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Improved neuropsychological outcomes following proton therapy relative to X-ray therapy for pediatric brain tumor patients

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Abstract

Background. Survivors of pediatric brain tumors are at risk for impaired development in multiple neuropsychological domains. The purpose of this study was to compare neuropsychological outcomes of pediatric brain tumor patients who underwent X-ray radiotherapy (XRT) versus proton radiotherapy (PRT).

Methods. Pediatric patients who underwent either XRT or PRT and received posttreatment age-appropriate neuropsychological evaluation—including measures of intelligence (IQ), attention, memory, visuographic skills, academic skills, and parent-reported adaptive functioning—were identified. Multivariate analyses were performed to assess differences in neuropsychological outcomes and included tests for interaction between treatment cohort and follow-up time.

Results. Between 1998 and 2017, 125 patients with tumors located in the supratentorial (17.6%), midline (28.8%), or posterior fossa (53.6%) compartments received radiation and had posttreatment neuropsychological evaluation. Median age at treatment was 7.4 years. The PRT patient cohort had higher estimated SES and shorter median time from radiotherapy completion to last neuropsychological evaluation (6.7 vs 2.6 y, $P < 0.001$). On multivariable analysis, PRT was associated with higher full-scale IQ ($\beta = 10.6$, $P = 0.048$) and processing speed ($\beta = 14.4$, $P = 0.007$) relative to XRT, with trend toward higher verbal IQ ($\beta = 9.9$, $P = 0.06$) and general adaptive functioning ($\beta = 11.4$, $P = 0.07$). Planned sensitivity analyses truncating follow-up interval in the XRT cohort re-demonstrated higher verbal IQ ($P = 0.01$) and IQ ($P = 0.04$) following PRT, with trend toward improved processing speed ($P = 0.09$).

Conclusions. PRT is associated with favorable outcomes for intelligence and processing speed. Combined with other strategies for treatment de-intensification, PRT may further reduce neuropsychological morbidity of brain tumor treatment.

Key Points

1. PRT is associated with favorable neuropsychological outcomes compared with XRT.
2. Age, craniospinal irradiation, and hydrocephalus requiring shunt are also predictors.

Importance of the Study

Proton therapy confers favorable radiation dose profiles relative to conventional X-ray therapy; however, the long-term cognitive benefit of proton therapy has not been fully established. This study provides evidence that sparing healthy brain tissue in children is associated with favorable neuropsychological outcomes. Proton therapy combined with other strategies for treatment de-intensification may further reduce the neuropsychological morbidity of treatment.

Given the increasing population of long-term survivors of pediatric brain tumors, neuropsychological outcomes play an increasing role in understanding the impact of treatment and guiding survivorship care. It is well known that long-term survivors of pediatric brain tumors are less likely to complete higher education, successfully hold competitive jobs, marry, live independently, or receive appropriate health care compared with their peers.[1–6]These indicators of poorer quality of life are linked to lower standardized scores across multiple neuropsychological domains.[7,8] Since exposure to brain irradiation is associated with impaired neuropsychological development, early detection of impairments in patients receiving radiotherapy is critical to the development of mitigation strategies to improve long-term outcomes.[9,10] Understanding which specific deficits arise after treatment is crucial for remediation and prevention of associated problems in school and extracurricular settings.[11]

Neuropsychological assessment can be useful in guiding advances in cancer treatment strategies. For instance, in some subgroups of children with medulloblastoma undergoing radiotherapy, lower doses of craniospinal irradiation (CSI) and smaller boost volumes have been associated with better neuropsychological outcomes without impacting survival outcome.[12–16] The recognition that for pediatric brain tumor patients requiring radiotherapy, the dose and volume of irradiated healthy brain tissue directly correlates with neuropsychological outcomes has been an important driving force in current treatment paradigms. Thus, recent cooperative group trials such as the Children's Oncology Group (COG) ACNS0331 have investigated decreasing the dose of CSI and/or the size of radiotherapy target volumes. In addition, further molecular characterization of favorable tumor subgroups with the potential to greatly reduce or eliminate brain irradiation, such as WNT-positive medulloblastoma, may have implications for long-term functional outcomes.[17]

Advances in radiation treatment delivery may also lead to improved neuropsychological outcomes. Studies have reported favorable outcomes for IQ, learning, and adaptive functioning following highly conformal and intensity-modulated radiotherapy (IMRT) techniques.[18–21] Proton radiotherapy (PRT) is another means of decreasing exposure to off-target healthy brain tissues in children requiring cranial irradiation and has been associated with favorable neuropsychological function.[22–27] Protons deposit much of their energy into the tumor target and stop thereafter, as opposed to X-ray radiotherapy (XRT), which continues to deposit dose beyond the tumor. Although there is much enthusiasm and promise with this approach, few studies have been published comparing XRT with PRT across a limited number of neuropsychological domains. In addition, the impact of alterations to treatment volume and prescribed tumor dose, which have direct effects on the dose and volume of healthy brain tissue irradiated, has not been extensively evaluated.

