

Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma

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We sought to assess the feasibility and estimate the benefit of sparing the neurogenic niches when irradiating the brain of pediatric patients with medulloblastoma (MB) based on clinical outcome data. Pediatric MB survivors experience a high risk of neurocognitive adverse effects, often attributed to the whole-brain irradiation that is part of standard management. Neurogenesis is very sensitive to radiation, and limiting the radiation dose to the hippocampus and the subventricular zone (SVZ) may preserve neurocognitive function. Radiotherapy plans were created using 4 techniques: standard opposing fields, intensity-modulated radiotherapy (IMRT), intensity-modulated arc therapy (IMAT), and

intensity-modulated proton therapy (IMPT). Mean dose to the hippocampus and SVZ (mean for both sites) could be limited to 88.3% (range, 83.6%–91.0%), 77.1% (range, 71.5%–81.3%), and 42.3% (range, 26.6%–51.2%) with IMAT, IMRT, and IMPT, respectively, while maintaining at least 95% of the prescribed dose in 95% of the whole-brain target volume. Estimated risks for developing memory impairment after a prescribed dose of 23.4 Gy were 47% (95% confidence interval [CI], 21%–69%), 44% (95% CI, 21%–65%), 41% (95% CI, 22%–60%), and 33% (95% CI, 23%–44%) with opposing fields, IMAT, IMRT, and IMPT, respectively. Neurogenic niche sparing during cranial irradiation of pediatric patients with MB is feasible and is estimated to lower the risks of long-term neurocognitive sequelae. Greatest sparing is achieved with intensity-modulated proton therapy, thus making this an attractive option to be tested in a prospective clinical trial.

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Radiotherapy is one of the most effective therapeutic modalities for malignant central nervous system (CNS) tumors. Medulloblastoma (MB) accounts for about 20% of CNS tumors in children, and the peak incidence is at 5 years of age.¹ The prognosis of MB, which is a primitive neuro-ectodermal tumor (PNET) located in the cerebellum or the fourth ventricle, improved considerably with the introduction of adjuvant radiotherapy.¹ This success has generated a growing population of children surviving their cancer. Irradiation of the CNS is, however, associated with a risk of severe adverse effects, including neurocognitive sequelae. Younger age at treatment is correlated with more severe cognitive deficits.^{2,3} The detailed pathogenesis of cognitive dysfunction after radiotherapy is yet unknown, but several mechanisms likely play a role.⁴ Post-irradiation MRI reveals multiple changes, including white matter microstructure disruptions,⁵ decreased size of corpus callosum and subregions,⁶ and abnormal hippocampal development.⁷ In mammals, neurogenesis occurs at 2 major sites, the subgranular zone (SGZ) in the dentate gyrus of the hippocampus^{8,9} and the subventricular zone (SVZ) of the lateral ventricles.^{10,11} The stem and progenitor cells in these niches are sensitive to irradiation, and recent discoveries in neural stem cell biology and brain plasticity have provided clues toward a deeper understanding of the effects of ionizing radiation of the developing brain.¹²⁻¹⁹ In rodents, neurogenesis has been shown to be important for hippocampal-dependent memory formation.^{20,21} Several human studies demonstrate a relationship between absorbed dose to the brain and cognitive outcome,²²⁻²⁵ and recent studies show more specifically a correlation between temporal lobe irradiation and neurocognitive sequelae.^{26,27} Thus, because neurogenesis is important for hippocampal-dependent memory and the hippocampus is situated in the temporal lobe, it seems reasonable to hypothesize that the hippocampus is the main critical structure for radiotherapy-related cognitive function impairment. The role of SVZ irradiation for cognitive outcome shown is less clear; however, because of the proposed regenerative features of neurogenesis, the SVZ is included as an organ at risk (OAR) in this study.

New radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), intensity-modulated arc therapy (IMAT), and intensity-modulated proton therapy (IMPT), have facilitated the delivery of highly conformal dose distributions. Defining the hippocampus and the SVZ as OARs on a pre-radiotherapy magnetic resonance (MR) examination fused with CT scan facilitates reducing the dose to these regions during craniospinal irradiation (CSI). This would be particularly relevant for the hippocampus, because this region is important for memory function.²⁸ With a dose prescription of 23.4–36 Gy, which is used for patients with MB, neurocognitive dysfunction is reported to be a common adverse effect.^{29,30} If a significant reduction in dose to the OARs can be achieved, a reduction in late cognitive

adverse effects would be expected. A steep dose gradient would be needed to achieve a homogeneous dose to the rest of the brain while sparing the hippocampus and SVZ.

Inverse-planned intensity-modulated therapy aims at optimizing the dose distribution inside the patient's body, guided by dose-volume objectives for tumor and OARs. The dose distribution is thus shaped around the target volume, often with a steep dose gradient to the neighboring tissue. The trade-off between treating the target to a sufficient and homogeneous dose and avoiding the OARs can be manipulated by the choice of planning dose-volume objectives. Conventional therapy, IMRT, and IMAT use photon beams for radiation dose deposition. Protons deposit their energy in tissue in a very different fashion than do photons, and their main characteristic is the sharp dose gradient at the distal edge of the beam. The IMPT technique therefore allows intensity modulation with a sharper dose fall-off, compared with the photon techniques.

Our aim with this retrospective dose planning study, focusing on the cranial component of the CSI course, was to evaluate how much modern radiation therapy techniques can reduce the absorbed dose to the hippocampus and SVZ and still treat the rest of the brain to an adequate radiation dose. We also evaluated the potential clinical benefit of this dose reduction based on dose-response data from a large clinical series with long-term follow-up on neurocognitive function of pediatric patients treated with radiation. In this study, we intend to explore the technological foundation for a prospective clinical trial based on dose-sparing of the hippocampus and SVZ.

Materials and Methods

Patients and Treatment Planning

Six patients with MB who all received CSI during 2002–2007 at Sahlgrenska University Hospital, Gothenburg, Sweden, were re-planned. Their age at time of treatment ranged from 6 to 11 years (median, 7.5 years). The clinical target volume (CTV) in this study comprised the whole brain, disregarding the spinal part of the target. The dose contribution to the hippocampus and SVZ from the boost treatment was assumed to be negligible in the present analysis. In reality, this dose contribution could be important depending on the size and location of the primary tumor, the treatment strategy used (treating the whole posterior fossa or only the tumor bed with a margin), and the treatment technique. Thus, the estimates presented in this study will apply to cases in which the assumption of a zero dose contribution to the hippocampus and SVZ from the boost is reasonable.

The OARs consisted of the hippocampus, the SVZ, and the eyes, which were delineated in each of the patients based on fused T1 and T2 MRI and CT scans. Target and OARs were delineated by an experienced neuroradiologist. The SVZ was defined as the lateral wall of the lateral ventricles with a margin of 2 mm.

Figure 1 illustrates the SVZ and hippocampus overlaid on a transversal MRI scan. The prescribed dose was set to 36 Gy or 23.4 Gy, in 1.8 Gy/fraction. All treatment plans were generated using the Eclipse treatment planning system, version 10 (Varian Medical Systems).

Treatment planning was performed with the aim of minimizing the mean absorbed dose to the hippocampus and the SVZ without compromising CTV coverage. Four different radiotherapy delivery techniques were tested in this study, as shown in Fig. 2: 2 opposing cranial fields (which is still commonly used for cranial irradiation during the CSI course), IMRT with 7 fields, IMAT with 3 arcs (2 360 degree arcs and 1 noncoplanar 180 degree arc), and spot-scanned IMPT with 3 incident fields.

