
9 Gy_{RBE}	39.4%	3.1	37.5%	7.4	18.4%	3.6
12 Gy_{RBE}	32.9%	2.9	33.8%	7.3	16.4%	3.6
15 Gy_{RBE}	25.4%	2.8	29.0%	7.1	13.9%	3.6

Notes: All parameters presented here are statistically significant compared to their closest higher neighboring value ($p < .001$).
Abbreviations: RBE: radiobiological effect; CSI: craniospinal irradiation; SD: standard deviation.

Proton radiation generally show dosimetric benefits compared to photon radiation, however, any clinical benefit in terms of reduction in cognitive impairment is still uncertain [33,34]. We investigated the predicted risk of neurocognitive impairment and therefore any conclusions to whether sparing of the hippocampus translates into a clinical benefit remain exploratory since there are many areas of the brain that may contribute to cognitive function.

We estimated the clinical benefit in terms of the reduced risk of neurocognitive impairment using published dose-response models. These dose-response models are of course subject to considerable uncertainty but a lower dose to the hippocampus clearly estimates a reduced risk of neurocognitive impairment. The available TCP model is not stratified based on different molecular subgroups or patient's performance status and is based on data from standard-risk MB patients [5,24,25]. The current multimodality treatment results in a five-year EFS of 75–80% for standard-risk patients [35] which compares well to our TCP estimates of a five-year EFS of 78.5–80.5%. As the hippocampus constitutes only a small volume of the whole brain, a very limited drop in estimated TCP was found for our HS treatment plans.

According to our risk estimates, there is a statistically significant reduction in the risk of cognitive impairment for all dose levels where the hippocampus was avoided. Goda et al. [36] found that a hippocampal mean dose of less than 30 Gy did not affect intelligence quotient in children, adolescents and young adults. Although not fully comparable to our results, these studies further support treatment strategies avoiding irradiation of the hippocampi.

When sparing a critical OAR such as the hippocampus, it is crucial that the delineation is correct, which is not always trivial [37]. Uncertainties in volume delineation have been demonstrated and some studies indicate that inconsistencies presumably are some of the most substantial types of errors [38,39]. This predominantly applies to target delineation but in many cases also to OARs. In an attempt to mitigate the uncertainties surrounding the hippocampus, all plans were robustly optimized on this structure. Another challenge is the central location and somewhat odd shape of the hippocampus where the use of IMPT might be of particular advantage. It is, however, important to consider the complexities of linear energy transfer of protons and the relative biological effect along the proton beam, where physical dose may no longer be the best indicator of biologic effect [40,41]. Encouragingly, a recent study found no increase in CNS injury from proton treatment for MB, and no correlation with RBE compared to photon treatments [42].

In conclusion, we demonstrate the potential clinical benefit of reduced neurocognitive impairment based on robustly optimized HS IMPT plans, with marginal effect to target coverage and thereby estimated tumor control.

Disclosure statement

No conflict of interest was reported by the author(s).

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Data availability statement

Raw data were generated at Rigshospitalet. Derived data supporting the findings of this study are available from the corresponding author DG on request.

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