The purpose of our study was to compare neuropsychological outcomes for pediatric brain tumor patients undergoing XRT versus PRT across multiple domains. Given the importance of radiation parameters on neuropsychological outcomes, we hypothesized that by decreasing the off-target volume and dose of brain tissue irradiated, PRT may mitigate certain neuropsychological sequelae of radiation treatment relative to XRT.

Materials and Methods

Patients and Procedures

This retrospective cohort study was approved by the institutional review board at the Ann and Robert H. Lurie Children's Hospital of Chicago with waiver of informed consent due to minimal risk. Pediatric patients identified through the electronic medical record all had first diagnosis of primary central nervous system (CNS) tumors of any histology and received treatment determined by the current standard of care for their diagnosis. Patients received XRT or PRT based on the discretion of the referring physician, the availability of PRT, and the ability of patients and their families to travel for treatment. Patients who had previously received CNS radiotherapy or radiosurgery or had premorbid neurofibromatosis type 1 or autism spectrum disorders were excluded. Patients received either fractionated XRT with conformal radiotherapy or intensity-modulated radiotherapy or PRT with passive scatter or active scanning (uniform or pencil beam) techniques as adjuvant or definitive treatment, with or without concurrent chemotherapy. All patients received CT- and MRI-based planning.

Information about covariates was recorded, including age at irradiation, socioeconomic status (SES; estimated by the median household income of the patient's zip code[28]), race, sex, hydrocephalus requiring shunt, chemotherapy regimen, tumor histology, tumor location, number of craniotomies, CSI dose, total radiation dose, complications such as posterior fossa syndrome, hearing loss requiring assistive devices, and vision loss. Volume of brain irradiated was evaluated by characterization of the radiation treatment as (1) *limited*, focal brain treatment

only; (2) *moderate*, whole ventricle irradiation, treatment to multiple lobes simultaneously, or CSI with anatomically constrained volumetric expansion of a tumor volume; or (3) *extensive*, CSI with boost volume defined as encompassing an entire compartment such as the posterior fossa, or encompassing several tumor volumes for patients with multifocal disease.

Neuropsychological Testing and Follow-Up

Patients received clinical follow-up as dictated by each particular tumor and patient-specific scenario. All patients included in this study received at least one posttreatment age-appropriate neuropsychological evaluation at the Ann and Robert H. Lurie Children's Hospital of Chicago, a large and metropolitan tertiary care children's hospital. Children were referred for neuropsychological testing on the basis of either physician- or parent-identified clinical need, and all evaluations were overseen by pediatric neuropsychologists, with some tasks administered by experienced psychometricians. When a patient had received more than one neuropsychological evaluation, the results of the most recent were used for analyses. The following cognitive domains and their respective tests were sampled:

- **Intellectual Skills:** Measures included general intellectual ability, per the Full-Scale IQ (FSIQ) of the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) or General Ability Index (GAI) of the Wechsler Intelligence Scale for Children, Fourth or Fifth Edition (WISC-IV/V) or Wechsler Adult Intelligence Scales, Third or Fourth Edition (WAIS-III/IV); verbal reasoning (VIQ), per the WISC/WAIS Verbal Comprehension Index or WASI Verbal IQ; nonverbal reasoning (PIQ), per the WISC/WAIS Perceptual Reasoning Index or WASI Performance IQ; and WISC/WAIS Processing Speed Index (PSI).
- **Working Memory:** Measured with the Digit Span (DS) subtest of the age-appropriate Wechsler intelligence scale.
- **Memory:** Measured with the delayed story memory task (delayed SM) from either the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2) or the Children's Memory Scale (CMS).
- **Visuographic (drawing) Skills:** Measured with the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI).
- **Academic Skills:** Measured with single-word reading/decoding and written calculation tasks from either the Wechsler Individual Achievement Test, Third Edition (WIAT-III) or the Woodcock-Johnson Tests of Achievement, Third or Fourth Edition (WJ-III/IV ACH).
- **Adaptive Functions:** Measured with parent ratings of independence skills using the Adaptive Behavior Assessment System, Second or Third Edition (ABAS-II/ABAS-3), including the General Adaptive Composite (GAC) and Conceptual, Social, and Practical domains.

The indices of FSIQ/GAI, VIQ, PIQ, PSI, VMI, reading/decoding, written calculations, and parent-rated adaptive functions are reported as age-adjusted standard scores (mean = 100, SD = 15). Digit Span and delayed story memory results are reported as scaled scores based on age-adjusted norms (mean = 10, SD = 3). Across tests, higher scores represent better performance or ability.