For the opposing field technique, the OAR sparing was limited to partial shielding of the eyes and the oral cavity. To ensure that the results of the treatment planning in this study were as user-independent as possible, we defined a fixed set of dose-volume objectives for the 3 inversely-optimized techniques: IMRT, IMAT, and IMPT. The objectives were defined in relation to 4 different levels of OAR sparing priority as shown in Table 1, with the intent of finding how the CTV radiation dose homogeneity was affected by the different levels of OAR sparing. We derived a linear correlation between the mean dose received by the hippocampus and the SVZ, further referred to as neurocognitive OAR dose,

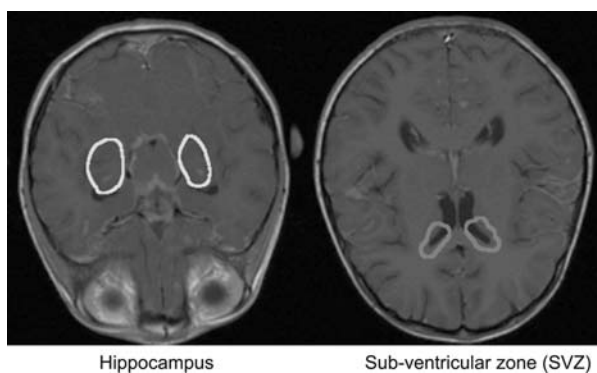


Fig. 1. The sub-ventricular zone (*magenta*) and hippocampus (*yellow*) overlaid on a transversal T1-weighted MRI scan.

and volume of the CTV receiving at least 95% of the prescribed dose, the V95. We then estimated what OAR sparing could be achieved, for each individual patient, with the different techniques if the V95 was set to be at least either 98% or 95%, with the mean target dose fixed at 100% of the prescribed dose for all techniques. By doing so, we attempted to obtain an objective measure of how much the different techniques were able to spare the neurocognitive OARs and how this was affected by the limit chosen as the acceptable target coverage.

Estimating the Risk of Neurocognitive Impairment

A dose-response relationship for neurocognitive outcome was, until recently, available from animal studies only. However, Armstrong et al. provided dose-response data based on long-term survivors of childhood CNS malignancies.²⁷ The authors found a correlation between radiation dose to the temporal lobe, while controlling for dose to other parts of the brain, and the risk of reduced task efficiency, organization, and memory. The assumption in the present study is that sparing the hippocampus and SVZ would be as effective as sparing the whole temporal lobe in terms of reducing neurocognitive adverse effects. Stratifying their data into a separate MB/PNET group, Armstrong et al. published odds ratios (ORs) with 95% confidence intervals (CIs), per 10 Gy increase in temporal lobe dose, for developing various neurological sequelae. From these ORs and the baseline risk of impairment with no temporal lobe irradiation, we derived logistic dose-response functions as follows:

$$\left. \begin{aligned} OR_D &= \frac{p_D/(1-p_D)}{p_0/(1-p_0)} \\ OR_D &= OR_{10}^{\frac{D}{10}} \end{aligned} \right\} \Rightarrow p_D = \frac{OR_{10}^{\frac{D}{10}}}{\left(\frac{1}{p_0} - 1\right) + OR_{10}^{\frac{D}{10}}} \quad (1)$$

where D is the dose in Gy, OR_{10} is the corresponding OR at 10 Gy, p_0 is the baseline risk of impairment at zero dose, and p_D is the risk of impairment at dose D . The baseline risk was estimated from patients from the whole cohort who had not received any temporal lobe irradiation, not only from the stratified group. Separate estimates were not given, possibly because there were