Statistical Analyses

The primary endpoint of this study was neuropsychological performance in terms of FSIQ/GAI, VIQ, PIQ, PSI, Digit Span, story memory, VMI, reading/decoding, written calculations, and adaptive functions from the most recent available neuropsychological evaluation. Fisher's exact test was used to assess differences in categorical variables between groups and independent-samples *t*-tests were used to assess differences in continuous variables. Patient demographic characteristics, tumor-related factors, and treatment-related factors were all included in univariate analyses for each neuropsychological endpoint to explore the unadjusted association between variable and outcome. For this analysis, univariate linear regression was constructed with a generalized linear model with Gaussian distribution. Variables with $P < 0.1$ were considered relevant for inclusion for further multivariable analyses. Next, multivariable linear models for each neurocognitive endpoint were constructed based on the variables shown to be relevant by univariable analyses.

Since radiation-induced neuropsychological deficits can evolve over time, we utilized 2 approaches to account for potential differences in the neuropsychological follow-up interval for patients receiving either XRT or PRT. First, for each multivariate linear regression model where RT modality was included, we also tested for the interaction between RT modality and interval of neuropsychological follow-up for that particular domain. RT modality was considered significant on multivariate analysis if the *P*-value for the slope coefficient was <0.05 and the interaction term was nonsignificant. Next, we performed a planned sensitivity analysis by truncation whereby scores for patients in the XRT cohort were removed to allow a cohort matched on interval to the PRT group. In addition, since historically PRT had not been widely available and the first patient in the PRT cohort was treated in 2004, for this sensitivity analysis we excluded patients in the XRT cohort treated before 2004. Once the dataset was modified in this way, univariate and then multivariate linear regression analyses were repeated to determine significant covariates. Given the potential confounding effects of SES on neuropsychological performance, an additional sensitivity analysis was performed. The median SES for the entire cohort was $70 000 with interquartile range (IQR) $50 000–$90 000. Socioeconomic status was coded as a categorical variable with "low" SES defined as median household income by zip code <$50 000, "high" SES household income >$90 000, and "average" as in-between. Multivariable analyses were repeated for domains on which SES had been a significant contributing factor (VIQ, PIQ, and FSIQ/GAI) but included SES as a categorical variable ("low," "average," "high") instead of being a continuous variable in the regression model. For all measures, a $P < 0.05$ was considered statistically significant, with no adjustments for multiple testing. Analyses were performed

with R 3.4.1[29] using the ggplot2[30] and Visreg[31] packages for plotting.

Results

Patient Demographics

Between 1998 and 2017, 934 patients with primary brain tumors who had received radiotherapy in addition to surgery, chemotherapy, or both were seen at the Ann and Robert H. Lurie Children's Hospital of Chicago. Of those, 141 (15.1%) received at least one neuropsychological evaluation, and 125 patients met all inclusion criteria (Table 1). The overall median age at the time of radiotherapy was 7.4 years (IQR 5.2–11.6), and the median time from completion of radiotherapy to the patient's last neuropsychological evaluation was 3.2 years (IQR 1.8–4.7). Of the 67 patients who received XRT, 26 (38.8%) received 3D conformal therapy while 41 (61.2%) received IMRT. Of the 58 patients who received PRT, 11 (19.0%) received treatment with passive scatter techniques and 47 (81.0%) received active scanning. Patients receiving either XRT or PRT were well balanced across the majority of covariates assessed. However, patients treated with XRT had lower estimated SES ($62 000, IQR $51 000–80 000 vs $74 000, IQR $56 000–92 000, P = 0.03), longer interval between completion of treatment and last neuropsychological evaluation (6.7 years, IQR 3.6–9.7 vs 2.6 years, IQR 1.4–3.6, $P < 0.001$), a higher proportion of posterior fossa tumors (65.7% vs 39.7%, $P = 0.003$), and higher proportion of hearing impairment at the time of neuropsychological evaluation (49.3% vs 25.9%, $P = 0.01$).

Neuropsychological Outcomes: Univariate and Multivariate Analyses

Comparisons of group means for patients treated with XRT or PRT for each neuropsychological domain are presented in Table 2. Univariate analyses demonstrated that relative to patients receiving XRT, PRT was associated with higher FSIQ/GAI (96.0 vs 88.6, $P = 0.019$), VIQ (99.7 vs 92.8, $P = 0.033$), PIQ (90.7 vs 87.8, $P = 0.056$), PSI (87.1 vs 80.0, $P = 0.03$), VMI (87.2 vs 80.8, $P = 0.035$), Digit Span (8.1 vs 7.6, $P = 0.03$), reading/decoding (94.1 vs 86.4, $P = 0.02$), and written calculations (90.4 vs 83.1, $P = 0.042$). Parent ratings of adaptive skills were similarly higher in the PRT group, evident across the composite GAC (92.0 vs 80.7, $P = 0.001$) as well as all domains (Conceptual 95.1 vs 84.1, $P = 0.001$; Social 95.0 vs 86.2, $P = 0.002$; Practical 91.8 vs 78.9, $P = 0.001$). On multivariate analysis, proton therapy was associated with higher FSIQ/GAI ($\beta = 10.6$, $P = 0.048$; interaction term nonsignificant [n.s.]) and PSI ($\beta = 14.4$, $P = 0.007$; interaction term n.s.), with a trend toward higher VIQ ($\beta = 9.9$, $P = 0.06$; interaction term n.s.) and parent ratings of adaptive functioning across domains (GAC $\beta = 11.4$, $P = 0.07$; interaction n.s.; Conceptual $\beta = 10.6$, $P = 0.09$; interaction n.s.; Social $\beta = 9.7$, $P = 0.07$; interaction n.s.; Practical $\beta = 12.3$, $P = 0.08$; interaction n.s.). Age at the time of radiotherapy predicted neuropsychological outcomes across multiple domains including VIQ ($\beta = 0.9$, $P = 0.01$), Digit Span ($\beta = 0.1$, $P = 0.04$), and parent ratings on the Conceptual Domain of the ABAS ($\beta = 1.1$, $P = 0.03$). Multiple neuropsychologic domains were also impacted by hydrocephalus requiring shunt (FSIQ/GAI: $\beta = 7.8$, $P = 0.049$; story memory: $\beta = 1.5$, $P = 0.04$; written calculations: $\beta = 9.2$, $P = 0.04$), CSI at 36 Gy (PSI: $\beta = 13.8$, $P = 0.03$; VMI: $\beta = 11.0$, $P = 0.04$; written calculations: $\beta = 14.0$, $P = 0.03$), and CSI at 23.4 Gy (VMI: $\beta = 12.0$, $P = 0.04$). Other patient demographic and treatment variables associated with neuropsychological outcome on multivariate analysis are presented in Table 3.

Sensitivity Analyses

After truncating the dataset to include subjects with equal neuropsychological follow-up intervals across the cohorts, a total of 115 patients were evaluable. The median time from end of radiotherapy to neuropsychological evaluation was 3.5 years for the XRT cohort ($n = 57$, IQR 1.2–4.8) and 2.6 years for the PRT cohort ($n = 58$, IQR 1.4–3.6, $P = 0.3$). The general trends observed in the original analysis were re-demonstrated. Similar to the original analysis, on multivariate analysis patients treated with PRT had higher FSIQ/GAI scores ($\beta = 11.1$, $P = 0.04$, interaction term n.s.) and VIQ ($\beta = 13.4$, $P = 0.01$, interaction term n.s.) and trended toward higher PSI ($\beta = 9.1$, $P = 0.09$, interaction term n.s.). For the other domains where PRT was associated with improved outcomes in the original analysis (parent-reported adaptive functions), PRT was significant on univariate analysis, but no covariates including PRT were significant on multivariate analysis.

Next, SES was categorized as "low," "average," or "high." In the XRT cohort 18 (26.9%) were low SES, 39 (58.2%) were average SES, and 10 (14.9%) were high SES, while in the PRT cohort 8 (13.8%) were low SES, 34 (58.6%) were average SES, and 16 (27.6%) were high SES ($P = 0.063$). On sensitivity analysis coding SES as a categorical variable, significant predictors of VIQ included age ($\beta = 1.1$, $P = 0.002$) and SES "high" ($\beta = 10.1$, $P = 0.03$); however, PRT was no longer significant. For PIQ, significant covariates were PRT ($\beta = 8.6$, $P = 0.048$), SES "average" ($\beta = 8.9$, $P = 0.003$), hydrocephalus requiring shunt ($\beta = -10.8$, $P = 0.004$) and CSI 23.4 Gy ($\beta = -8.7$, $P = 0.002$). Finally, for FSIQ/GAI, significant covariates were PRT ($\beta = 11.1$, $P = 0.046$), SES "high" ($\beta = 9.9$, $P = 0.04$), shunt ($\beta = -9.9$, $P = 0.01$), and age ($\beta = 0.87$, $P = 0.015$).