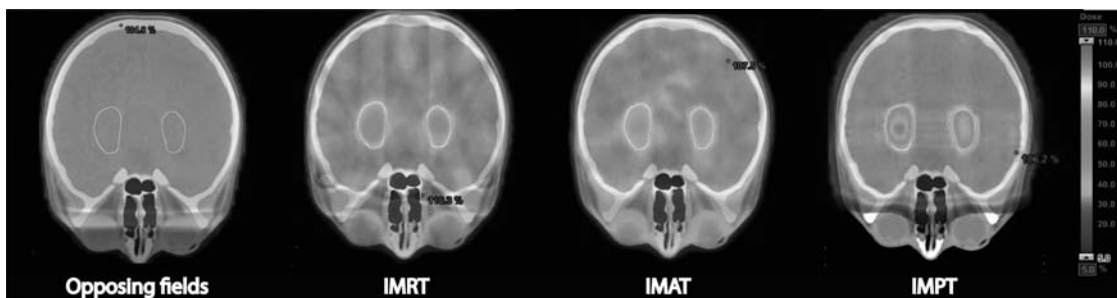


Fig. 2. Absorbed radiation dose shown in color-wash for (from left) opposing fields, IMRT, IMAT, and IMPT with the hippocampus segmented as the yellow contour. Treatment planning parameters corresponded to OAR setting 1 as given in Table 1.

only 5 patients in the MB/PNET group who did not receive any cranial irradiation,³¹ which was too few to obtain a reliable baseline estimate. Applying the neurocognitive OAR doses from the treatment planning to the derived dose-response relations, risks of neurocognitive impairment between radiotherapy techniques were estimated for 2 prescribed dose levels: 23.4 Gy and 36 Gy.

Table 1. Dose-volume objectives used in the inversely-optimized treatment planning. The same priority was applied for the eyes, hippocampus, and SVZ in each of the various OAR settings

Structure	Volume (%)	Dose (Gy)	Priority
Body	0	37.5	250
CTV	0	36.5	225
	100	35.5	225
OAR setting 0	–	–	–
OAR setting 1	0	5	65
OAR setting 2	0	5	120
OAR setting 3	0	5	160

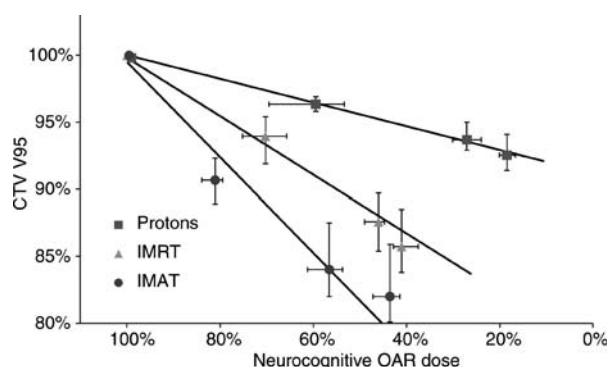


Fig. 3. Mean values for the 6 patients showing how the coverage (V95) of the whole-brain target volume is affected by lowering the dose to the neurocognitive OARs. No priority settings were possible for the opposing-field technique. The solid lines represent linear regressions through the 4 data points and the uncertainty bars show the range of doses within the patient group.

Table 2. Mean doses (range) to neurocognitive organs at risk represented as percentage of the prescribed treatment dose.

Technique	Hippocampus (%)	SVZ (%)	Neurocognitive OAR (%)
	CTV V95 = 98%		
Protons	77.0 (71.0–80.6)	79.2 (71.6–87.0)	78.0 (71.3–81.1)
IMRT	89.7 (87.0–92.7)	90.5 (86.5–93.3)	90.0 (86.9–93.0)
IMAT	97.2 (95.9–98.4)	98.7 (96.6–101.7)	97.8 (96.2–99.8)
Opposing fields	98.0 (97.2–99.3)	100.4 (99.4–101.3)	99.2 (98.9–100.0)
	CTV V95 = 95%		
Protons	41.9 (25.9–50.3)	42.7 (27.4–51.5)	42.3 (26.6–51.2)
IMRT	77.1 (72.5–81.1)	77.2 (70.6–81.5)	77.1 (71.5–81.3)
IMAT	87.1 (82.9–89.4)	89.6 (84.3–94.2)	88.3 (83.6–91.0)
Opposing fields	98.0 (97.2–99.3)	100.4 (99.4–101.3)	99.2 (98.9–100.0)

Note: The neurocognitive OAR dose was taken as the average dose of the hippocampus and the SVZ.