Subset Analyses: Focal Irradiation and CSI

Cohorts were separated into those receiving focal brain treatments (XRT, $n = 23$ and PRT, $n = 27$) and CSI (XRT, $n = 43$ and PRT, $n = 32$). Comparisons of group means for patients treated with focal brain radiation and CSI, with either XRT or PRT are described in Table 4. For patients receiving focal brain treatment, on multivariate analysis PRT was associated with higher PSI relative to XRT ($\beta = 22.5$, $P = 0.01$; interaction term n.s.). Among patients receiving CSI, on multivariate analysis PRT was associated with higher VIQ ($\beta = 16.8$, $P = 0.01$; interaction term n.s.) and FSIQ/GAI ($\beta = 19.1$, $P = 0.01$; interaction term n.s.). An additional analysis was performed for patients receiving CSI to compare

Table 1 Patient demographic and treatment characteristics by RT modality ($n = 125$)

	XRT ($n = 67$)	PRT ($n = 58$)	*P*-value
Age at radiation treatment, median (IQR)	7.35 (4.57–11.03)	8.50 (5.75–11.81)	0.15
Sex, no. (%)			0.37
Male	37 (55.2)	37 (63.8)	
Female	30 (44.8)	21 (36.2)	
Race, no. (%)			**0. 023**
Black	8 (11)	0 (0)	
Latino	15 (22.4)	12 (20.7)	
Other	6 (9)	10 (17.2)	
White	38 (56.7)	36 (63.8)	
Socioeconomic Status, continuous, median (IQR)[1]	6.2 (5.07–8.03)	7.38 (5.61–9.20)	**0.031**
Socioeconomic Status, categorical, no. (%)			0.063
Low, <5	18 (26.9)	8 (13.8)	
Average, ≥5 and <9	39 (58.2)	34 (58.6)	
High, ≥9	10 (14.9)	16 (27.6)	
Time from treatment to last assessment, y, median (IQR)	6.7 (3.6–9.7)	2.6 (1.4–3.6)	**<0.001**
No. of neuropsychological assessments, no. (%)			0.11
1	33 (49.3)	39 (67.2)	
2	25 (37.2)	12 (20.7)	
3 or more	9 (13.4)	7 (12.1)	
Tumor histology, no. (%)			0.09
Craniopharyngioma	1 (1.5)	5 (8.6)	
Medulloblastoma/PNET	41 (61.2)	26 (44.8)	
Ependymoma	11 (16.4)	5 (8.6)	
Germinoma	5 (7.5)	9 (15.5)	
Glioma	7 (10.4)	9 (15.5)	
Other	1 (3.0)	4 (6.9)	
Tumor location, no. (%)			**0.003**
Cerebral hemispheres	12 (17.9)	10 (17.2)	
Midline/thalamic	11 (16.4)	25 (43.1)	
Posterior fossa	44 (65.7)	23 (39.7)	
Number of craniotomy operations, no. (%)			0.42
None	7 (10.4)	11 (19.0)	
1	48 (71.6)	37 (63.8)	
2 or more	12 (17.9)	10 (17.2)	
Hydrocephalus requiring shunt, no. (%)	10 (14.9)	14 (24.1)	0.30
Craniospinal irradiation, no. (%)			0.11
None	26 (38.8)	33 (56.9)	
23.4 Gy or Gy(RBE)	24 (35.8)	13 (22.4)	
36 Gy or Gy(RBE)	17 (25.4)	12 (20.7)	
Chemotherapy, no. (%)			
Carboplatin	20 (29.9)	28 (48.3)	**0.035**
Etoposide	11 (16.4)	14 (24.1)	0.29
Vincristine	44 (65.7)	33 (56.9)	0.32
Cisplatin	42 (62.7)	26 (44.8)	**0.046**
Treatment-related complications, no. (%)			
Posterior fossa syndrome	12 (17.9)	8 (13.8)	0.63
Hearing loss requiring assistive device	22 (32.8)	15 (25.9)	0.37
Visual impairment	12 (17.9)	8 (13.8)	0.63

PNET = primitive neuroectodermal tumor; RBE = relative biological effectiveness.
[1]SES defined as median household income by patient zip code/10000.

Table 2 Neuropsychological assessment results at most recent evaluation by radiotherapy modality

	XRT	PRT	*P*-value
Full-scale IQ/General Ability Index,[1] mean (95% CI)	88.6 (84.0–93.1)	96.0 (91.8–100.3)	**0.0019**
Calculated from , no. (%)			0.31
WISC or WAIS	29 (43.3)	19 (32.8)	
WASI-II	38 (56.7)	39 (67.2)	
Verbal IQ,[1] mean (95% CI)	92.8 (88.4–97.3)	99.7 (95.3–104.1)	**0.033**
Performance IQ,[1] mean (95% CI)	87.8 (82.0–98.0)	90.7 (82.5–98.8)	0.056
Processing Speed Index,[1] mean (95% CI)	80.0 (76.2–83.8)	87.1 (82.0–92.3)	**0.03**
Digit Span,[2] mean (95% CI)	7.6 (6.7–8.4)	8.1 (7.3–8.8)	**0.03**
Story Memory,[2] mean (95% CI)	8.7 (7.8–9.6)	9.5 (8.7–10.4)	0.2
Visual Motor Integration,[1] mean (95% CI)	80.8 (76.7–85.0)	87.2 (82.9–91.5)	**0.035**
Word Reading/decoding,[1] mean (95% CI)	86.4 (81.6–91.2)	94.1 (89.8–93.4)	**0.02**
Written Calculations,[1] mean (95% CI)	83.1 (78.2–88.0)	90.4 (85.4–95.4)	**0.042**
Parent-reported General Adaptive Composite,[1]mean (95% CI)	80.7 (76.0–85.4)	92.0 (87.2–96.7)	**0.001**
ABAS Conceptual Domain,[1] mean (95% CI)	84.1 (79.1–89.1)	95.1 (90.7–99.5)	**0.001**
ABAS Social Domain,[1] mean (95% CI)	86.2 (82.6–89.8)	95.0 (90.9–99.2)	**0.002**
ABAS Practical Domain,[1] mean (95% CI)	78.9 (73.2–84.7)	91.8 (87.1–96.5)	**0.0001**

[1]Standardized score, mean for normal = 100, standard deviation = 15.
[2]Scaled score, mean for normal = 10, standard deviation = 3.

those who received IMRT ($n = 24$) with those who received PRT ($n = 32$). Although VIQ trended toward statistical significance on multivariable analysis ($\beta = 3.2$, $P = 0.09$), FSIQ/GAI did reach significance favoring PRT ($\beta = 19.6$, $P = 0.03$), age ($\beta = 2.5$, $P = 0.001$), and hydrocephalus requiring shunt ($\beta = -12.5$, $P = 0.02$).

Discussion

Our study found that pediatric brain tumor patients receiving PRT experience favorable neuropsychological outcomes relative to those receiving XRT as assessed by measures of intelligence (FSIQ/GAI), processing speed, and parent-reported adaptive functioning. These results were demonstrated after accounting for differences in neuropsychological follow-up intervals between the groups and were confirmed by sensitivity analyses. Subgroup analyses suggest that, for patients receiving CSI, PRT is associated with greater sparing of general intellectual function, and for patients requiring focal brain treatments, PRT preserves processing speed relative to XRT. We hypothesize that lower overall doses to supratentorial structures such as the hippocampi, temporal lobes, and white matter tracts following focal PRT and even CSI when the boost portion of treatment is considered relative to XRT may lead to significantly improved neuropsychological outcomes. This highlights the potential for proton therapy to mitigate multiple neuropsychological sequelae of radiation treatment, potentially leading to improved long-term quality of life and psychosocial functioning in adult survivors of pediatric brain tumors.

The results of our study provide further evidence for a mechanistic link between the neuropsychological sequelae and biological mechanisms of neurological injury following radiotherapy. Preclinical studies have identified white matter and hippocampal substructures as critical regions for radiation-induced cognitive impairment.[32–35] Furthermore, the specific neuropsychological impairments noted after cranial radiotherapy, such as deficits in attention, processing speed, visual-spatial integration, and perceptual reasoning, are shared across many nonmalignant conditions thought to be related to white matter injury, including benign hydrocephalus.[36,37] Childhood is a critical time for brain growth and development, with significant increases in white matter volume—for example, in the corpus callosum (up to adolescence) and association bundles (into early adulthood).[38–40] Furthermore, numerous radiologic studies have correlated neuropsychological impairment to dose-related imaging changes in supratentorial white matter pathways. Connor et al studied 15 patients with high-grade gliomas receiving radiation with or without chemotherapy and analyzed white matter changes at various time intervals posttreatment. They noted significant white matter changes of increasing intensity with higher doses of radiation, but changes were noticeable even after low doses of 10 Gy or less.[41] Similarly, post-radiotherapy decreased white matter volume and integrity has been associated with declines in full scale IQ, processing speed, and executive function.[42–45] After addressing the confounding effects of SES, our study found that PRT was associated with higher perceptual reasoning, full-scale IQ/GAI, and processing speed, but not verbal comprehension. These results are consistent with current theories about the late core deficits following

Table 3 Multivariate linear regression demonstrates covariates predicting neuropsychological outcome