Statistical Analysis

The largest source of uncertainty in this study was the OR estimates from Armstrong et al. on which we based our dose-response functions. To test whether the risks of impairment between treatment techniques were significantly different, a paired random number (Monte Carlo) test comparing the OR between 2 treatment techniques was performed. Samples were drawn randomly from log-normal distributions corresponding to the mean and 95% CI of the dose-response parameters. For each of the different neurocognitive end points, the OR between techniques with 95% CI was calculated by inverse variance weighting. To account, to some extent, for the possible underestimation of the variance resulting from the small number of patients, a bootstrapping procedure was applied. Ten million samples of the 6 patients were drawn with replacement. A mean point estimate OR with CI was then calculated for each of the 10 million samples and a normal distribution matched to each one. Finally, 1 sample was randomly drawn from each of the 10 million distributions, giving the final OR and 95% CI as the mean and 2.5–97.5 percentile of the randomly drawn samples.

Results

There was a clear effect on CTV coverage when tightening the OAR dose constraint in the treatment planning process, as shown in Fig. 3. The CTV coverage was least affected for the IMPT plans, suggesting that that the OARs can be spared to a greater extent with the proton technique. Of the highly conformal photon techniques, IMRT was slightly more effective than IMAT at sparing the neurocognitive OARs.

On the basis of the data in Fig. 3, it was deemed reasonable to describe the correlation between CTV V95 and neurocognitive OAR dose by a simple linear relation. The neurocognitive OAR doses, corresponding to CTV V95 equal to either 98% or 95%, were calculated using the linear regressions in Fig. 3 and are given in Table 2. These doses thus represented the lowest neurocognitive OAR dose achievable, with the different techniques, for a CTV coverage of V95 at either 98% or 95%.

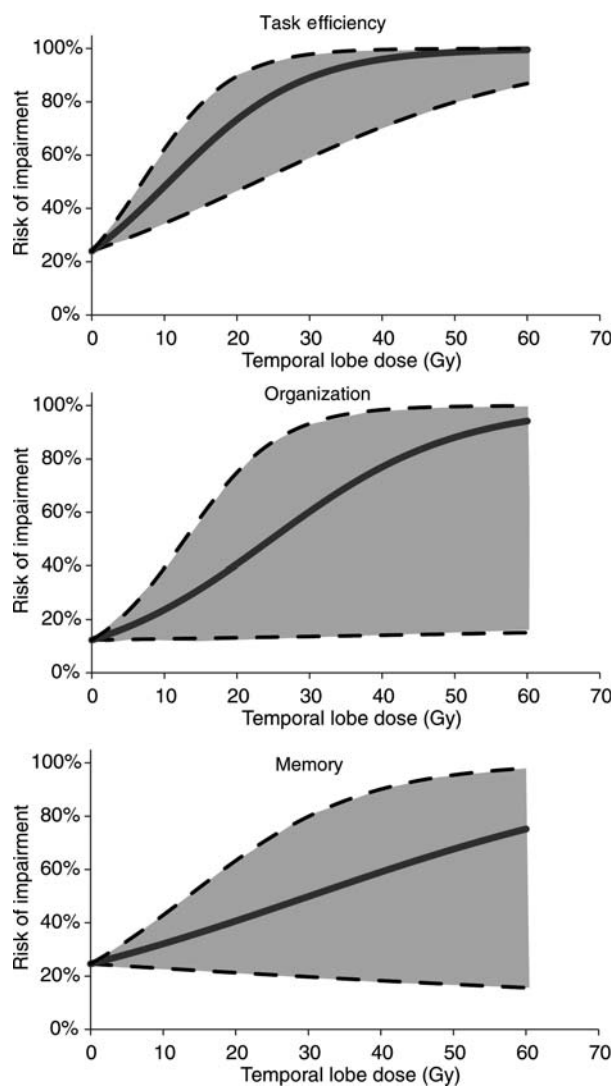


Fig. 4. Logistic dose-response functions relating to task efficiency, organization, and memory. The blue line shows the estimated dose-response relation and the shaded area the corresponding 95% confidence intervals (CI). Based on odds ratios (95% CI) of 2.95 (1.66–5.22), 2.21 (1.04–4.70) and 1.45 (0.91–2.30) for task efficiency, organization, and memory respectively. Baseline risks at zero Gy were taken from the group of patients not receiving any temporal lobe irradiation in Armstrong et al.

The logistic dose-response relationships shown in Fig. 4 were derived from the ORs and baseline risks in Armstrong et al. according to Equation 1. Figure 5 shows the estimated incidence of neurological sequelae based on the doses in Table 2 and the derived dose-response relationships.

As shown in Fig. 5, the risks of developing various neurological impairments were estimated to be lower with IMPT, compared with photon therapy. In addition, relaxing the CTV coverage constraint has a large impact on the possible neurocognitive function sparing with IMPT but little impact for the photon techniques.

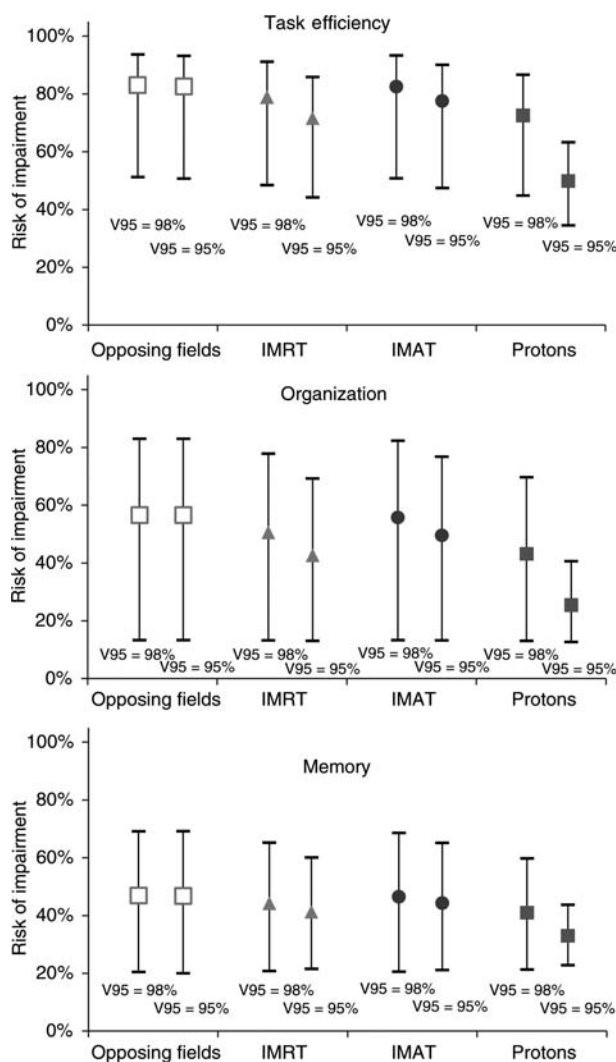


Fig. 5. Mean values for the 6 patients of the estimated complication incidences, given with 95% confidence intervals, for a prescribed target dose of 23.4 Gy. Comparisons are made between radiotherapy techniques and the choice of acceptable target coverage. Estimates are based on the dose-response curves derived from Armstrong et al. and Monte Carlo sampled to yield the confidence limits.