Intellectual Skills	Working and Long-term Memory Skills	Visuographic Skills	Academic Skills	Adaptive Functioning
Verbal IQ *Proton therapy* (β = 9.9, *P* = 0.06; interaction term n.s.) *Age at irradiation* (β = 0.9, *P* = 0.01) *Socioeconomic status* (β = 1.4, *P* = 0.02) ***Performance IQ*** *Socioeconomic status* (β = 1.7, *P* = 0.004) *Hydrocephalus requiring shunt* (β = −9.4, *P* = 0.01) *Craniospinal irradiation 23.4 Gy* (β = −12.5, *P* = 0.0002) ***Full-scale IQ/General Ability Index*** *Proton therapy* (β = 10.6, *P* = 0.048; interaction term n.s.) *Hydrocephalus requiring shunt* (β = −7.8, *P* = 0.049) ***Processing Speed Index*** *Proton therapy* (β = 14.4, *P* = 0.007; interaction term n.s.) *Craniospinal irradiation 36 Gy* (β = −13.8, *P* = 0.03) *Posterior fossa syndrome* (β = −10.1, *P* = 0.04)	***Digit Span*** *Age at irradiation* (β = 0.1, *P* = 0.04) ***Story Memory*** *Socioeconomic status* (β = 0.3, *P* = 0.02) *Race* (white β = 2.6, *P* = 0.02; other β = 3.2, *P* = 0.03) *Hydrocephalus requiring shunt* (β = −1.5, *P* = 0.04)	***Visual-Motor Integration*** *Craniospinal irradiation 23.4 Gy* (β = −12.0, *P* = 0.04) *Craniospinal irradiation 36 Gy* (β = −11.0, *P* = 0.04) *Time from completion of RT to last neuropsych eval* (β = −0.9, *P* = 0.03)	***Written Calculations*** *Socioeconomic status* (β = −2.0, *P* = 0.003) *Hydrocephalus requiring shunt* (β = −9.2, *P* = 0.04) *Craniospinal irradiation 36 Gy* (β = −14.0, *P* = 0.03)	***ABAS General Adaptive Composite*** *Proton therapy* (β = 11.4, *P* = 0.07; interaction n.s.) ***ABAS Conceptual Domain*** *Proton therapy* (β = 10.6, *P* = 0.09; interaction n.s.) *Age at irradiation* (β = 1.1, *P* = 0.03) ***ABAS Social Domain*** *Proton therapy* (β = 9.7, *P* = 0.07; *interaction* n.s.) ***ABAS Practical Domain*** *Proton therapy* (β = 12.3, *P* = 0.08; interaction n.s.)

cranial radiation in children, particularly with respect to preserving white matter integrity.

Advanced radiotherapy technologies that enable tighter conformality of dose around targets and less spillover to white matter or other sensitive brain structures have been shown to improve neuropsychological outcomes. Merchant et al found that percent volume of supratentorial brain receiving 0–20 Gy, 20–40 Gy, and 40–65 Gy were each significant predictors of longitudinal IQ in 88 patients with localized ependymoma receiving conformal XRT.[18] Preservation of longitudinal IQ, learning, and adaptive functioning has also been demonstrated following similar conformal techniques in patients with pediatric craniopharyngioma and low-grade glioma.[21,46] Proton therapy, and in particular intensity-modulated proton therapy, represents the most advanced currently available radiotherapy modality to spare sensitive neurocognitive structures, eliminating high volumes of low-dose radiation exposure to the supratentorial brain and improving conformality in moderate and high-dose regions. Yock et al prospectively examined 59 pediatric patients with medulloblastoma receiving proton therapy risk-adapted CSI and posterior fossa boost; at a median follow-up of 5.2 years, patients displayed stable overall IQ but declines in processing speed scores.[23] An expanded analysis from the same group has demonstrated relative preservation of IQ and adaptive functioning in 155 patients treated with proton therapy at a median follow-up of 3.6 years.[27] Kahalley compared IQ scores for 60 pediatric brain tumor patients receiving conformal XRT versus 90 patients receiving PRT and found no change in IQ over time with the proton cohort, whereas the X-ray cohort had average decline of 1.1 points per year.[25] The same group updated their findings with a cohort of 39 patients treated with PRT (21 CSI and 18 focal) and found preserved attention and executive function, but impaired processing speed for all patients.[26]

Our study further supports and expands the evidence that PRT preserves neuropsychological function presumably by significantly decreasing low-dose irradiation to healthy brain tissue. However, there are several key limitations that need to be considered. First, due to the increased availability of PRT at a local center relatively late in the study time period, significant differences exist between the cohorts in terms of the timing of neuropsychological follow-up. It is well known that radiation-induced neuropsychological deficits can emerge and worsen over time; therefore, a sensitivity analysis was performed to assess the impact of radiotherapy modality in cohorts with similar neuropsychological follow-up intervals. Smaller patient numbers in the truncated sensitivity analysis limited statistical power; however, results observed in the original analysis were re-demonstrated, with PRT being associated with higher VIQ, FSIQ/GAI, and trend toward higher processing speed. Differences in SES between the XRT and PRT cohorts are an important factor, as not only may patients coming from higher SES households have greater access to education, but SES is known to correlate with cognitive functioning, particularly verbal ability.[46,47] As economic barriers including insurance coverage, logistics, and travel may prohibit some patients from receiving PRT, SES and neuropsychological function in the population of