Discussion

The clinical relevance of low radiation doses to the CNS remains controversial, with a few studies reporting measurable decline in mental functioning after doses as low as 2 Gy and below.^{32,33} However, there is no doubt that the high doses of radiation prescribed for treating MB lead to neurocognitive deficits and are likely to influence later academic achievements and social life.^{34–36} Sparing the entire temporal lobe from irradiation would considerably reduce the dose to a large part of the target volume in MB and, thereby, likely increase the risk of relapse. Here, we assume that sparing the hippocampus and SVZ provides the same cognitive function sparing, but with the ability of maintaining a

Table 3. Estimates of odds ratios between the different treatment techniques and the 2 different dose prescriptions with corresponding 95% confidence intervals (CIs)

	Task efficiency		Organization		Memory	
	36 Gy	23.4 Gy	36 Gy	23.4 Gy	36 Gy	23.4 Gy
Protons/IMRT V95 = 98%	0.64 (0.58–0.71)	0.75 (0.70–0.80)	0.73 (0.66–0.81)	0.82 (0.76–0.88)	0.87 (0.80–0.93)	0.91 (0.87–0.95)
Protons/IMRT V95 = 95%	0.28 (0.23–0.33)	0.44 (0.38–0.49)	0.43 (0.35–0.51)	0.56 (0.49–0.65)	0.67 (0.57–0.78)	0.76 (0.68–0.86)
IMRT/IMAT V95 = 98%	0.77 (0.70–0.84)	0.84 (0.78–0.89)	0.83 (0.75–0.90)	0.88 (0.82–0.93)	0.92 (0.87–0.96)	0.94 (0.91–0.98)
IMRT/IMAT V95 = 95%	0.68 (0.61–0.74)	0.78 (0.72–0.83)	0.76 (0.68–0.84)	0.83 (0.77–0.89)	0.88 (0.82–0.94)	0.92 (0.88–0.96)

Note: An upper CI limit below 1.00 represents significantly different odds ratios between techniques in the paired Monte Carlo test.

CTV coverage of V95 at either 95% or 98%. We show that advanced radiation therapy techniques can reduce the dose to the hippocampus and SVZ without compromising the dose coverage of the whole-brain target volume.

To put our dosimetric findings into a clinical context, the risks of developing various neurocognitive sequelae were estimated, based on data from long-term follow-up of pediatric MB survivors.²⁷ IMPT is superior to the conventional technique and also significantly better than IMRT and IMAT. When the CTV V95 constraint is relaxed from 98% to 95%, this gives a benefit mainly with the IMPT technique. In practice, however, this could partly be offset by the risk involved in lowering the target coverage constraints for IMPT because of the sharp dose fall-off at the distal field edge.

Slightly lower risk of impairment is estimated for IMRT than for IMAT but with wide CI, resulting from uncertainty in the dose-response parameters. However, the paired Monte Carlo test shows that ORs between techniques are all significantly different at the 95% level (Table 3). The high level of significance in the paired test reflects that, in each comparison, the estimates for all 6 patients favored the same technique, albeit to varying degrees. For a linear correlation between dose and the logarithm of the OR as assumed by Armstrong et al.,²⁷ a lower dose will always give a lower OR as long as the slope is positive (OR, >1). Consequently, the paired comparison of techniques circumvents the effect of uncertainty in the magnitude of a positive slope of the dose-response curve. Indeed, any positive dose-response function will retain the relative ranking of the plans. However, systematic errors could affect the comparison, for example, if mean dose is a poor predictor of toxicity or if there is a negative dose-response over a range of dose. Such systematic effects are not accounted for in the CI in Table 3. Furthermore, the small number of patients could lower the generalizability of our findings to a larger patient cohort.

Our estimated risks of neurological impairment are based on translating results from a study by Armstrong et al.²⁷ based on long-term survivors of pediatric CNS malignancies. Our estimates are, thus, subject to the

limitations of that study, such as the collection of data through questionnaires designed for neurocognitive function estimation. There are likely also some uncertainties in the radiation dosimetry, because this was based on retrospective evaluation of individual radiotherapy records and the fact that the majority of these patients were treated with older radiation delivery techniques. Despite these caveats, the data in this study are based on a large patient material followed up for a long time and with complete records of cranial radiotherapy for the 818 patients included. They also stratified patients specifically into a MB/PNET group, making the application in our study suitable.

The dose-response relationship between temporal lobe irradiation and neurocognitive impairment shown by Armstrong et al. was not limited to the MB/PNET group. For the whole patient cohort, the risk of task efficiency impairment was 24.0%, 34.7%, 48.3%, and 47.3% for temporal lobe doses of 0 Gy, 0–30 Gy, 30–50 Gy, and >50 Gy, respectively. The corresponding risks of organizational impairment were 12.3%, 12.2%, 17.0%, and 22.6% and 24.6%, 33.3%, 45.1%, and 51.4% for impaired memory function. In health-related quality of life estimates they saw a correlation between temporal lobe irradiation and social functioning, physical limitations, and general health difficulties. Armstrong et al. also showed that patients in the MB/PNET group have a steeper temporal lobe dose-response, compared with survivors of other CNS tumors. ORs per 10 Gy-dose increase were 2.95 (95% CI, 1.66–5.22), 2.21 (95% CI, 1.04–4.70), and 1.45 (95% CI, 0.91–2.30) for task efficiency, organization, and memory, respectively, in the MB/PNET group and 1.10 (95% CI, 1.00–1.21), 1.12 (95% CI, 0.99–1.26), and 1.14 (95% CI, 1.03–1.25) for all other CNS tumors. The authors stipulate that a possible contributor to the substantial neurocognitive impairment in MB survivors could be the high-dose posterior fossa boost, the hypothesis being that this could cause loss of supratentorial connections between the cerebellum and the frontal region of the brain, which might affect executive functioning. This could possibly bias the baseline estimates of neurocognitive function at low temporal lobe doses but will probably not affect the steepness of the

dose-response relationships. The practice change in many centers towards boosting only the tumor bed with a margin, rather than the whole posterior fossa, means that neurocognitive decline attributable to cerebellar irradiation would depend on the size and location of the tumor. Unfortunately, despite extensive research, the cerebellar contribution to cognitive and affective regulation remains poorly understood.³⁷

The potential risk of tumor relapse from hippocampal-sparing radiotherapy needs to be defined. However, the hippocampus and SVZ made up only 1.3% of the whole-brain volume on average for the patients in our study. Thus, only a small portion of the target is underdosed.

Our study extends the recent study by Redmond et al., in that we compare not only IMRT with standard opposing fields but also IMAT and IMPT.³⁸ IMRT is generally used with caution in children because of concerns about secondary malignancies when exposing large areas to low doses of radiation. In proton therapy, the risk of developing radiation-induced cancers due to secondary neutron irradiation is of special concern in children.³⁹ The IMPT plans in this study used spot-scanned delivery, which exposes the patient to considerably lower secondary neutron doses than passive scattering techniques. Although beyond the scope of this study, the risk of secondary malignancies needs to be considered in the choice of treatment modality, especially when addressing the spinal part of a CSI treatment course. Furthermore, Merchant et al. have stated that a reduction in low- and medium-dose volumes in the supratentorial brain benefits long-term cognitive outcome, which again favors the IMPT technique.⁴⁰

In summary, we demonstrate the dosimetric feasibility of sparing the hippocampus and SVZ during cranial irradiation, along with estimates of the potential clinical benefit. Our estimates show that the frequency of neurological adverse effects of radiotherapy could be considerably reduced, especially with intensity-modulated proton therapy. Validation of this strategy should come from large prospective clinical trials. Hopefully, our study can inspire such a trial, preferably with IMPT, because this technique is predicted to offer the greatest patient benefit.

Conflict of interest statement. P.M.R. has a research agreement with Varian Medical Systems. All other authors: None declared.

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