Table 4 Neuropsychological assessment results at most recent evaluation, XRT and PRT by CSI vs focal

	XRT, CSI ($n = 43$)	PRT, CSI ($n = 32$)	*P*-value	XRT, Focal ($n = 23$)	PRT, Focal ($n = 27$)	*P*-value
FSIQ/General Ability Index,[1] mean (95% CI)	86.7 (80.9–992.4)	96.4 (90.1–102.7)	**0.014**	92.3 (84.4–100.2)	95.6 (89.6–101.6)	0.49
Verbal IQ,[1] mean (95% CI)	90.8 (85.5–96.2)	100.7 (93.9–107.5)	**0.019**	96.8 (88.2–1005.3)	98.5 (92.9–104.0)	0.41
Performance IQ,[1] mean (95% CI)	84.6 (76.0–94.0)	93.2 (77.0–106.0)	0.055	94.3 (84.0–100.0)	94.9 (85.0–103.0)	0.91
Processing Speed Index,[1] mean (95% CI)	78.6 (73.5–83.7)	81.9 (76.3–87.4)	0.19	82.8 (77.2–88.3)	94.0 (84.9–103.1)	**0.042**
Digit Span,[2] mean (95% CI)	7.3 (6.2–8.3)	7.8 (7.0–8.6)	**0.043**	8.2 (6.8–9.6)	8.6 (7.0–10.1)	0.46
Story Memory,[2] mean (95% CI)	8.1 (6.9–9.2)	9.5 (8.2–10.8)	0.083	10.1 (8.9–11.2)	9.6 (8.5–10.7)	0.63
Visual-Motor Integration,[1] mean (95% CI)	79.2 (73.9–84.5)	85.4 (79.8–91.0)	0.13	84.0 (77.4–90.7)	89.5 (82.4–96.5)	0.22
Word Reading/Decoding,[1] mean (95% CI)	84.2 (78.0–90.5)	94.2 (87.7–100.8)	**0.001**	91.1 (83.8–98.3)	93.9 (88.0–99.8)	0.74
Written Calculations,[1] mean (95% CI)	80.1 (74.2–85.9)	89.0 (82.2–95.8)	**0.041**	89.8 (80.80–98.8)	92.2 (84.3–100.1)	0.84
Parent-reported General Adaptive Composite,[1] mean (95% CI)	78.3 (72.5–84.1)	92.1 (86.2–97.6)	**0.009**	86.3 (78.3–94.3)	91.8 (83.0–100.7)	0.40
ABAS Conceptual Domain,[1] mean (95% CI)	80.6 (74.2–87.0)	95.1 (89.5–100.6)	**0.010**	92.6 (86.5–98.6)	95.2 (87.1–103.3)	0.60
ABAS Social Domain,[1] mean (95% CI)	84.8 (80.6–89.0)	95.7 (90.3–101.1)	**0.010**	89.5 (82.1–96.9)	94.1 (86.8–101.3)	0.40
ABAS Practical Domain,[1] mean (95% CI)	76.1 (68.2–83.0)	91.9 (86.4–97.3)	**0.009**	85.6 (74.7–96.5)	91.8 (82.4–101.1)	0.40

[1]Standardized score, mean for normal = 100, standard deviation = 15.
[2]Scaled score, mean for normal = 10, standard deviation = 3.

pediatric brain tumor survivors require further study. In addition, given the retrospective, cross-sectional nature of this study, a heterogeneous group of tumor types were included with more patients in the XRT cohort with posterior fossa tumors and more in the PRT cohort with midline tumors. Finally, although multivariable analysis was performed to account for covariates such as age at irradiation, estimated SES, hydrocephalus requiring shunting, and CSI dose, our lack of knowledge of pre-radiotherapy baselines limits a more detailed understanding of these results, as deficits can exist prior to radiation due to the tumor, surgery, and chemotherapy.[48,49]

In conclusion, utilizing a comprehensive battery of neuropsychological domains, our study demonstrated that neurocognitive performance of pediatric brain tumor patients is most impacted by age, estimated SES, hydrocephalus requiring shunt, CSI, and posterior fossa syndrome. Accounting for these factors, PRT is associated with favorable neuropsychological outcomes relative to XRT in terms of VIQ, PIQ, FSIQ/GAI, PSI, as well as parent-reported adaptive function. Future longitudinal and prospective studies of neuropsychological outcomes following PRT should assess how de-escalation of dose or target volume using molecular subgrouping, dosimetric modeling and advanced treatment planning, and improved educational and pharmacological interventions for patients with unavoidable risk can continue to decrease the neuropsychological morbidity of treatment.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

neuropsychologic outcomes | pediatrics | proton therapy | radiotherapy

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